

ANGLIA RUSKIN UNIVERSITY

FACULTY OF SCIENCE AND TECHNOLOGY

A CRITICAL APPRAISAL OF THE PARITY OF INTERNATIONAL  
PHARMACEUTICAL PRODUCTS

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A thesis in fulfilment of the requirements of Anglia  
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ANGLIA RUSKIN UNIVERSITY

ABSTRACT

FACULTY OF SCIENCE AND TECHNOLOGY

PROFESSIONAL DOCTORATE

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This research project sought to critically assess the parity, with respect to safety and quality, of internationally manufactured drug products when contrasted against domestically manufactured products. The pharmaceutical industry is a global industry with major markets importing up to 80% of drug products utilised by their citizens, it is essential that all manufacturers meet the same minimum quality standard. The researcher has utilised a mixed methods approach of questionnaire and interviews of subject matter experts and regulators. In conjunction with the interviews and surveys, key data was harvested from regulatory agency publications and under freedom of information requests from The United States of America Food & Drug Administration, The United Kingdom's Medicines and Healthcare Products Regulatory Agency and Australia's Therapeutic Goods Administration.

The interviews and surveys demonstrated a high level of concern that internationally manufactured drug products were of inferior quality to those manufactured domestically. In addition Regulatory agency data demonstrated for the past six years large decreases in the number of regulatory inspections overall and an even greater decrease in foreign site inspections. In one documented instance product recalls had increased by 500% in the past six years.

Participants in this research study overwhelmingly felt that the issues on non-parity were due to a number of factors including ambiguous and conflicting regulations, poor or decreasing Regulatory agency oversight, a lack of expertise and a lack of engagement and sharing best practice.

This research concluded that the generation of a model for total product quality and a global standard would be beneficial for the formation of a global framework for a minimum quality standard, it would aid industry and regulators in assessment of quality and ultimately aim to improve patient safety.

Key words: Pharmaceutical, Regulation. Globalisation, Safety, Efficacy, MHRA, FDA, TGA

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## PROLOGUE

I am not a perfectionist, I do however believe that there is a minimum quality in everything, everything we do, everything we manufacture and in what we attempt to do. Sometimes those quality attributes generate great success, sometimes they give great satisfaction and sometimes they save lives or help people.

I started my career in the pharmacy unit of a major London teaching hospital in the early 1980s, learning my craft on the job, dealing with patients, working with pharmacists and medics and, more importantly to my latter career choices, working within the “specials” unit. Specials within a pharmacy framework are those drug products that are generally not commercially available, sometimes one-off formulations that are required to assist and treat patients. Admittedly sometimes these are driven by financial consideration, however, during this phase of my career these were unique drug presentations that were required for immediate use and generated in me great fascination. These founding years were important to me and have driven me since, in my mind’s eye I can still walk the corridors of that pharmacy unit and where particular products that fascinated me were stored or manufactured.



Working in a hospital I was proud; I was making a difference. By interacting with patients daily I felt engaged and empowered. Having the fire of research and development instilled inside me, my move into the pharmaceutical industry was a natural progression and likewise, once ensconced in the industry, I felt I was in a position to make an even greater impact, I could help patients by developing safe, efficacious and essential medicines.

During my early career I struggled with the term of ethical pharmaceuticals, this term was often used to describe prescription medicines that were manufactured by the originator as distinct from those manufactured by generic competitors, the inference being that these products were better, more ethical. However, with ever increasing drug costs, the emergence, and in some markets dominance, of costed managed healthcare schemes and in the UK the National Institute for Health and Care Excellence (NICE) it is clear to all that all pharmaceuticals are ethical, they have to be, and it is incumbent on all in the industry to make sure they are the best possible products.

I commenced this research in 2017, driven by the sum of my career experiences and especially by my latter consultant career as a global pharmaceutical development expert. In this global role my experience in reviewing the quality of available medicines, production facilities and the general understanding of, not only what is required in a pharmaceutical product from a chemistry perspective, but also what makes it safe and efficacious and comparable when manufactured in different factories, countries and continents, this gave given me great concerns that my industry does not always understand and apply the “**what we need**” and the “**why we need it**”. The public deserve safe and efficacious medicines and we have a responsibility to do our utmost to provide them.

By viewing global data and the globally driven demand for cheaper and sustainable healthcare through, not only the prism of my own professional experiences but also that of other subject matter experts, in this thesis I strive to understand the key drivers and influencers for my industry. An industry that generally receives a negative public image and is frequently used as a political vote grabber, to demonstrate how the industry can evolve and grow to increase its positive impact on human health. The global COVID-19 pandemic that touched so many people that arose during my research clearly demonstrates the importance of a successful, quality driven and responsive pharmaceutical industry. What I have strived to do is to incorporate a reflexive component to these challenging times, to learn, to understand and to develop. The reader will note that I have punctuated the narrative in this thesis with mind maps, these maps evolved during the course of my research and are used to demonstrate my emerging thought processes during data gathering. These help the reader to follow the flow and development of my primary conclusions.

My research and this resulting thesis were born out of frustration: My frustration in an industry that does great good on a global scale, but that could be even better. This prologue is my voice, my professional experience, my motivation. The research is neutral, data driven, as expected from a scientist. I have also tried to develop this data into formats that are familiar and usable to the pharmaceutical industry, to demonstrate how this research can assist the pharmaceutical industry that I have strived to contribute to in my career to date. Discussions of components of “Lean” production systems, as originally devised by Toyota, to eliminate the three major causes of deviations and inefficient use of resources. In the past decade this process has been introduced to varying degrees into the pharmaceutical industry and will be discussed.

As an emic researcher utilising the existing regulatory frameworks that all regulated pharmaceutical countries develop to support product regulation, combined with the richness of global subject matter experts, I have attempted to start that discussion, to improve my industry, to improve patient health and to be proud in the global pharmaceutical industry that has driven my career for decades.

(Paul J Cummings July 2022)

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Thanks go to my colleagues in the pharmaceutical industry who participated in the research with the provision of their time and open willingness to help make our industry even better.

Finally thank you to my family, my daughters Emily, Laura and Sarah for putting up with my complaints and long days in the office writing, or planning to write, and a special thank you to my wife, Karen, for not only having to read and re-read this thesis many times but also for her patience in teaching me the nuances in Microsoft Word, a challenge I find far greater than formulating medicinal drug products!

## ABBREVIATIONS

ABPI	Association of the British Pharmaceutical Industry
ANVISA	Agência Nacional de Vigilância Sanitária
ATMP	Advanced therapy medicinal product
CA	Competent Authority
CDER	Center for Drug Evaluation and Research
CHMP	Committee for Medicinal products for Human Use
CFDA	Chinese Food and Drug Administration
CMC	Chemistry, Manufacturing and Controls
CMS	Concerned Member State
EU	European Union
EMA	European Medicines Agency
FDA	Food and Drug Administration
FTE	Fixed Term Equivalent
ICH	International Conference on Harmonisation
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IP	Intellectual Property
MHRA	Medicines and Healthcare Regulatory Agency
NCE	New Chemical Entities
NDA	New Drug Application
PIC/S	Pharmaceutical Inspection Cooperation Scheme
OPQ	Office of Pharmaceutical Quality
PDA	Parenteral Drug Association
QbD	Quality by Design
QRM	Quality Risk Management
R&D	Research and Development
RMS	Reference Member State
SPC	Summary of Product Characteristics
TPQ	Total Product Quality

## CHAPTER ONE: INTRODUCTION

### *1.0 The registration of pharmaceutical products*

The pharmaceutical industry is a highly regulated industry. However even with improved international interactions such as of the International Congress on Harmonization (ICH) there is no worldwide common regulatory framework on which to base product development and commercial manufacture. The development of new pharmaceutical products takes on average 13 years from inception to market, costs in the region of £300-£600 million (Global Pharmaceutical Industry Statistica, 2014) to get to the market phase of the product lifecycle and will involve the expertise of hundreds of scientists in various disciplines to progress.

### *1.1 The generic drug approval process*

All pharmaceutical products require a substantial and convincing set of data to facilitate an approval for sale. Regulatory Agencies exist in every country (Table 1) to independently review and subsequently approve both new product applications and variations to existing pharmaceutical product licenses.

**Table 1: Regulatory Agencies listed by country**

Country	Name of regulatory agency	Country	Name of regulatory agency
USA	Food and Drug Administration (FDA)	Ukraine	Ministry of Health
UK	Medicines and healthcare products Regulatory Agency (MHRA)	Singapore	Centre for Pharmaceutical Administration Health Science Authority
Australia	Therapeutic Good Administration (TGA)	Hong Kong	Department of health: Pharmaceutical Services
India	Central Drug Standard Control Organisation (CDSCO)	Paraguay	Ministry of Health
Canada	Health Canada	Sweden	Medical Products Agency (MPA)
Europe	European Medicines Agency (EMA)	Thailand	Ministry of Public Health
Denmark	Danish Medicines Agency	China	State Food and Drug Administration
Costa Rica	Ministry of Health	Germany	Federal Institute for Drugs and Medical Devices
New Zealand	Medsafe – Medicines and Medical Devices Safety Authority	Malaysia	National Pharmaceutical Control Bureau, Ministry of Health
Sweden	Medical Products Agency (MPA)	Pakistan	Drugs Control Organisation, Ministry of Health
Netherlands	Medicines Evaluation Board	South Africa	Medicines Control Council
Ireland	Irish Medicines Board	Sri Lanka	SPC, Ministry of Health
Italy	Italian Pharmaceutical Agency	Switzerland	Swissmedic, Swiss Agency for Therapeutic Products
Nigeria	Nation agency for Food and Drug Administration and Control (AFDAC)	Uganda	Uganda National Council for Science and Technology (UNCST)

Many major agencies, such as Medicines and Healthcare Regulatory Agency (MHRA) in the United Kingdom and Food and Drug Administration (FDA) in the United States of America, lead the way in regulatory approval processes and the level of expertise applied to the role of a reviewing inspector. Whilst technical experts may review the individual technical components of a new submission in areas such as clinical interpretation or the pharmaceuticals component, known as the “chemistry, manufacturing and controls section”, there is still a single individual that takes responsibility for the final approval and issue of a product license. This individual is at liberty to ignore or accept advice from their appointed technical experts and therefore has great impact upon the approval or non-approval of a new drug application. I have observed such instances where data was ignored, and decisions based upon erroneous assumptions. As scientists we should make reasoned decisions based upon data especially when patient safety is in question.

Considering the actions observed over many years working as a scientist seeking to register new products it has become clear that consideration of the receiving party, in this case the regulator, has primarily been minimised. The documentation of these experiences and by, in time, adding a collective experience can only add value (Bruner, 2002, p.89). The researcher’s review of the registration process from a regulation perspective shows that there is little or no understanding of the actual or potential impact of the increasing regulatory burden on patient compliance and safety. Many successful pharmaceuticals are now past their patent expiry and still provide a safe, efficacious benefit to the patients that take them, despite not meeting current registration requirements if a licence application is submitted now. There are, in many cases, complex drug molecules with varying levels of manufacturing complexity which were developed and manufactured and indeed continue to be manufactured under processes that were in place over 25 years ago. The UK Orange Guide (MHRA, 2017) issued by Medicines & Healthcare Regulatory Authority (MHRA, the guide for good manufacturing practice) has ballooned from circa 111 pages in 1983, 432 pages in 2007, to 806 pages in 2017. The researcher questions if this regulator-led increase in regulation is truly representative of an increase in knowledge or a response to a cultural change within the regulatory agency. The resultant impact on safety and efficacy has not been demonstrated.

To describe these experiences in a narrative that highlights the positives, whilst expanding the potential issues that the scientist and the regulator may experience, adds value to understanding the depth and breadth of their relationship (Bolton, 2014).

Pharmaceutical regulations for the development and manufacture of pharmaceutical products vary from market to market. There is significant common ground between North America, Western Europe, and Japan. However, the rest of the world, including large developing markets such as China and the Far East, do not meet these same quality goals as found in Western Europe. Historically, these other markets appear to face large numbers of patient deaths partially attributed to poor control and oversight (Medpage Today, 2011). Table 1 lists most of the major country agencies associated with pharmaceutical approvals.

Whilst working with agencies from many of the above countries the researcher has found a wide variety of approaches, some extremely conservative whilst others were not based upon skills or knowledge with an appreciable lack of subject matter experts. One such agency approved a parenteral product for European registration, the product was lacking appropriate safety data for use in humans and the facility was lacking the expected environmental controls that would support safe manufacture of sterile products. The underlying cause in this case was that the agency concerned had no experience of parenteral manufacture, having up until that point no approved sterile product facility under its jurisdiction and therefore no base experience to call upon. On reflection that outcome seems to be obvious, however the agency responsibility retains a legal obligation, if the company concerned had engaged earlier and developed the product and facility in conjunction with the agency then this could be mitigated, and the knowledge base increased. This would add value to the company, the agency and the patient ultimately taking the medication. There are a number of theoretical issues that would need to be identified and overcome to facilitate a greater interaction between Industry and Agency. There are barriers such as intellectual property and confidentiality that would need to be resolved, in addition to an element of education, the latter being more acute in areas of new technology or new disease therapies.

## 1.2 European Union drug approval process

Within Europe the regulations for pharmaceutical development and manufacture, Eudralex guidelines (European Commission, GMP 2017), are enshrined within the laws of each member country. These controls cover all dosage forms, at all stages of development/manufacture. Specific annexes are listed for products that require special conditions. Eudralex Annex 1 of the UK guidance on parenteral products is currently under review and a substantive draft was issued in late 2016, these reviews are often driven by emerging technological developments or issues that have come to light that require remediation and regulatory control. However, it is documented in current textbooks how to manufacture sterile products to a suitable quality and robustness (Cummings, 2013). These requirements do not change because an annex is reissued; they are fundamental to good product development. Some of these controls are added to correct poor practise however are all of these controls for development and manufacture necessary for quality and efficacy or do some even stifle development of new products?

EU Annex 15 (Eudralex) promotes a science and risk-based approach, why is this approach not being adopted more widely? As a science-based industry the processes contained therein should be based upon sound scientific data and an understanding of 'risk' is key to that process, especially with regards to patient safety. What is the actual impact on drug safety, recalls and unexpected serious adverse events? Is there a tangible correlation between regulatory control and safety or is this a perceived relationship based on erroneous data and perception from high profile cases of product adulteration, contamination, or just poor practice?

To answer the questions posed above it would be beneficial to study the relationship between the pharmaceutical industry and respective Regulatory Agencies across key markets in the western world and emerging markets with respect to safety and efficacy of pharmaceuticals. A more detailed critique of the processes involved the data reviews and challenges with regards to specific disease states will add a level of detail that will support a basis for further analysis. In addition, the many country agencies routinely capture data required of all pharmaceuticals concerning efficacy and safety but there is no global or continental alignment of this data or sharing of findings routinely. In Europe

this is via the European Clinical Trials Database and the ICH E2B compliant Serious Adverse Events submission process. The addition of this published data in context with the aforementioned process understanding would add context and focus to this research. Identification of the key data sets will assist in that attainment of the granularity sought.

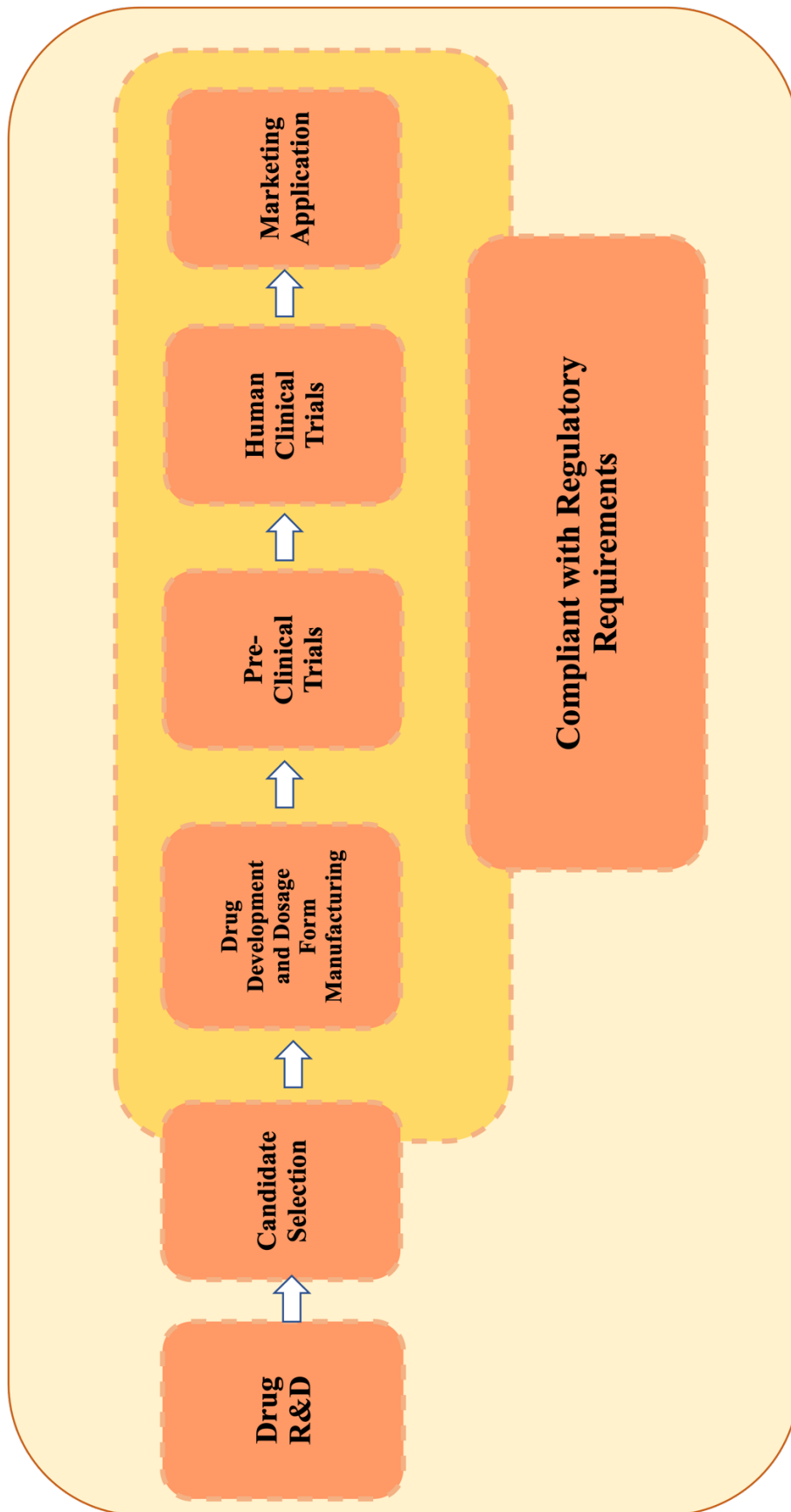
As shown in Table 1 there are individual Regulatory Agencies for each country worldwide, some smaller countries have amalgamated their agencies to form an overarching agency with legal empowerment enshrined into law by the individual countries concerned to make the agency decisions legally binding, such as EMA and ANVISA. However, countries with more established agencies have developed their own processes. For the purpose of this review, we will consider three agencies.

The Medicines and Healthcare Regulatory Agency (MHRA) are tasked by statute to determine if a new or modified medicine is fit for purpose and what the definition of that purpose should be. Likewise, the US Food and Drug (FDA) Administration has jurisdiction over the United States of America and the European Medicines Agency (EMA) can approve drugs for sale throughout the European Union member states.

Before considering the wider global implications of medicinal safety and equivalence that results from the importation of drugs from other countries it is worth considering the approval processes for the European and North American markets in the first instance.

### 1.3 The approval process summary

The overall process for approval of new drugs or modified dosage forms follows a similar pattern worldwide and this simplified process can be seen in Figure 1 below:



**Figure 1: A simplification of the drug product approval process**

The marketing application contains a comprehensive summary of all the key data and is subject to scrutiny and review/auditing; it is called many things such as the Marketing Approval Application (MAA) in the United Kingdom, New Drug Application (NDA) in the United States of America or (Biological Drug Application (BLA)), however, overall the content is similar. Alternatively, in the case of a modified dosage form or new presentation, it is captured on an Abbreviated New Drug Application (ANDA) in the United States of America, whilst in the United Kingdom this is still called a MAA, albeit with some data cross-referenced from the original submission.

These submissions and differing nomenclature all have a common thread. The medication should be safe (subject to normal side effect profiles and risk benefit analysis relative on the disease state to be treated) and be efficacious in the disease state it is intended to treat. For the purpose of this thesis the use of off-label medication, for example the use of a drug for a purpose for which it was not approved is excluded.

The procedure for gaining market entry for a new pharmaceutical product is a partnership between the pharmaceutical industry and the respective regulatory agencies. It is now common for globally active pharmaceutical companies to develop a single process or a structured range of formulations that will suffice for all global markets. These companies are often well versed in the individual nuances of registration in differing countries.

Where a company manufactures a product that does not meet the regulations in place in the target market, such as a product being exported from India to the UK, currently that responsibility for safety and efficacy sits within the regulatory agency of the importing country. This is defined in the Human Medicines Regulations 2012.

The role of the importing country Regulatory Agency is to ensure these essential criteria are met and the product is fit for purpose. For a new drug approval, a full application including safety and efficacy data as well as manufacturing data would be required, as with a domestically manufactured product. For a generic drug the regulatory burden is vastly reduced and only comparability to the originator or existing product is needed.

This is obviously a key issue of regulatory compliance; before we consider the movement of material from one country to another it is essential to understand the current regulatory

framework that exists to register new products. The actual registration process that is conducted within the responsible agencies between countries can vary.

### **1.3.1 The dual drug approval processes in Europe**

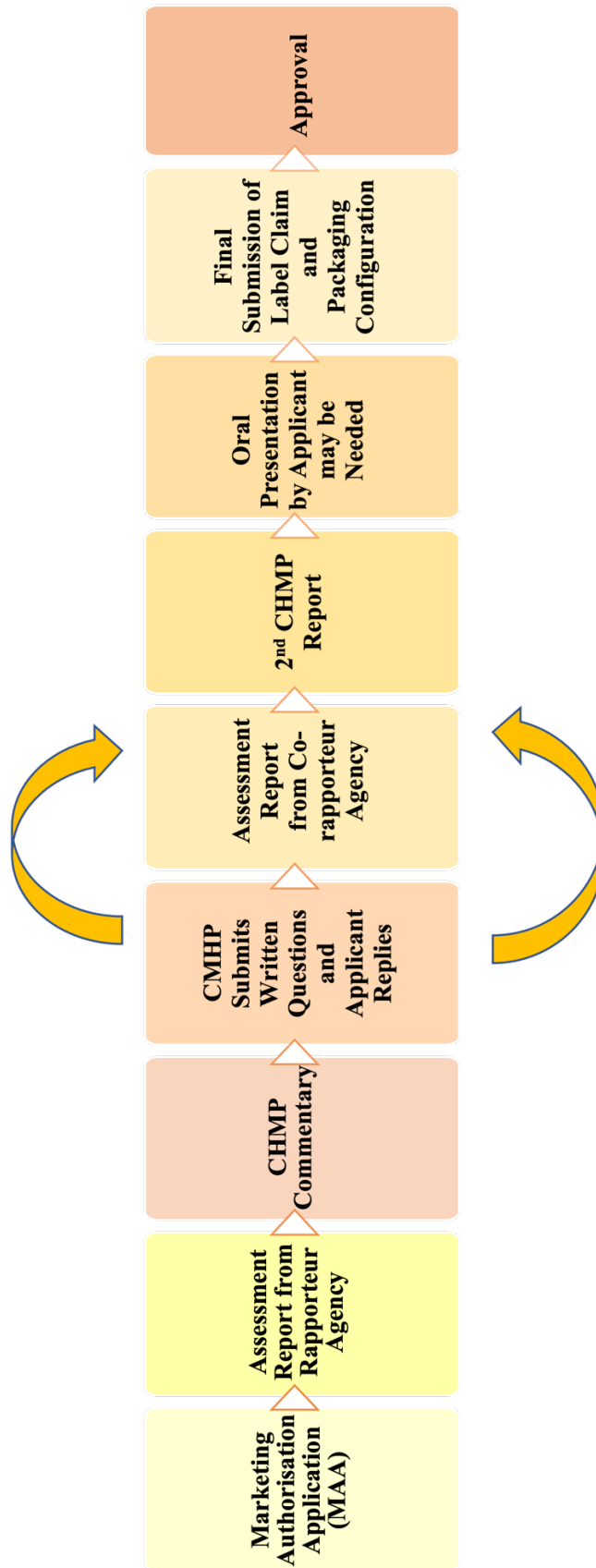
Within the remit of the European Union (EU) member states there are two main potential routes for product licensing. These are legislated under European directives 2001/83/EC Article 28 and EC 726/2004:

- A centralised authorisation procedure (EC 726/2004)
- A decentralised authorisation procedure (2001/83/EC Art.28)

Other routes exist including national agency authorisations based upon mutual recognition (partly covered by 2001/83/EC Art.28) and single member state approvals however these are not discussed in this thesis.

Both processes will ultimately yield a product license if the submission and data warrant it. However, they are fundamentally different in the way that technical expertise and review are used.

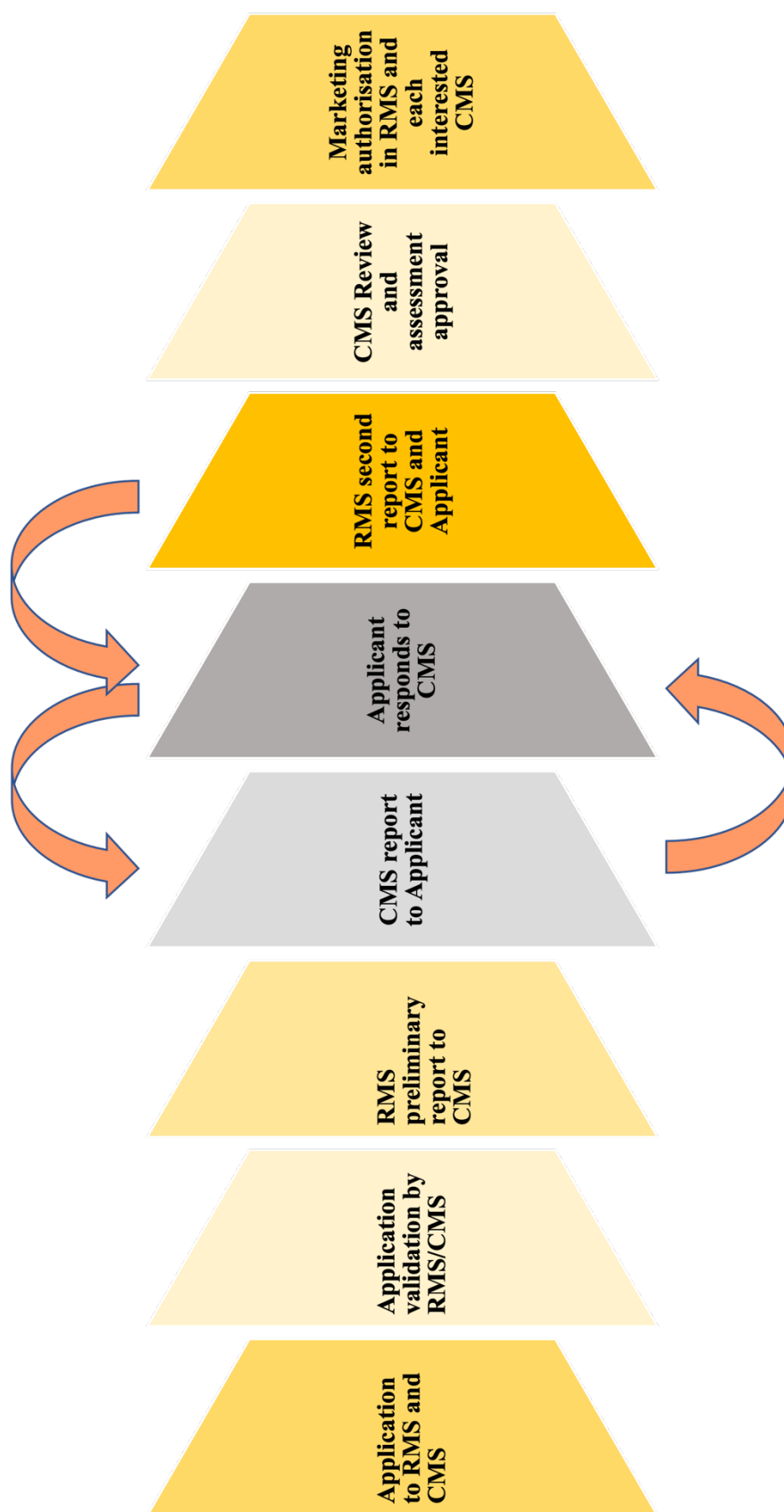
Submissions via the European centralised procedure (EMA Centralised Approval Process, 2017) are administered under the auspices of the European medicines Agency (EMA), currently based in London. This process is summarised below in Figure 2.



**Figure 2: The EMA centralised drug product approval process**

The EMA centralised approval process is the regulatory process that is utilised by applicants who wish to file and market their pharmaceutical products throughout the member states of the EU in addition to Norway and Iceland. It is compulsory for materials of a biological origin, orphan drugs and drugs that are intended for the treatment of HIV/Aids, neurodegenerative diseases, and immune dysfunction diseases. It is intended for products that are new to the EU or have undergone major amendments since initial submission and process validation and an optional process for all other standard small molecule pharmaceuticals

The EMA decentralised process (Figure 3) is intended to be used for pharmaceuticals to gain an approval in one or more member states simultaneously, but not all states. This process is designed for drugs that are already on sale in one member state (the reference member state (RMS)), also known as the rapporteur state, and that the applicant is seeking a wider approval via European mutual regulatory recognition to be granted another license by another member state (the concerned member state (CMS)). In addition, the pharmaceutical must not be in the category of medicines listed as compulsory for the centralised procedure. Across the twenty-eight EU member states there has been a choice of submission process running successfully for over a decade, whilst this process is not without fault or challenge it does provide a stable framework for safe pharmaceuticals. It does not, however, capture the issues faced by importation of pharmaceuticals from outside the EU. Such imports are subject to differing processes that will be discussed later in this thesis.



**Figure 3: The EMA decentralised drug product approval process**

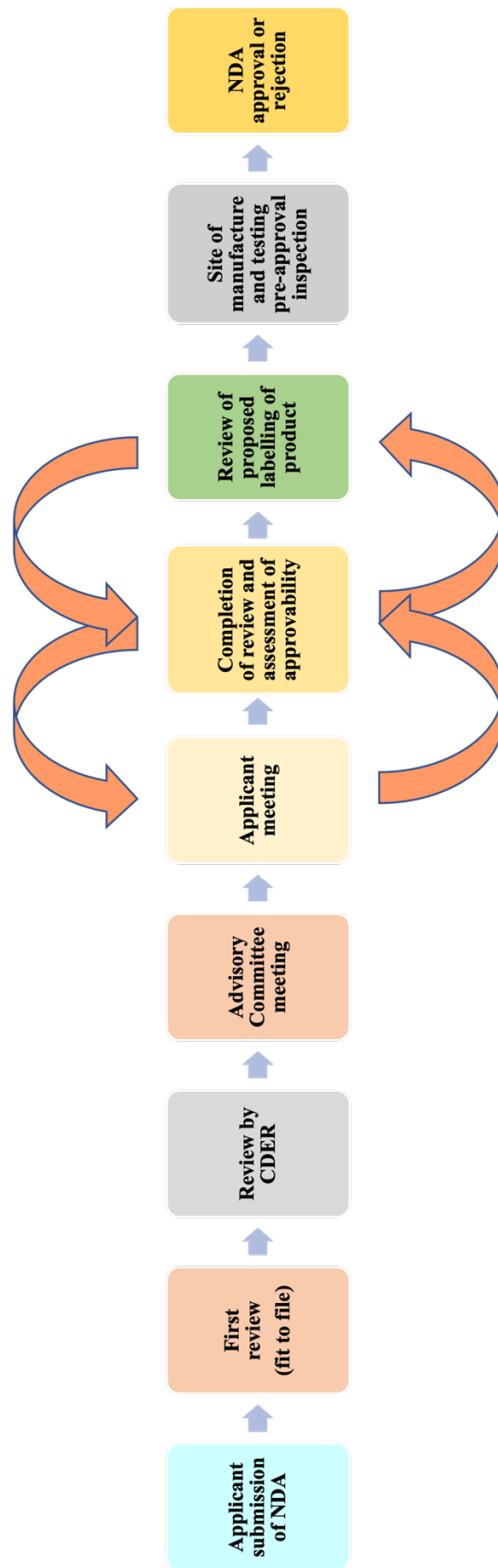
### 1.3.2 Drug approvals in The United States of America

In the United States of America all pharmaceuticals including new chemical entities (NCEs) have to be submitted via the process shown in Figure 4, below (FDA, Drug development process, 2017). The Centre for Drug Evaluation and Research (CDER) review part of the process utilizes a group of technical experts split into functional groups as shown below:

- Chemistry
- Medical
- Pharmacology
- Biopharmaceutical
- Microbiology
- Statistical

These functional experts are tasked with reviewing the technical aspects of the submission that fall within their area of expertise and then to report back to the Advisory Committee, who will then consider that technical review. The Advisory Committee are not under any obligation to accept the review of the technical experts within CDER, however, to date the Advisory Committee have demonstrated in the past a holistic approach to drug development and registration and are unlikely to challenge the CDER review unless there are other impacting aspects that lay outside the limit of CDER that would guide Advisory Committee decision.

It is easy to see from the above list a logical progression of a submission review to assess the suitability of a new product as each of the technical areas hold a respective expertise that is essential to a safe and efficacious pharmaceutical. The process, whilst differing in the actual stages of review required, does commit the registration data submitted to a rigorous and expert driven review, elements that are essential to a safe and efficacious product.



**Figure 4: The FDA new drug approval application (NDA) approval process**

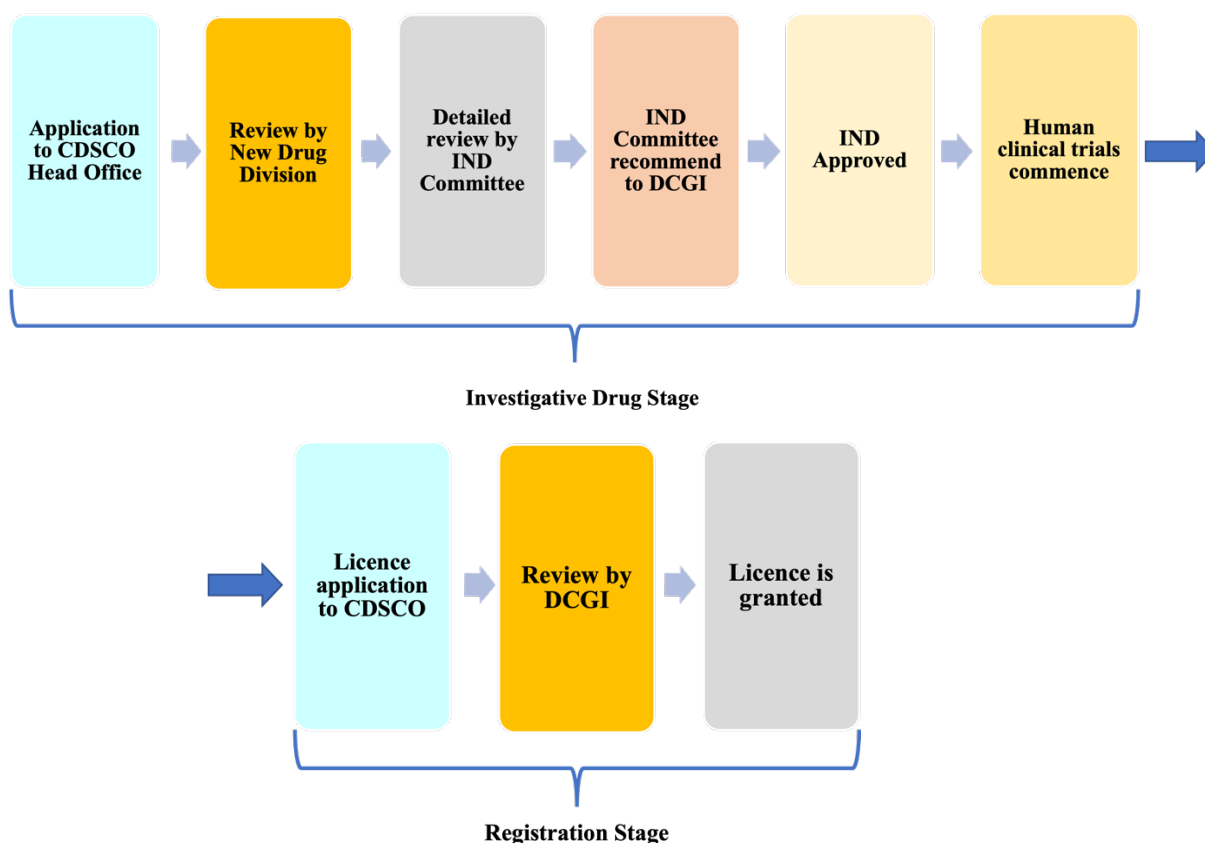
### 1.3.3 The EMA decentralised process and the US Food & Drug Administration

The process flows shown in Figures 2-4 show a commonality that meets with the generalised process flow shown in Figure 1. The process of submission, review, applicant dialogue and subsequent approval, or rejection, would appear to show a common framework. There is a component of technical dialogue, an exchange between experts of data and interpretation, of data driven decisions and ultimately a common goal. There are however areas of ambiguity and *variation in how expertise is applied, how data is reviewed and ultimately in interpretation*. In the researcher's professional experience this has been observed between the US and EU markets and is now seen to an even greater degree when considering materials imported from China, India, and other large emerging markets. These areas are the areas of greatest concern when considering the approval rate of new products and the ability of an agency to fulfil its statutory duty.

For the purposes of pharmaceuticals, emerging markets are markets that have some of the characteristics to be a developed market but do not meet the standards to be a developed market as discussed by Attieh and Tannoury (2017)

### *1.4 The impact of emerging markets*

Considering emerging markets and contrasting those with the previous examples, China and India have their own regulatory systems. However, as can be seen in below there is a certain level of commonality between the processes.

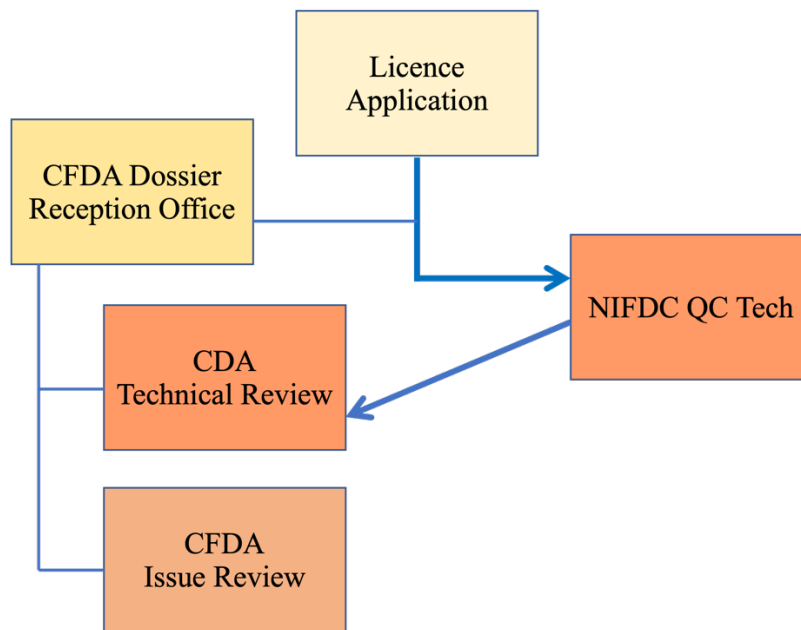


**Figure 5: The new drug product application process for India**

There are varying aspects of the process that appear to be common with the European and United States of America models, however how comparable are these without a deeper understanding of the drivers and the level of expertise application involved?

#### **1.4.1 Drug approval by the Chinese Food & Drug Administration**

The Chinese process for drug approval is based around the requirements of the Chinese Food and Drug Association (CFDA). The CFDA, have on paper, a simplified model (Hong, et al., 2017) which was recently reformed to streamline its review and approval system, mainly due to the fact that there was a 2-3 year backlog of applications that had yet to be considered. The CFDA initiated a pilot scheme to facilitate Innovator Companies to file a submission with transfer to an approved Chinese manufacturing site during the review period. The CFDA have a centralised review process, which can dictate to individual provinces within China, the existing parallel system of local approval by provincial agencies is becoming less favourable.



**Figure 6: The Chinese new drug approval process**

Within the researcher's professional experience there is always a certain political component to all approvals within China, there are also a number of agencies, which also have a role to play in the approval of new medicines. There is the aforementioned CFDA which forms part of the Chinese ministry of health, but they also require key opinions from the Centre for Drug Evaluation (CDE), the National Institute for Food and Drug Control (NIFDC) and the Province Institute for Food and Drug Control (PIFDC) and it is not unheard of, again in the researcher's experience, for some of these other organisations to have unclear reporting lines to the ministry of health.

This adds confusion and does not further support the comparability of assessment process for each drug. In 2005 the head of the CFDA was executed for corruption and for failure to carry out his duties and to ensure the duties of his agency ensured patient safety, this is in itself cause for concern and questions the validity of approvals at the highest level.

*How do we ensure that nondomestic market approvals for imported medicines reach the same standards as those adopted for local market approval, in our case those products approved within the EU?*

### **1.4.2 The issue of comparable quality on importation**

With the global market approach to pharmaceutical outsourcing the question of comparable quality of pharmaceuticals must be considered. Whilst regulatory agencies of foreign states will provide certification and oversight within their local jurisdictions, the quality standard to which they are assessed, in the researcher's professional opinion, must be considered non-equivalent until proven otherwise. Major agencies such as MHRA and FDA will conduct international overseas audits, however it is observed that resources are constrained and there are many ongoing negotiations on mutual recognition of other agencies inspections currently underway and will be for decades to come.

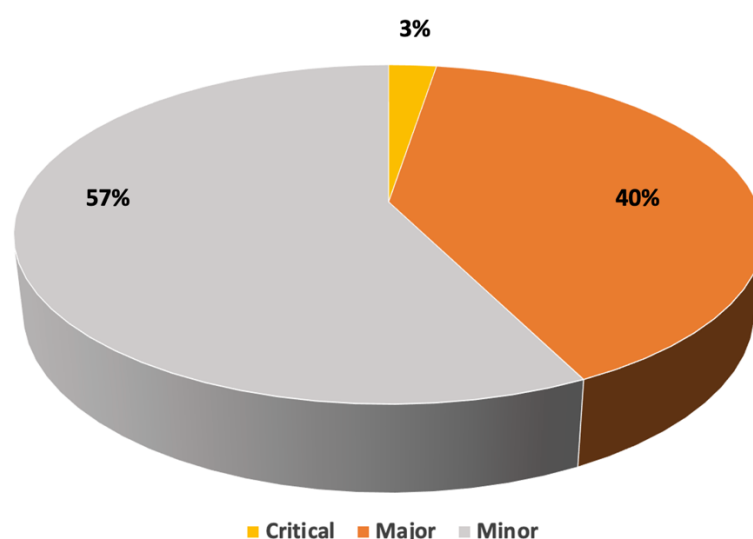
The major pharmaceutical markets of EU, North America and Japan are often sought by foreign companies as a lucrative market and the potential cost reduction that can be applied to imported pharmaceuticals will appeal to healthcare providers such as Medicare and the National Health Service. However, without a common regulatory framework how do national agencies such as MHRA ensure that all pharmaceuticals are safe and efficacious?

Some agencies claim that licenced drug products are equivalent to international standards, such as Agência Nacional de Vigilância Sanitária (ANVISA) claim equivalence to other regulatory agencies via a process of direct comparison of site inspection data. ANVISA are responsible for the sixth largest pharmaceutical market in the world. They are based in Brazil and also have jurisdiction over products from Chile, Columbia and Venezuela. ANVISA utilise a measure of deficiency detection and classification against the United States FDA as a tool to determine equivalency.

### **1.4.3 ANVISA parity assessments**

ANVISA publish yearly metrics on the findings identified during their inspections and similarly to other agencies these are categorised into Critical, Major, and Minor (Geyer, 2017). This is useful to a limited degree as it shows the level of deficiencies based upon the understanding and perspective of ANVISA personnel, however it does not align these deficiencies with the similar definitions utilised by other agencies. This gives the published ANVISA data limited usage when comparing to agencies external to ANVISA.

Figure 7 below shows the 2016 summary of deficiencies as observed by ANVISA during pharmaceutical site inspections.



**Figure 7: ANVISA declared deficiencies from on-site inspections in 2016**

(Geyer, ARC. 2017. ANVISA Regulatory Inspections. In: International Conference on GMP, GCP, and Quality Control. Chicago, United States of America, 25-26 September 2017)

The classification of deficiencies into minor, major and critical are a common approach. The detail, however, as to what constitutes each category is still open to some interpretation and that is an area that in itself prevents the comparison of this data to others to be an appropriate measure. ANVISA are keen to compare to US FDA findings and the general classifications for deficiencies as a percentage of overall deficiencies and have in the past claimed parity (Geyer, ARC. 2017. ANVISA Regulatory Inspections. In: International Conference on GMP, GCP, and Quality Control. Chicago, United States of America, 25-26 September 2017).

This is a poor comparison as insufficient data is available to make such a claim. The pharmaceutical industry and regulatory agencies are often driven to make such comparison, the claims can be of parity or inequality depending upon what data the reviewer wishes to exploit as highlighted by Rohra et al. (2006), however the result is that sometimes safe and efficacious medicines and suppliers are rejected, and poor medicines can be approved.

It is often not considered, even within the industry, how difficult it is for an agency to ensure parity of imported materials with their local market counterparts. In some situations this is even more difficult as the originator or manufacturing companies do not openly assist agency staff in determining whether an imported material is safe for patients, especially when compared to their own internal database or company generated safety and toxicology data (Ross, Gross and Krumholz 2011). There exists within the EU a system termed the ‘clinical trials database’, the EudraCT (European Union Drug Regulating Authorities Clinical Trials) (EU Drug Regulatory Clinical Trial database, 2017). The majority of EU inspectors have come from an Industry background and, when considering the poor level of partnership with industry, it can be anticipated that these frustrations will ultimately lead to decisions being made which are not always based on good science (due to lack of data), good knowledge (due to lack of communication and knowledge management) and that are not sometimes ultimately conducive to the public good.

Inspectors are often considered as confrontational rather than as part of a partnership and this approach can be greatly understood when you consider the environment within which an inspector has to function, especially when considering their potentially poor industry experiences in their role as inspectors. *How do we overcome this barrier to communication between Industry and Agency to develop a partnership rather than a potentially confrontational approach? Such as the use of scientific advice meetings and regular project updates that already occur in some situations, such as small biotech companies. These meetings, whilst not legally binding allow agency staff interactions during product development. There is inherent variability in the current process (Meyer, 1998 and Ussaarts et al. 2017) from many sources, what is needed to overcome those variables to ensure a safe pharmaceutical?*

## 1.5 Movement of products within a single market

The pharmaceutical sales involved are considerable. Table 2 lists the top 5 countries exporting pharmaceuticals into Germany in the period 2006 to 2011. Whilst this is not an exhaustive list it does demonstrate the scale of movement of products concerned. These statistics however do not include other countries exporting smaller volumes, countries such as India, China, and Taiwan.

**Table 2: Countries exporting pharmaceuticals to Germany 2006-2011 (in £ millions)**

	2006	2007	2008	2009	2010	2011
Switzerland	2430.12	4008.16	3857.59	4313.07	4863.71	5676.28
USA	4475.2	5280.45	5787.55	6403.88	5566.85	5099.19
Ireland	7374.24	7679.39	7998.36	7063.59	6010.13	4142.31
Netherlands	847.94	1218.69	1090.42	1052.65	1740.28	3674.24
United Kingdom	1616.21	1644.89	1497.93	2047.1	2287.47	2949.84

In addition, in the United States there is an average inspection rate of overseas plants every 13 years, whilst domestic manufacturing plants within continental United States are inspected every 2.7 years on average (Woodcock, 2019). The perception within the industry of this disparity is that internally FDA is primarily budget driven rather in addition to a quality risk assessment based decision process driven (Yu and Woodcock, 2015).

The United States, along with the European markets, are classified as closed markets. This requires all drugs that are prescribed within those areas to be approved by their responsible regulatory agency in some form.

The use of tax efficient manufacturers and offshore dependencies are all viewed as potential assets whilst the actual interactions with the agencies concerned are viewed as a confrontational and bureaucratic necessity rather than as a process that could add value to the product being developed. This has been experienced as a cultural issue with staff being actively discouraged from engaging agency staff in any direct discussions. To be

able to demonstrate the benefits of a transparent and open dialogue between agency and industry can only be to the benefit of industry and ultimately patients. Agencies have a sole role, the review and approval of pharmaceuticals, their aim is safety of materials dosed into patients. The identification of the drivers in this relationship between industry and agency, the benefits to all parties concerned and the production of safe pharmaceuticals in a manner that facilitates industrial research and development that is both cost effective and efficient would lead to significant improvements in the current processes.

## 1 . 6 S u m m a r y

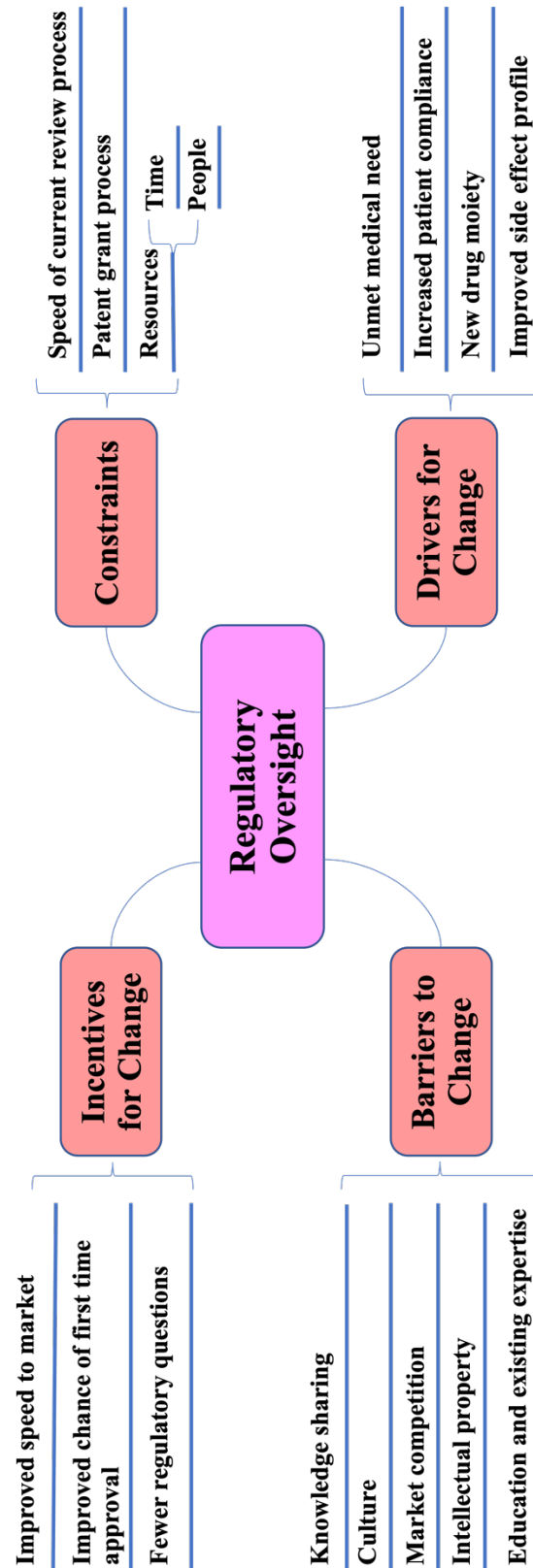
The pharmaceutical industry is one of the most regulated industries in the world. There is a cyclical process of Research & Development leading to trials and ultimately product launch, however for many scientists this prompts questions into the nature of the relationship between Regulators and Industry. Is there a risk/benefit nature to that relationship from the perspective of the patient and is this supported by the perception of industry of that same interaction?

The control of medicines in the UK has evolved over time. The transition from a voluntary code to legislative control has been well documented and the processes now followed contains a logic that is in many cases hard to refute according to Griffen (2013). With approved trading partners, such as within the EU, there is a degree of relatively easy importation of materials as there is an assumption of parity, often driven by political rather than scientific justification as demonstrated by the current legislation within the EU. In the researcher's professional experience working in industry there is a perception of the agency role as something to be endured, something that needs to be considered and overcome. After leaving industry and moving into a role driven by expertise rather than milestones and data rather than corporate culture, this researcher has a different appreciation of the role of regulators and a greater understanding of the challenges they face and in some cases the pressure that is put on them by industry. It is the researcher's experience that the perception in industry is that regulators cannot add value, rather they impart delays and stifle industrial innovation. This is not based upon knowledge; it is based upon a misconception of the role of the agency inspector. It is sensed and believed

rather than based upon knowledge. Whilst it is common for industry-experienced personnel to move into regulatory agencies, there is therefore limited opportunity for knowledge sharing and the development of a common good based upon experience.

Once an individual leaves these institutions and views their activities with an external mindset it is clearer to see how process and ultimately products can be improved. Product development for pharmaceuticals should be based upon science and knowledge, not fitting into a preordained pattern. In contrast, smaller companies that serve a smaller local market are not necessarily either experienced or have access to the knowledge that would support a registration in other countries. It is this lack of global knowledge and application of data that often introduces variables into the product that may impact efficacy and/or safety of the drug product (Regnstrom et al. 2010). The evaluation of the processes of data review, the application of expertise and, where appropriate, education in the review process will need further evaluation to provide a meaningful platform for process change and cultural shift, ultimately to achieve an open, transparent and satisfactory development and review process.

It is not unreasonable to assemble a chain of reasoning (Fisher, 2011, p37) that concludes that the breadth of industry led technological advancement or speed of advancement is not always matched by the speed of regulators knowledge and understanding. Figure 8 below captures the main factors that influence regulatory processes and highlights some of the main data sets that would aid in assessment of the current process.



**Figure 8: Visual conceptualisation of the factors impacting regulatory oversight processes**

As described in this chapter the pharmaceutical industry is a complex global industry. It is established across all continents to provide medicinal drug products whilst adhering to a defined regulatory framework. This regulatory framework however differs from country to country. In this thesis the researcher aims to describe the current state of the industry with regards to product quality and to discuss, using subject matter experts' experiences and regulatory data, the state of quality parity across the global marketplace. Chapter two of this thesis will critically analyse current literature relating to pharmaceutical quality, whilst chapter three will investigate different research methodologies to define the process undertaken to research this topic. Chapter three will summarise both subject matter expert and regulatory opinion, professional experiences, and data, with the focus on product quality. Finally, chapter five will discuss in detail the outcome of this research and potential impact on the industry and further work.

## CHAPTER TWO: LITERATURE REVIEW

### *2.0 Existing literature*

A five-stage process was conducted to undertake the literature review, these stages are summarised below:

1. Initially the scope of work was identified as pharmaceutical quality in the global context, regulation, and equivalence.
2. An initial list of relevant publications was assembled to commence the search, these included medical journals, pharmaceutical and related professional body publications regulatory/governmental publications.
3. A list of appropriate keywords or word combinations were assembled.
4. A search was conducted using these key words, such as ‘pharmaceutical quality’, ‘quality systems’, ‘regulatory assessment’. In addition, phrases such as ‘product quality parity’ and ‘regulatory recognition’ were used. Also, as papers were identified the cross references in those papers were also sought where relevant. Journals such as medical journals, PDA Journal of Pharmaceutical Science and Technology and related publications were key starting points. More than fifty key words or key word combinations were utilised.
5. The researcher started with a review of the most recent publications and then work progressively backwards, Given the >ten-year timeframe for drug development and commercialisation no initial limit ion timeframe was established.

The pharmaceutical product approval processes currently in place share many common goals for product registrations across major markets, however all have some areas of variability and ultimately areas that can potentially impact safety and efficacy. It has been demonstrated that systems are in place to attempt to achieve the complex roles that are required of regulatory agencies; there is however variable success in delivering the safe and efficacious medicines that are expected by patients and regulators.

The challenges faced by regulators are often misunderstood or the complexities are poorly appreciated by patients and governments, likewise the commercial and often challenging scientific hurdles faced by industry are often not considered in sufficient detail. Whilst there is a common thread within the majority of regulatory agency review processes there are other factors that impact equivalence of these practices, such as local levels of expertise, sufficient empowerment of reviewers, specialist knowledge of emerging or new technologies and a significant political will to achieve public health whilst ensuring costs are minimised. This chapter will critically review a range of published literature that captures current analysis of the complex interactions between geopolitical factors, innovative Research and Development (R&D) and ethics, both within the pharmaceutical industry and ethical approaches within relevant international country markets.

### *2.1 Self-regulation and the pharmaceutical Agencies*

The pharmaceutical business paradigm is changing with greater clarity demanded by patients and regulators. It is clear that many advances have been made in this area, not least of which is the requirement for a clinical trials database, of which many have been created across various international markets to increase the visibility and accessibility of resultant trial data, both good and bad.

From the industry perspective the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) and Shaw and Whitney (2016) suggest that the pharmaceutical industry model of self-regulation is evolutionary and developed by the industry leaders. This view seems in contrast to those expressed by regulators, the Food and Drug Administration (FDA) of the United States of America who have a list of more than sixty guides for industry. These guides are distinct from legislation that is already enshrined in law and add to the regulatory expectations of industry. It does not represent a distant oversight of a self-regulated industry as implied by IFPMA. Indeed, similar guides exist across Europe via the European Medicines Agency (EMA) and, in addition, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for aligned countries. The ICH application of harmonisation will be discussed later in this chapter.

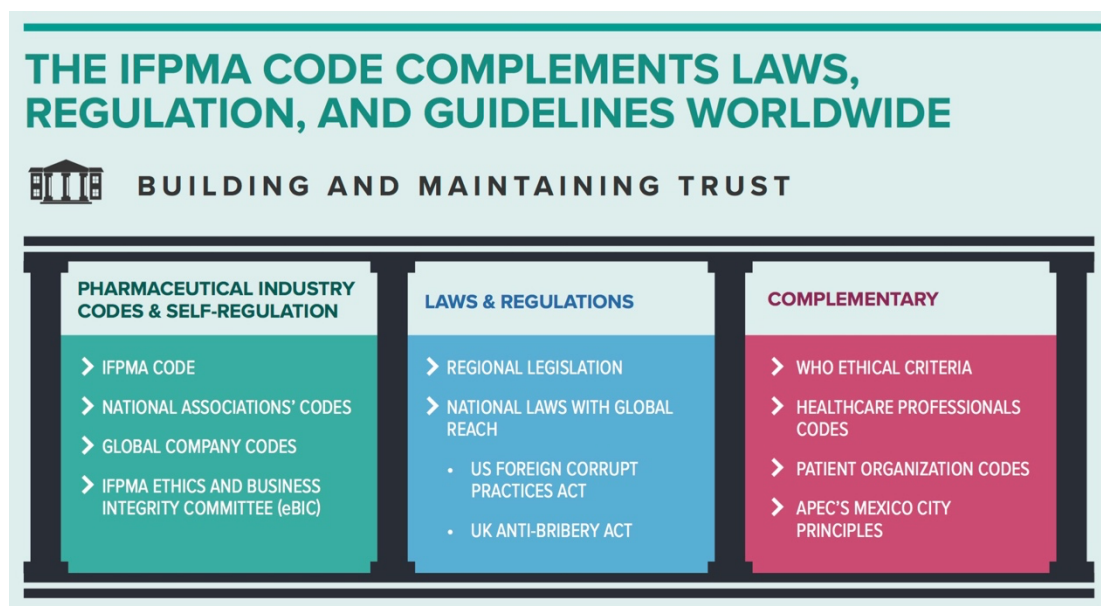
In contrast to the drive for harmonisation, research conducted by Light (2013) suggests that it is the FDA that cannot be trusted. Light claims that approximately 90% of drugs licensed between 1983 to 2013 are no more effective than existing medications, yet the industry is allowed to manufacture and market these drugs as offering improvement to patients either in efficacy or patient compliance friendly forms, but rarely in cost. This research leads one to question the balance of regulatory oversight on behalf of the patients as being driven by financial aspects rather than patient need.

The specific comparisons and claims made by Light (2013) will be discussed in more detail later in this chapter, however, Light concludes that many factors influence FDA policy and decision making, such as congressional support via fund raising and industrial lobby groups. Many of these claims could be made against other major agencies.

## *2.2 The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)*

The IFPMA, like other member organisations such as the Association of the British Pharmaceutical Industry (ABPI) promotes itself as a leader in ensuring safe and efficacious medicines. However its own ethics statement states “Disclosure UK is part of a Europe-wide initiative to increase transparency between pharmaceutical companies and the doctors, nurses, pharmacists and other health professionals and organisations it works with.” This statement, whilst clearly stating its aims, does not include regulators, a key body that the industry needs to work with.

The IFPMA suggests that their policies and guides work in a complimentary manner with regulators as shown in Figure 9 below.



**Figure 9: The IFPMA relationship between ethical regulations**

(extracted from IFPMA Health and trust in the innovative pharmaceutical industry.

IFPMA Infographic, 2014)

However, there is little visible reference between the two groups and certainly little literature.

### 2.3 Industry logistics

The tone of literature issued directly from the Pharmaceutical Industry as research papers is, not unexpectedly, focused on development of their portfolio and/or sales. For example, these publications often contain direct comparisons of products with competitors or market leaders to enhance the authors or authors sponsor's position. An example of these includes the paper written by Maton, et al., (1999) comparing Omeprazole, at the time a relatively new proton pump inhibitor versus Ranitidine, an established H<sub>2</sub> antagonist. Both drugs were and are effective therapies in various gastrointestinal diseases however this paper sought to demonstrate that the newer competition (Omeprazole) was indeed superior. The study was in part funded by the originators of Omeprazole, it is doubtful that the paper would have been published if the result had been different.

Industry also issues research papers that support their research and development focus, such as the Pfizer pipeline review (Pfizer May 2017). In these cases it appears to be

primarily to facilitate stockholder and investor relations and not a sharing of best practice or indeed strategy that will impact or improve patient safety or compliance. These types of papers serve as promotional materials only and should be considered as such.

Alternatively, some publications are focused on the development of an understanding of a disease state, such as the use of Rivipansel to treat complications in individuals with sickle cell disease (Pfizer 2015). In the latter cases this is often to prepare Regulatory Agencies understanding of the issue prior to a candidate asset being developed and specifically discussed with the agency. The use of scientific advice meetings initiated by industry partners with specific regulatory agencies is not used sufficiently to guide industry developments or to educate and assist agency staff for new and emerging technologies.

It has been well documented by Breckenridge, et al., (2012) that industry has taken a view of asset management that results in the asset lifecycle management process becoming a hugely influential driver. The aim to maximize return on asset development and also to minimize the risk of direct generic competition often guides the development process. This process forces companies to constantly readdress their portfolio to seek opportunities and enhancements rather than one approval for the life of the patent in a potentially world-wide scenario. Kabir (2013) suggests that increased control of logistics within the industry such as supply and demand and 'just in time' manufacturing have in themselves contributed to increases in quality of these impacted products. Kabir presents the argument that 'reverse logistics' assessments, such as free movement of materials and internationally recognised safety and quality standards give the industry incentives, both financial and increases in public perception that are warranted and especially welcome in products that are reaching the end of their product lifecycle.

This conclusion was supported in part by Owusu, et al., (2014) who claim that evidence of reverse logistics, such as those proposed by Kabir (2013) has demonstrable benefits by the application of systems introduced by the pharmaceutical industry in Ghana. Although it should be noted that the Ghanaian Pharmaceutical Industry is relatively small once international companies are excluded and this in itself may be skewing the data and the conclusions presented in that paper.

## *2.4 The impact of regulation*

Research undertaken by Danzon, and Chao (2000) showed that increased levels of regulation led to decreased competition between ‘ethical’ pharmaceuticals. In this context ‘ethical’ means products distinct from product line extensions based around an initial innovator product or generic products. The same such regulations had less impact on generic marketed substitutes to the gold standard market leaders (the innovator). This leads to the conclusion that there is a distinct difference between price regulated and industry regulated controls and the impact they have on the pharmaceutical industry. However, research by Lichtenberg (2001) disputes this analysis and claims the profit margin drives innovation and therefore a greater impact on markets with lower manufacturing costs.

Larssen, et al., (2012), argued that reanalysis of existing data determines that the increased focus on increasing health for the lowest possible cost is a key criterion for continued healthcare and that efforts should at that time be redirected towards determining suitable interventions in the pharmaceutical industry. These interventions to increase the understanding and optimisation of health economics, for example, the balance between effectiveness and cost, and also, to include a wider base of clinicians and lay public rather than political only representations.

## *2.5 The facet of dwindling innovation in industry.*

Claims that the pharmaceutical industry is facing an ever-decreasing exhibition of innovation has been discussed by Comanor and Scherer (2013) who in previous studies proposed that the apparent decreases in innovation of major pharmaceutical research and development is partially impacted by mergers and acquisitions. They postulate that there are four key aspects to this, these are:

- Shareholder pressure to increase profitability by decreasing costs and this includes R&D costs.
- Rationalisation of Pharmaceutical companies R&D functions into key areas, such

as expertise into neurological agents or cardiovascular agents, the so called “Centres of Excellence”.

- The apparent decrease in innovation is more accurately a reflection of Research and Development synergies rather than an actual decrease in innovation with Research and Development centres.
- Decreases in innovation drives importation, mergers and acquisitions driven by lack of local market availability.

This proposition therefore fits with that of Breckenridge, et al., (2012) who conclude that lifecycle asset management plays a significant part, maximizes asset returns whilst minimizing investment, such as is seen in the decrease in new to market drugs that already have a market leader or “gold standard” in their intended therapeutic area. This view is contrasted by that of Schmid (2005) who claims that this decrease in innovation is in fact perception rather than fact and they present data to demonstrate their claim that the pharmaceutical industry is in fact under undeserved attack on this point and that the industry is going through a phase of increased innovation and productivity at the time of publication. A contrasting view to Breckenridge, et al., (2012) that could potentially be due to differences in the data sets reviewed rather than a true reflection of the actual position, the papers being published at different points in the pharmaceutical products lifecycle however a true reflection on this point would be difficult to conclude.

A different approach is described by Katz (2007) who claims that the time taken by the Food and Drug Administration in the United States of America to approve a new drug product, based upon a new active moiety, for sale is a key driver for companies who are not willing to invest in innovative products. The financial barrier and the perceived risk to achieve a product registration is too great. Katz also proposes that the role of the regulatory agency, certainly in the United States of America, is of benefit to the industry and not a burden, primarily because it deflects potential court challenges if a company claims that it had full disclosure with the agency and the agency independently agreed to approve the company’s product.

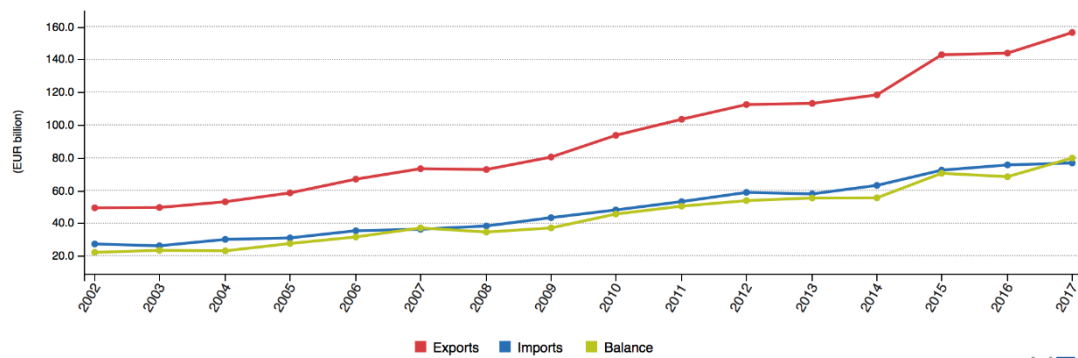
Pharmaceutical innovation is a topic worthy of great discussion due to its evident impact on available pharmaceutical products. Whilst the industry is driven in part by economic

considerations there is a clear impact of regulation on innovation as discussed by Varol, et al., (2012). Varol demonstrated that between 1968 and 2008 of a total of 845 distinct active molecules, the majority suffered a lag on market introduction after the introductions of the Hatch-Waxman Act (1984) in the United States of America and the creation of the European Medicines Agency (1995) in Europe. In the USA market entry was delayed and products repositioned as the Hatch-Waxman Act facilitated the now common emergence of price competition and the formation of the now accepted generic drug industry. In the European Union the primary concern appears to be the issue of price dependency across multiple European Union markets, both policies clearly impacting the supply of new innovative medicines. However, research conducted by Houy and Jelovac (2015) is directly contradictory of Varol. They concluded that there was no influence on market entry or market selection by either local or international pricing structures and legislation when referring to generic medicinal products. This is most likely a direct reflection of the difference between innovator and generic products.

## *2.6 Public and/or Governmental Pressure*

In a separate paper Philipson (2002) reviewed the impact of public intervention, via taxes and other financial incentives on the pharmaceutical industry. Philipson concluded that in terms of state sponsored interventions, such as Medicaid provision or UK/EU reimbursement rates, the impact on industry was significant and ultimately drove investment decisions. These policies directly impact the proportion of imported medicines and locally produced medicines.

Within the European Union and in the United States of America there is an ongoing political pressure to reduce cost and improve safety of medicines as demonstrated by the Parliamentary Office for Science and Technology 2010 and Greenberg, 2000. However, within the EU there exists a large trade deficit across the main 28 countries of the EU with external markets as shown in Figure 10 below.



**Figure 10: EU international trade balance in pharmaceutical goods**

(extracted from Eurostat [http://ec.europa.eu/eurostat/statistics-explained/index.php?title=international\\_trade\\_in\\_medicinal\\_and pharmaceutical products](http://ec.europa.eu/eurostat/statistics-explained/index.php?title=international_trade_in_medicinal_and_pharmaceutical_products))

In the United States of America Greenberg (2000) highlighted the continual pressure on drug manufacturers to reduce cost and increase effectiveness contrary to the assertions of the pharmaceutical industry that such pressure was not required. Greenberg claims that this is primarily driven by the increasing cost of pharmaceutical drug products becoming an ever-increasing larger proportion of healthcare expenditure. As such this raised the political pressure on the pharmaceutical industry and as discussed further by Greenberg initiated a mobilisation of the pharmaceutical lobby in the United States of America to counter political pressures.

## *2.7 The issue of comparable quality on importation*

There have, over the past twenty years, been substantial efforts by companies, individuals, and agencies to initiate a form of regulatory mutual recognition.

Such incentives have been captured by Hong (2007), Moran (2013) and Colin (2001), their collective assessments conclude that quality, safety, and efficacy are all equally weighted drivers for the assessment of equivalence between parallel markets. Indeed, this view is partly mirrored by Janise-de Hoog (2007) who claims that process of mutual recognition is in itself a process that ensures parity, rather than a process that assesses parity, and that the Mutual Recognition Facilitation Group is itself under experienced in

this area, certainly at the time of that review. The timescale covered by such reviews when considering updates to market authorisation procedures can be many years. On 17<sup>th</sup> July 2018 the European Union announced that drug substances would be included in the EU-Japan Trade Deal that was negotiated in 2004, a significant delay considering the vital and complex nature of the products concerned.

This expansion of recognition of parity can be claimed to be a form of regulatory trust. Indeed Abraham (2008) postulates from his case studies that there are two forms of trust between industry and agency and also between agencies. He suggests the two forms are “acquiescent” and “investigative” trust. These are further defined as:

- **Investigative trust:** Pharmaceutical companies have to assume that their data will be interrogated and not accepted without challenge.
- **Acquiescent trust:** A more permissive form of trust that allows industry to progress with less oversight and more faith in their internal systems.

This implies that whilst a product maybe approved by an agency, and therefore meets that agency’s standard, should that standard be therefore questioned if the product is not suitable for wider use? As can be seen by the number of regulatory deficiencies against established manufacturers and products acquiescent trust in insufficient on its own to ensure quality.

Abrahams (2008) further suggests that acquiescent trust ultimately leads to greater patient risk as there is increased chances of a patient taking medication that has less evidence of either safety or efficacy.

An area of key importance to the industry is that of understanding risk and ultimately communicating that risk not only to regulatory agencies but also to the intended patient populations who will use the medications. Edwards and Chakraborty (2012) discussed the need for clear risk communication strategies and how risk can be put into an acceptable and understandable perspective for the audience. They use the Summary of Product Characteristics (SPEC) which is agreed with an agency and shared with all medical staff and patients. It details labelling and usage and should help communicate the ‘risk’ of

taking the medication. As demonstrated in this literature this often fails and they highlight that there has been little or no definitive research in this area to determine a satisfactory method to achieve this. This poor communication may be a factor to be considered in the overall acceptance of parity when considering patient safety. In addition, poor communication between industry and agency partners and also between inter agencies and inter industry counterparts has a significant impact.

### **International parity assessments**

There is specific regulation in the European Union that gives guidance to regulatory agency and industry on importation of medicinal products and the application of good manufacturing practice. This is detailed in Annex 21 of Eudralex volume 4 of the EU guidelines for good manufacturing practice for human use. This regulation which is legally binding across member states via Directive 2001/83/EC Article 47 should provide a basis for equality, at least with regards to quality, of imported medicinal products. However, data to date from national statistics would seem to indicate that the application is somewhat erratic across all states. This data is illustrated by the industry oversight data published by for example Alerts and recalls for drugs and medical devices. (MHRA), 2019.

In addition to his regulatory guidance many Industry professional bodies strive to define what is ‘best practice’ and what is required from their industrial perspective for a product registration.

For example:

- Association of the British Pharmaceutical Industry (ABPI)
- Parenteral Drug Association (PDA)
- International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)

It should be considered when reviewing these types of literature that these bodies are populated by industry-based employees and subject matter experts alike and as such, do

not provide an independent holistic view of the majority of topics they cover. In this context its worth considering Shaw and Whitney (2016) view of IFPMA who claim that “Industry self-regulation is evolutionary and led by industry leaders”. This would appear to be contradictory when viewed in an industry of Intellectual Property and non-disclosure agreements. How can best practice be shared when the ‘best practice’ is shrouded in secrecy?

As previously discussed, Breckenridge, et al., (2012) reviewed the impact of lifecycle management and how that impacted innovation and regulation. Their theories on the data studied raise two pertinent questions for the products quoted in their publication. They question whether regulation is driven by innovation and quality or was innovation and quality driven by regulation? In reality there is most likely not a clear answer and additional drivers such as product or disease complexity need to be considered.

Current approaches for Quality by Design (QbD) submissions based upon scientific knowledge and control, risk management etc. would now appear to support the assertion that regulation is the driver as demonstrated by ICH Q8 and ICH Q8(R1 and R2). These publications claim that the only way to ensure quality and safety of process and products is based upon process knowledge, understanding, scientific justification and sound risk-based decision making. Whilst this sounds sensible and indeed justified it should be viewed within the context of over 98% of approved marketed drugs are based upon historical processes developed prior to ICH Q8. This ICH view was reinforced by Patel, et al., (2013) in their paper on the benefits of Quality by Design in ensuring quality and safety and to enhance reproducibility and parity between suppliers especially when dealing with generic drugs.

There have been a number of papers that have postulated why products are inequivalent, either from a quality, innovative or safety perspective. Anant (2017) proposed that quality and innovation are not incompatible, a view that is generally shared by the major international regulatory agencies. However, the regulatory onus on industry is significant and the view of Anant (2017) contrasts that held by Towse & Danzon (2010) who use the term “globalization of scientific standardization” as an indicator of quality and safety and as an industry wide intention to increase ethical equivalence and therefore minimise the

impact of regulatory agencies. This prompts the authors question of “*Does this result in Industry driven equivalence between markets or are Regulators the correct body to assess in the absence of commercial considerations?*”

Ethical market equivalence is dealt with via regulation of drug lists and controls at the Regulatory Agency level. These have a huge impact on the pharmaceutical industry processes. Publications such as the EU Falsified Medicines Directive (Directive 2011/EU/62) has impacted all companies that manufacture or import in the European Union. However, this literature is lacking, although written by committee it assumes deliberate adulteration rather than poor processes. Does this in itself drive quality and product equivalence?

Market equivalence has been a perennial question for pharmaceutical safety. This is not new data and was explored by Nair (2013). Nair reviewed how importation from outside the EU can impact patient safety where materials were sought from suppliers outside the EU Quality Management System. This, however, is not supported by Kanavos and Vondoros (2010) who postulate that it is price and not competition or quality that drives importation. It was proposed by Garattini and Bertele (2001) that, with the expansion of the European Union and the formation of the then newly appointed European Medicines Agency (EMA), patient needs would change across the EU with the exposure and merging of multiple drug markets and that the processes to ensure quality would need to evolve too in response to the changes in public health needs. Garattini and Chalmers (2009) further developed Garattini’s initial thoughts on market and development equivalence in their 2009 paper in the British Medical Journal claiming that the pharmaceutical industry needed to change to reflect wider populations and disease states that require more urgent consideration, rather than having primarily agendas that are driven by industry priorities rather than public health priorities.

Many researchers explored the ethical element with respect to development and registration of pharmaceutical products. Davis and Abraham (2012) propose four primary processes for ethical and innovative pharmaceuticals whilst exploring the market equivalence dynamic. The four processes they propose are:

- Disease politics
- Corporate politics
- Industrial partnerships
- Cultural interest and values

The ethical element of research was also described in a paper by Backhaus (1983), describing the industry as having two forms of regulation. At that time Backhaus described the concerns of drug regulation on a Europe wide scale and the issues that were faced by the industry and the regulators alike. The author draws a comparison between the EU and United States of America and claims both markets faced the same challenges and that, at that point, innovation and safety of products was not always a focus of the regulatory agencies and that the regulation of quality vs the regulation of price was not always on the side of the patient. Elements of this cultural discussion can still be seen in some of the literature described in this paper in the years between 1983 and 2018.

It is worth considering Light's 2013 paper that discusses the view that the agency, the FDA in this paper, cannot be trusted. Light proposes that the FDA is under the influence of the pharmaceutical industry and with the then current fee-paying structure too dependent upon pharmaceuticals to be an effective oversight agency. This view is obviously challenged by the FDA by their existing policy publications.

The regulatory environment is a constantly evolving environment, driven by research, science and, of course, budgetary, and political influences. As discussed by Richards and Hudson (2016) the prominent agencies are prone to reactivity rather than proactive change. The focus on patient needs is supported by agency led initiatives and aid companies to navigate the existing regulatory processes. However, agency led support for innovation does not account for industry drivers such as cost, investment, and the commercial viability of products. Agency support for innovative products and the subsequent required industry investment is often at odds with the existence of parallel imports, the importation of products of claimed equivalence from other markets. As researched by Ganslandt and Maskus (2004) within Europe the existence and movement of these legitimately produced products are in conflict with the premise of local market

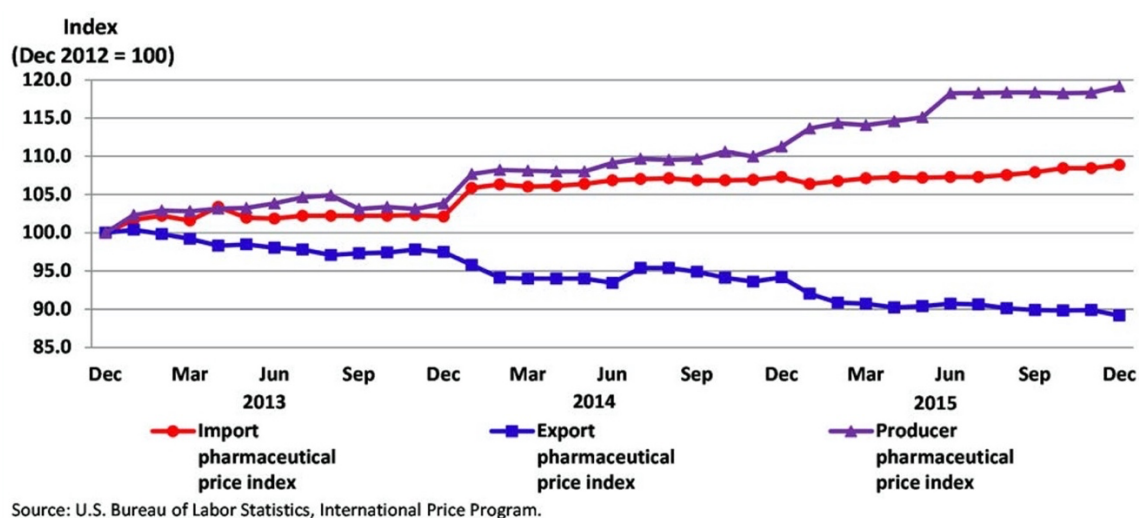
price controls. In their research Ganslandt and Maskus proposed two models, one where the presence of unlimited imports would induce manufacturer deterrence in certain markets to prevent importation and therefore weaken market introduction into a primary, potential more lucrative market. The second proposed model included the provision where industry adopted a universal price strategy that would then negate local market controls and the subsequent movement of product. In reality the data reviewed in this research supported both hypothetical models to varying degrees, with the single price application being slightly more favourable. However these models do not take into consideration the product types or the presence of other drivers such as medical need, premium price products due to cost of goods or indeed complex and in some cases propriety knowledge being utilised in manufacturing processes.

The impact of direct price controls has also been demonstrated to have a significant impact upon the introduction of new products. Kyle (2007) clearly demonstrated a link between price regulation and new product entry in eastern European countries, these specific countries then utilising importation rules and distribution deals with bulk brokers as a form of medication sourcing rather than direct market supply from the innovator company. This phenomenon is not new, data investigated by Danzon, et al., (2005) demonstrated that from twenty-five major pharmaceutical markets in the 1990s, including fourteen current European Union member countries at that time, there was a clear impact upon a statistically relevant proportion of products from the eighty-five new chemical entities launched between 1994 and 1998. The researchers utilised a Cox proportional hazard model for assessing launch parameters, noting that this model is often utilised in assessment of survival in medical assessments. It utilises a multi-variable and regression analysis to assess potential impact. The data from this study supports the premise from other researchers that price regulation is a major contributing factor. This is also supported by work conducted by Vogler, Zimmermann and Habimana (2016) who demonstrated via a multi-criteria decision analysis from European stakeholders a resounding perception of negativity towards policies that focused on pricing limits and support for innovation. The stakeholders in the study were distributed across governmental, patients and other consumers.

Obviously as well as price regulation it is important to consider the potential impact from intra-company trade. The U.S. Bureau of Labour Statistics price data (2016) clearly

demonstrated that between December 2012 to December 2013 there was an increase of 2.1% and 5.1% from December 2013 to December 2014, for locally, U.S. manufactured products whereas the overall price index increased by only 1.5%. In contrast the costs of imported drugs rose 8.9% for a three-year period from December 2012, in comparison producer prices (the cost of manufacture) rose by 19.2% over the same period. Bearing in mind that approximately 70% of imported drug products are from intra-company trade i.e. movement within the same manufacturer from sites external to the local market being imported into, this demonstrates that the movement of products is driven in part by the manufacturing costs in the country of manufacture and then often moved into a country of higher market value for sale. This data is interesting considering the US market for pharmaceutical imports alone totalled \$85.6 billion in 2013 increasing to \$110 billion in 2015 and then \$450 billion in 2017.

This contrast between producer costs and import export is shown in Figure 11 below.



**Figure 11: Import, export and producer price indexes in the United States of America**

(Extracted from <https://www.bls.gov/mxp/pharmaceutical.pdf>)

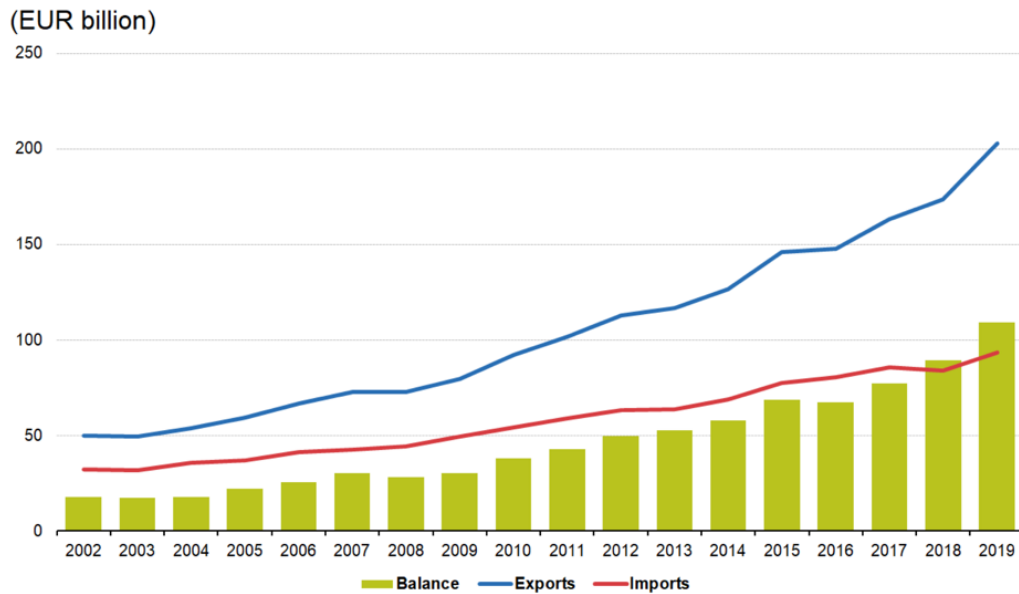
It has been claimed by amongst others Chaudhry and Walsh (1995) that the establishments of trade blocks such as the European Union and the North American Free Trade Agreement in themselves created a so called ‘grey market’ for importation of pharmaceuticals. Whilst this research did indeed consider such market blocks,

encompassing numerous countries, it does appear to facilitate a limited access market and there have been, in the subsequent years since this initial, research a number of legal challenges. However, these so called grey markets do not consider the phenomena of intra-company trade as previously identified. This has to be considered to form a holistic interpretation of the processes involved. Intra-company trading does not also consider the volume of drug products that whilst sold by the company are not manufactured by the company. The Parenteral Drug Association 2019 Technology Transfer Survey concluded that from 156 respondent companies 15.4% outsourced all of their product manufacturing, with only 21.8% conducting all manufacturing within the company facilities.

These challenges have placed limits upon internal markets based upon both quality and cost. Whilst some of these country or market blocks, in many instances, were promoting quality as a driver the framework to define “quality” as a measure was in many areas lacking.

India imports large volumes of cheaper active pharmaceutical ingredients from China, formulating into drug products then exporting large volumes to the EU, and USA. In 2018 India exported over half of all its manufactured pharmaceutical products to the E.U and USA (U.S. National Trade Commission 2018).

In a similar manner importation in the member countries of the European Union also continues to increase rapidly, between 2012 and 2019 up to a total of €93 billion as shown in Figure 12 below.



Source: Eurostat (online data code: DS-018995)

**Figure 12: EU trade in medicinal products 2002-2019**

(Extracted from <https://ec.europa.eu/eurostat/statistics-explained/pdfscache/8872.pdf>)

Exceptional situations do occur and during the course of this research the COVID-19 outbreak in 2020 caused significant strain on industry and regulatory agencies alike. Aspects of this strain on resources and the perception of universal quality were clearly observed in numerous publications, one of which published in March 2020 by the MHRA which gave official endorsement for a reduction in testing for imported medicines and an increase of the reliance on data from third party sources.

In a similar manner EMA issued clear guidance to industry during the pandemic to specifically cover regulatory expectation, and even considering the unprecedented challenge that the COVID-19 outbreak caused to industry and agencies alike, there was a clear expectation of quality in the supplied drug products. However, this quality would be incumbent upon the industry and there was no waiving of the obligations upon importers to ensure that the products imported were of sufficient quality for their intended use. This clear expectation fits with the aforementioned claims by Shaw and Whitney (2016) earlier in this chapter of industry being self-regulating. However, is that justified given the number of product defects and recalls that occur?

In parallel with EMA the FDA issued similar guidance in May 2020 stating that, whilst quality was an absolute necessity, the ability of the agency to maintain oversight during this period would be a challenge and that existing regulatory frameworks and interactions with other federal and country agencies would be utilised wherever possible to maintain a safe supply chain. In March 2020 the Australian Therapeutic Goods Administration and Health Canada issued similar statements showing a concerted approach between the ICH signatory countries.

Whilst there has been some effort to assess pharmaceutical processes quality measures, such as that conducted by Friedli, et al., (2019) at the University of St Gallen, their research concentrates on the measures to assess quality outside of the regulatory framework such as embedded patient focused/driven excellence rather than compelled by regulation. Whilst this data is interesting the focus is operation excellence from a business perspective and highlights ongoing cultural impacts. It does not however assess the parity of products from differing markets. The impact of culture on quality can be vast and the cultural diversity involved in international supply chains requires a robust, effective, and targeted pharmaceutical assessment process. This thesis will bridge that gap in knowledge.

## *2.8 Summary*

It is not unexpected that the existing literature base is vast and for the most part skewed to the position its author(s) or authors' sponsor wishes to highlight. However, it is evident that the assumption of a simple model for regulatory oversight and its related drivers would be naive. This researcher created such a visual representation early in the research for the thesis and this was shown in Figure 8.

As discussed in this chapter there is significant contribution by political and public influences, such as taxation, reimbursement rates and public and shareholder pressure. These pressures were not considered in the assessment summarised in Figure 8 and should be considered as influential inputs into the topic being researched.

The available literature requires a detailed and critical review due to the varying perspectives of the authors. Some papers are, by design, skewed, such as those published by companies which ultimately promote the message that the company's products are better, with respect to safety, price, or pharmacokinetics, than competitors. In such cases care needs to be taken to ensure that due weighting is given to data and publications that have an overt, or in some cases subtle, message. In counter point, the Regulatory Agency published papers give little comparative data. However, they do demonstrate a position of first intents for each individual agency and as such provide the framework on which regulatory oversight is based. As such this literature provides a wealth of information regarding a perception of industry from regulators as well as the guidance framework. The identification of key opinion leaders in each 'driver' field is hugely beneficial. Such opinion leaders, such as Danzon and Chao provide a starting point for data comparison and the initial influences judged to be worthy of investigation as key process drivers. Global data arising from international Regulatory Agencies should carry equal weighting, including Agency publications. Although there appears to be a primary focus purely on USA and EU regulations this must be extended to wider markets as the movement of material is not limited to the USA and UK only.

This raised the question "is there an objective, independent assessment of international equivalence that is robust and reliable in literature?"

Looking at the published literature and considering the industry structure and oversight there can be arguments constructed for considering pharmaceutical manufacture regulation in a positivistic and also interpretivistic manner. Indeed, elements of both co-exist within the current structures and the key points can be summarised as:

- Positivistic: Is the industry and its scientists shaped by agency policy? Or even does the industry develop and manufacture its products in such a way to be flexible to certain market dependent upon poetical will or inducements such as tax incentives or reimbursement values? Does policy cause a new 'normal' to evolve within the industry in certain pockets? However, a positivistic approach is certainly one that is considered comparable to a scientific approach such as research, quantitative data and deductive decision making.

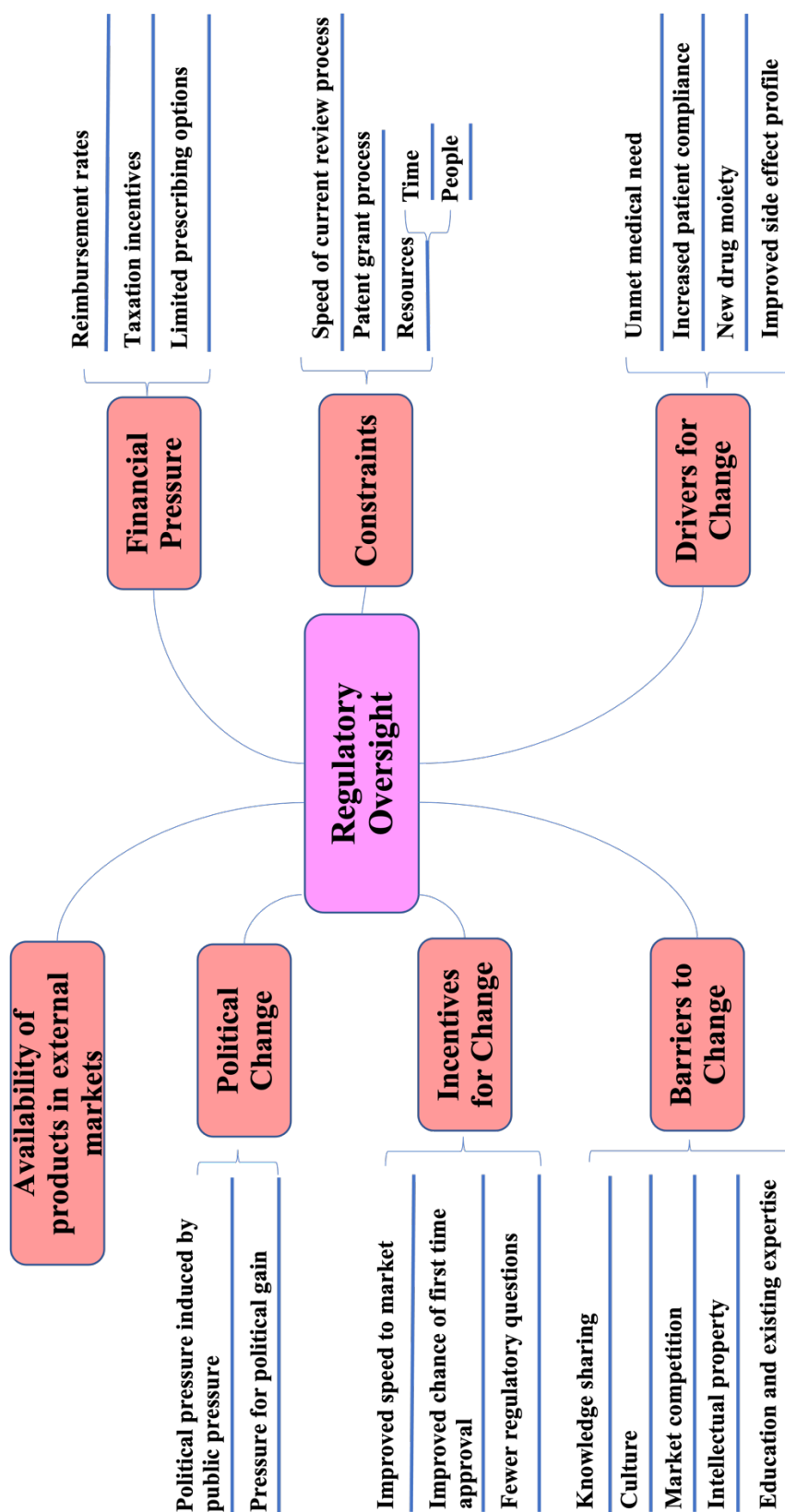
- Interpretivistic: Do companies and scientists act as individuals, guided by their own goals and insights? This could be applied in some situations. However, does this lead to subjective data interpretation and decisions that are not necessarily in the favour of patient safety? Judging by the number of product failures, recalls and agency refusals to grant product marketing licenses, the author poses that this seems to be applicable in some situations.

It can be seen from the above that arguments can be made for both approaches and the publications summarised in this chapter fall in these categories as described.

In summary it has been highlighted that there are specific drivers to the literature that a reviewer should be cognisant of such as political, public or sponsor pressure and influence. The identification of the symbiotic relationship between R&D, Public and Regulatory drivers will be difficult to ascertain from literature alone and should be considered as a multifaceted relationship.

A review of the literature to date prompts the question of whether it is appropriate to consider financial constraints on drug products as an indicator of quality or R&D output? Ultimately what is a true measure of innovation and equivalence with regards to safety and bioequivalence markers such as pharmacokinetics and other pharmaceutical parameters? These are some of the questions that are raised by literature in part but not fully answered.

In consideration of these points, it is appropriate to modify the visual conceptualisation proposed in Figure 8 based upon this literature review to that contained in Figure 13 below. The addition of the availability of the medicinal products in external markets, the role played by a changing political landscape within which the products are marketed and finally financial pressures on manufacturers and distributors must be considered and have been added to the visualisation in Figure 13.



**Figure 13: Revised visual conceptualisation of the factors impacting regulatory oversight processes**

This chapter has demonstrated that there are a wide range of drivers that impact patient safety and the importation or free cross market movement of pharmaceutical products to ensure safe and efficacious medicaments. There is a multi-faceted approach globally and whilst there is no current single global process for assurance of safety and efficacy there are areas of commonality and areas where improvement is required. How these improvements can be identified and implemented is the subject of this thesis and the data analysis herein.

### *2.9 Objectives of this research*

The process summarised in this chapter leads the researcher to a number of questions, the overarching objective of these questions is to determine if it is necessary to have parity of international pharmaceutical products?

To reach this objective a number of question milestones were posed, these are detailed in Table 3 below.

A greater understanding of the actual, rather than perceived, relationship between Regulators and Industry and how to enhance the benefits of that relationship, whilst also promoting development and progression of new therapeutic agents, would add value to all Agency/Industry interactions and promote a holistic and ultimately beneficial approach to development of new medications.

**Table 3: Summary questions raised by the existing processes**

<b>Proposed research objectives</b>	<b>The research task</b>
To determine how expertise is applied, how is data reviewed and ultimately interpreted on review?	To interrogate the level of expertise applied and the knowledge base existing within the agencies by review of the questions raised during agency review and, where available, the reasons for non-approval.
To determine how do we ensure that international approvals for imported medicines reach the same standards as those adopted for local market approval, in our case those products approved within the EU?	A review of the equivalence of EU member state approval processes and their adherence to Eudralex Volume IV, with emphasis on the differences between the centralised and de-centralised processes.
To determine if there is a barrier in communication between Industry and Agency to develop a partnership rather than a potentially confrontational approach?	An assessment of the Industry and Agency perceptions of the current process and interactions between the two groups.
To determine if there is inherent variability in the current process from many sources. What is needed to overcome those variables to ensure a safe pharmaceutical?	Identification of the key variables that may lead to an unsafe approval of a pharmaceutical and potential root cause analysis of the driving force behind such approval.
To determine the relevance of drug products approved (in another jurisdiction) is that approval current or even relevant to the actual material being imported?	The relevance of an existing approval and the potential impact on patient safety can be partially assessed by review of the comparability between differing agencies assessment processes and local industry supplied submission data.

## CHAPTER THREE: METHODOLOGY

### *3.0 Determination of methodology*

The questions posed by this researcher relate closely to patient safety and are based upon a perception of there being an issue around parallel quality systems not being of equal effectiveness or equal validity when applied to pharmaceutical products and their consumers. This is based upon the author's personal experience within the pharmaceutical industry and also emerges from publications and reported headline data in safety summaries. However, the causal link between the theory of a problem and the actual causes of the problem are not evident from current published data. In that regards the research question posed at this stage of the research project is based upon the epistemological stance of: Why do we think like that? What drives that perception of inequality? Therefore to satisfy those questions a methodology is required that not only defines the scope of the problem but also from what areas does it emerge, is that stance and experience within industry consistent or is it based upon a small minority of, but well published, cases? In a similar manner does the perception from agencies mirror that of industry or is that again different? Great care should be taken by the researcher when dealing with memory and recall then being perceived and postulated as fact. It has been quoted that memory is not a capacity for knowledge (Audi 2011) and as such personal recollections cannot always be relied upon. However, they do guide our professional behaviours in the form of intuitively based theories such as those discussed later in this section.

### *3.1 Perception, positivistic and relativistic approaches*

This issue with perception has been discussed by many reviewers and is summed up by Walliman (2011 p.24) as the difference between positivist and relativist approaches, the positivistic approach being that there is an issue with the products assessed or manufactured by non-approved and routine methods and we know that because it does

happen on occasions versus the relativistic approach that there is on occasion a problem. However, this is perceived differently between industry, agency, and patients' groups.

### *3.2 Ontological consideration*

If we consider for a moment an ontological perspective on the research question, then we need to understand why we believe there is a problem with product safety in certain situations and under certain conditions: What underpins that belief? What is the relationship to the question being posed whilst considering “why do we think like that”? To satisfy that epistemological stance we need to identify the data that supports the relationships and interactions between agencies and industry. The “what it is” and the “how it is” perspective of the research question.

### *3.3 Methodological Perspectives for Consideration*

Many previous reviewers have discussed research methodologies and their respective applications, reviewers such as Clough and Nutbrown (2012), Walliman (2018), Dawson (2010), Creswell (2018). This section will discuss and critique the primary methodologies that could potentially be applied to the research with consideration of ethics, patient safety and relationships in the pharmaceutical Industry

#### **3.3.1 Qualitative and quantitative methods**

For the purposes of this review we will initially consider qualitative and quantitative methods separately. Qualitative methodology has been summarised as the investigation of attitudes, behaviours, and personal experiences (Dawson 2010 p.14) utilising interviews, discussion or focus groups to tease out detailed information and opinion from individuals. Qualitative research methods would assist in identifying the problem in more detail and the data that underpins it. A focus group or multi-person discussion will not serve this research question well, due to the insular nature of the industry, whilst a well-developed semi-structured interview with key questions when applied to both industry and agency professionals alike may yield interesting and useful data. Care should be taken to ensure the questions are balanced such that no bias is introduced from the

perspective of the researcher and likewise with data analysis. One aspect of qualitative method that is worth further discussion is that of phenomenological research (Creswell and Creswell 2018 p.13), the use of interviews to find a define a common essence of experiences may well be a useful tool. Further analysis of the ‘lived experiences’ or in this researcher’s case the interpretation of ‘professional activities experience’ may yield insightful data.

Quantitative methodologies have been described as research that generates statistics via the use of questionnaires and fully structured interviews (Dawson 2010) and whilst this research can cover many more people than for example interviews and discussions held as qualitative research it may lack the depth and nuances required for this researcher’s topic. For example, in a situation where a product failed in one country due to stringent tests for particle size of an active chemical entity there may be no obvious correlation until the researcher potentially asks for the therapeutic category of the drug. In this example if that therapeutic area was oncology, then the use of a particular particle size maybe inducing inadvertent tumour specific drug targeting due to the physiology of the tumour (the presence of intra-tumour nano-tubules) storing particles of drug that meet a certain size range (typically <30nm), if this was found then this could then be described as poor development knowledge or agency reviewer knowledge. These nuances maybe key to some areas of this research.

Dawson (2010) suggests that all methodologies, both quantitative and qualitative, have strengths and weaknesses. Bearing that in mind this author suggests that it could therefore be considered that a mixture of methods may indeed be a better approach for this research topic. There is no overtly scientific method although some researchers claim that quantitative is better and more scientific than a qualitative method.

### **3.3.2 Examples of method applications**

To highlight the appropriateness of method selection and assesses its criticality when undertaking research and the potential sources of bias or a lack of transparency in how data are collected and interpreted it is worth critically considering the approaches taken by two research groups who undertook research into the pharmaceutical industry in 2014. These papers were selected to highlight a diversity of research methods and also to

demonstrate the outfalls of inappropriate methodology.

Miguel, et al., (2014) published a research paper titled “Recognition of pharmaceutical prescriptions across the European Union”. This paper attempted to address multiple questions in a single research piece, specifically:

- Mutual recognition across the EU states
- Country variations in quality standards
- Scientific and medical equivalence standards across five EU states

To achieve this they utilised three primary methods:

- A desktop review of policies and published prescription trends
- Conducting semi-structured interviews with thirty-seven national stakeholders
- Agency feedback utilising contacts with regulatory authority personnel via a purposely designed questionnaire

On review the authors appear to have taken an ethnographic research perspective (as defined by Creswell and Creswell 2018) driven by the assumptions that the existence and membership of the EU and EMA by process stakeholders will be a major process driver that will impact individual country regulatory agency decisions. This appears to be an assumption not grounded in either data or with a hypothesised theory to support this assumption although the data is collected from the individual agencies and over a protracted period of time. In addition, there is also the perceived fact that formation and membership of the European Medicines Agency (EMA) will also standardise the regulatory approach to reviewing of pharmaceutical products. These assumptions could in themselves devalue the research undertaken.

This approach of grouping data (in this case the decision to group based upon the perceived common ideals alluded to by joining or forming a cross country agency such as the EMA), potentially could work well with smaller groups as identified by Creswell (2013). However, in this case could the EU be defined as a culture sharing group or even having a common basis in culture (Harris, 1968) to facilitate the comparison? It is also

worth considering that the five authors represent five countries perspectives, does that imply a common purpose or shared quality standards?

This raises the question does the perceived ethnographic perspective stem from the member countries the authors originate from or from the common standards generally espoused in the EMA?

In contrast to the approach taken by Miguel, et al., (2014) it is worth considering a research paper published by Borg, et al., (2014). In this paper they utilised three main methods:

- Grounded theory (Glaser and Straus 1967)
- Hypothesis testing
- Six scenarios assessed for:
  - Causal conditions (what factors caused the issue?)
  - Intervening conditions (situational factors that influence strategy)

Borg, et al., have taken a grounded theory approach and used the data collected to expand and populate their proposed theory. However could there be researcher bias and how is this dealt with in the data capture and the subsequent discussion?

In addition to this it should be noted that the five authors come from five countries, that could imply a level of independence. However, this cannot be assessed from the data published in this paper and would be improved by further discussion.

It is disclosed that five of the seven authors come from existing member regulatory bodies (EMA, MA, NOM, IMA, MEB) and all of these member agencies are country members of the EMA. Whilst this is acknowledged in the paper there is no discussion of whether this may impact any subsequent analysis.

On review of the data and its conclusions there is little actual data to support the hypothesis proposed and for what data there is there are no specifics on how the data was captured, what methodologies were utilised. The researcher also uses the phrase within

the conclusion that this is part based upon their own personal experience. That statement implies that the paper is based on personal bias rather than data capture and analysis and does not try to answer the question that title poses ‘are there any challenges left?’, a question that is fundamental to the research question proposed at the start of their research. This statement results in the paper being driven by “intuitively based theories in use” as discussed by Schon (1983), rather than “espoused theories”, espoused theories being generally agreed upon theories based on data gathered. Generally espoused theories are accepted as the basis for professional practice (Brookfield 2001).

In addition to the above comments the structure of the propositions tested within Borg, et al., (2014) are two other key points. Firstly there is a perceived unreliability in the test scenarios presented and examined in this paper. This is due to a lack of supportive data or even a structural framework from which they would exist or potentially arise, such as causal factors and strategies. Without this assessment the paper fails to convince the reviewer to the validity of the models. The scenarios could happen but how realistic is it that they would? How can the reviewer interpret that from the data presented or the methodology used?

In additional the intrinsic bias installed due to personal recollection, intuitively based theories and the lack of data presented or in some cases even gathered makes the generalisability of the premises proposed extremely poor. The lack of data discussion and perspective on how the data was gathered makes this interpretation by a reviewer extremely difficult. The methodologies employed are unclear and muddled as described in their paper and could lead to a variation due to history or maturation (Creswell 2018) from when the original drivers for the scenarios existed. This may skew the hypothesis presented in the paper and again does not assist the reviewer in interpreting the validity or applicability of the research.

In summary, when comparing the two papers summarised above Borg, et al., fail to explore the question based upon data and understanding. Whilst striving for a grounded theory approach the research gets lost in personal recollection and partiality.

The conclusion reflects the personal experience of individuals superimposed upon current EMA policy and guidance whilst Miguel, et al., cover too broad a subject to garner a

single unified theory. The imbalances between the data specifics (subjects) captured and the causal factors identified does not apply to all EU states. The scope is too wide and the extrapolations too great.

Overall the risk of bias cannot be assessed from the paper alone nor can it be implied from the level of reflexivity expressed in the paper by the authors and therefore there is risk of being accused of assembling a collection of primary empirical data with limited deductive reasoning. This highlights the pitfalls of inappropriate method selection.

It is clear to see the pitfalls from the above method selection and how data is captured, interpreted and reported. To be able to present the data in a formal, structured, and meaningful manner whilst sharing sufficient information with the audience is key to the generation of a satisfactory theory, discussion and conclusion. These two research papers demonstrate that great care and consideration needs to be taken from the start to enable a researcher to make a valid claim and to support their conclusions.

### **3.3.3 Constant comparative data analysis**

Whilst considering methods and analysis an additional point worthy of discussion is the use of constant comparative data analysis (Creswell 2013 p.86). This analysis forms part of grounded theory as proposed by Strauss and Corbin (1990, 1998). They detail that the continual process of taking certain information from collected data and comparing it to existing and emerging categories may help in the formation and articulation of forming theories. This then directly relates back to the research question posed in this paper, the impact on safety of medicines from inappropriate standards or ineffective reviews and authorisations. This continual data collection already occurs, the interpretation and analysis however are not always appropriate or even conducted. This format of data analysis could be useful in the analysis of data for the proposed research questions.

### *3.4 Justification of Method Selection*

When considering quantitative research methods the questions of validity and reliability are key points the researcher should consider and discuss. The data captured should be done in a manner that demonstrates that the data is stable and that the potential for errors or personal bias is minimised as much as practicable. Personal bias may come from the researcher or from the source of the data itself. In either case this needs careful consideration. In the case of qualitative research methods it was proposed by Dawson 2010 that these methods may be unscientific due to the potential for personal bias primarily due to the very personal nature of the data capture process and analysis. For that reason alone the researcher concluded that a qualitative research method will not be adopted by this researcher for these research questions. A mixed methods approach was deemed most appropriate and the qualitative component will add a level of relevance to answering the research question.

#### **Research Planning Audits**

The approach described by Clough and Nutbrown (2012 p 179) of conducting a research planning audit could also be invaluable in further defining the techniques as well as the research question to a point such that definitive research would be possible. This would facilitate the researcher in developing and critiquing research plans to ensure they meet multiple acceptance criteria such as:

- Building upon the researcher's own professional experience and reflective considerations
- To define and then further refine the research question(s)
- To link and justify specific methodologies to the research question
- To justify the populations to be considered
- To review ethical considerations
- To ask, "why am I doing the research?"
- To consider and reflect upon "is my research question clear and researchable, does

it need revision?”

After considering these points during a research planning audit the justification for method(s) will emerge in specific relation to the research question(s) posed.

### *3.5 Ethical Considerations*

Considering the research questions posed to date the use of covert research would be counter-productive, there is also the consideration that many people in the pharmaceutical industry are ‘registered’ on professional registers such as the UK Royal Pharmaceutical Society or the Royal Society of Biology and as such to remain anonymous is not an option. To also conduct a research project such as this with semi-structured interviews and questionnaires could require a level of interaction to be able to tease out pertinent facts and data from participants. The choice of overt research over covert appears to be a frequent discussion topic that has over time shifted from one technique to the other based upon current beliefs and generally that overt research is preferably (Dawson 2010 p 151). The ethics of research is summarised by Booth, et al., (2016) as:

*“report it as a conversation between equals working toward greater knowledge and better understanding, the ethical demands you place on yourself should rebound to the benefit of all”.*

On application to pharmaceutical products the research undertaken should be aimed at improving communication and knowledge sharing to provide additional support for the development and manufacture of safer pharmaceutical products. Data collected should always be sought with honesty, transparency (Walliman 2011 p 43) (with respect to overt research) and impartiality. The data analysis should likewise represent the interpretation from the data gathered and not any preconceived perceptions from the researcher. In this case, the pharmaceutical industry is obviously dealing with patients/consumers.

However, the research in this instance will not be involving this group or subjects as the data from patients is already gathered by regulated groups within the regulatory agencies and as such is public information. What can be conducted potentially during data analysis

is to link the safety information, for example the number of types of serious adverse events with a particular dosage form approved via a certain country or agency.

### *3.6 Method Selected*

It can be seen from the summary of potential methodological approaches summarised in this chapter, specifically the concerns raised by Dawson (2010) and the type of data to be captured that a mixed methods approach would be beneficial for the research of the author's primary research question. It is noted by the author that the adoption of mixed methods is itself a complicated subject with some authors describing the incompatibility of mixing quantitative and qualitative methods (Smith 1983). However, it has become increasingly acknowledged that mixed methods research can add value to a research topic. This is well summarised by Preskil (2005):

*“...refers to the use of data collection methods that collect both quantitative and qualitative data. Mixed methods research acknowledges the fact that all methods have inherent biases and weaknesses; that using a mixed methods approach increases the likelihood that the sum of the data collected will be richer, more meaningful, and ultimately more useful in answering your research question”*

The choice of using mixed methods research is driven by the research question and is summarised well by Walliman (Walliman 2018 p 169) in fulfilling the following criteria:

- To explain and interpret a situation
- To explore a phenomenon
- To serve a theoretical purpose
- To compliment the strengths of a single design
- To overcome the weaknesses of a single design
- To address a question at different levels

- To address a theoretical perspective at different levels

It is also noted that Clarke and Creswell (2008) discuss the use of a sequential exploratory approach to mixed methods and the use of a qualitative approach initially then followed by a second phase of quantitative research based upon the data generated in the primary qualitative phase, to facilitate a more meaningful and applicable conclusion from the data gathered.

The selection of individuals to take part in research is also of paramount importance. As discussed by Palinkas et al (2015) purposeful sampling is a well stabilised technique used extensively in qualitative research for the identification and selection of data-rich individuals related to the area under research.

In summary, the choice of methodologies available to a researcher is both wide and complex. The selection of an appropriate methodology is key to successful research and whilst the researcher may attempt to select a meaningful method without bias or preconceived assumptions it is recognised that being comfortable with a certain methodology is not in itself a poor criterion for research (Walliman 2018 p.169) and it is noted that some researchers prefer quantitative over qualitative research methods and that will skew the selection and balance of methods selected. In this instance the author proposes to utilise comparative data analysis potentially combined with a sequential exploratory mixed methods approach to provide a deeper context to the data gathered.

It is worth considering the revised visual conceptualisation of the perceived factors impacting satisfactory regulatory oversight as previously discussed in this thesis.

Looking back to Figure 13 it can be seen that a mixed methods approach utilising interviews and questionnaires will deliver data for each of the selected sub-topic drivers as shown in the Figure. The use of a sequential exploratory approach will also facilitate the further understanding of the data whilst gaining an additional level of granularity.

Figure 14 below demonstrates how in this instance a mixed methods approach will function for the author's proposed research question.

The use of mixed methods may also assist in triangulation of the issue that is being researched by the author. It is anticipated that the research approach to the safety of pharmaceuticals from different points of view, in this case the pharmaceutical industry perspective and the pharmaceutical regulators' perspective, will enrich this research project.

On application to this research project the following section describes specific application of the research component.

Participants were selected based upon several categories such as relevant professional experience in the pharmaceutical industry and/or related sectors. Such as regulatory body careers, professional body membership, Qualified Persons or people directly associated with regulatory affairs. In addition, a broad scope was used to cover a breadth of international territories whether by experience or current activities. To seek participants the researcher utilised professional bodies such as the Royal Society of Biology and the Parenteral Drug Association in addition to information placed on networking sites such as LinkedIn and QP Alumni associations.

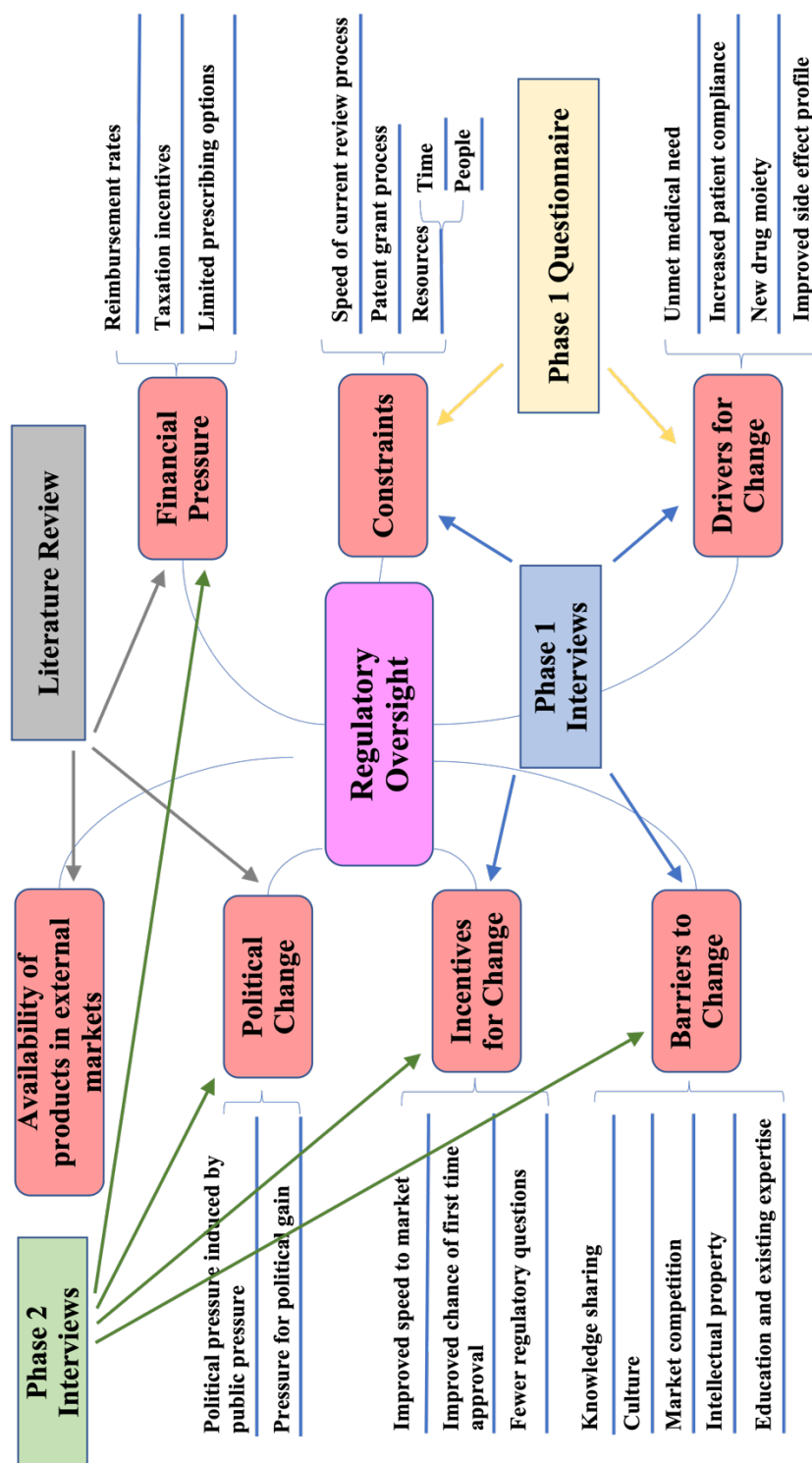


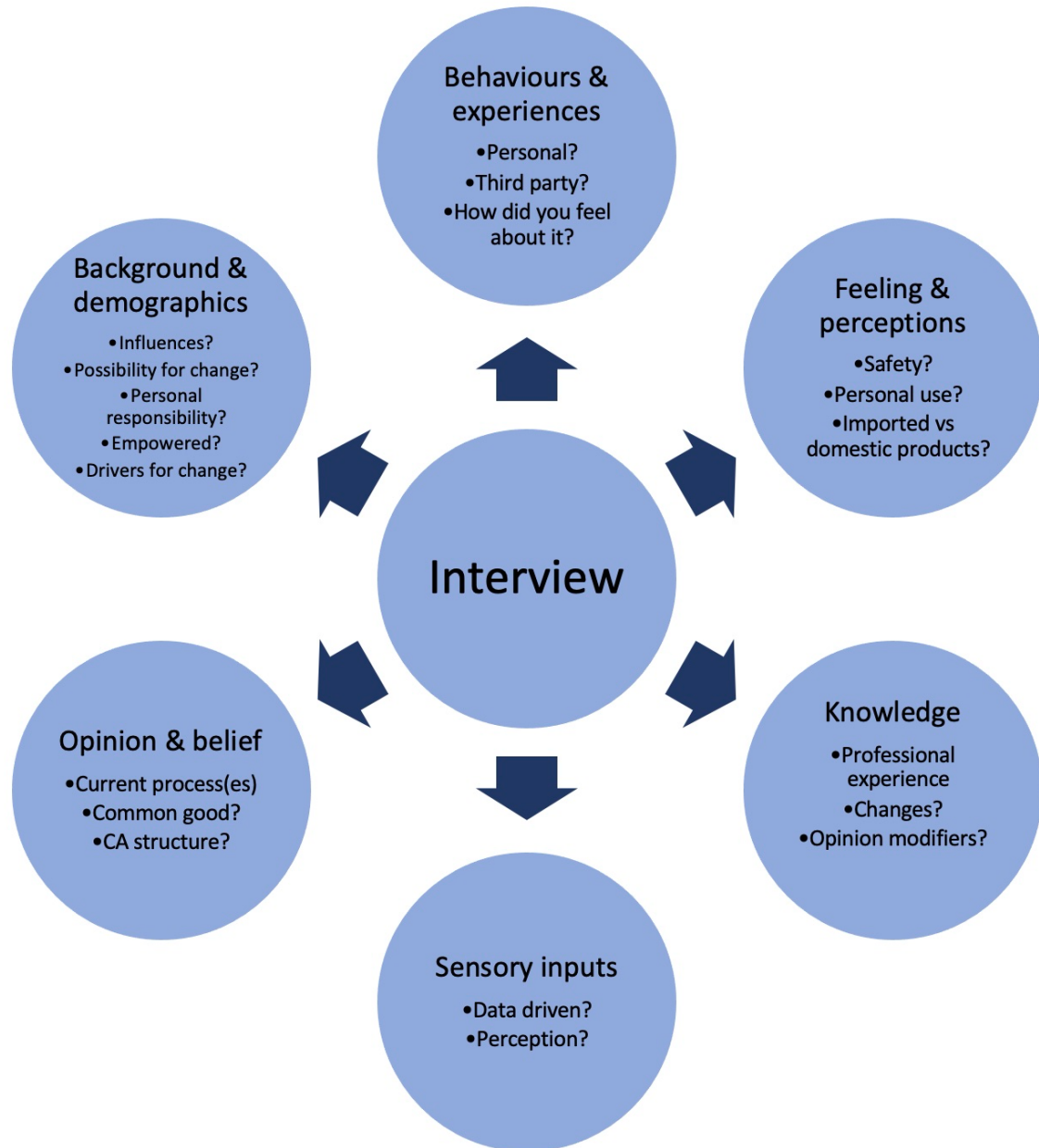
Figure 14: Revised visual conceptualisation of the factors impacting regulatory oversight processes including potential methodologies

### **3.6.1 The interview questions and structure**

The interview questions were based around the question structure already utilised in the pilot study and subsequently enhanced, in addition the areas discussed in the interviews were focussed around quality, parity, experience and behaviours into a conversation specifically to cover the following topics.

- Behavior and experiences
- Opinion and belief
- Feeling and perception
- Knowledge
- Sensory inputs
- Background and demographics
- Change

These questions were phrased slightly differently to each subject depending upon their experiences as became clear throughout the interviews, this can be clearly seen from the verbatim transcripts in the appendix of this thesis. Care was taken to avoid emphasis and bias at all times. In addition the choice of language was important as many were non-native English speakers (all interviews were conducted in English). The following schematic (Figure 15) highlights how these key topics were structured.



**Figure 15: Summation of interview topics structure**

Interviewees were assigned a random number identifier for confidentiality reasons. The researcher holds the random number identification list and this will not be made publicly available. Interviews were conducted in a free-form, non-time limited, manner via an online video platform due to the global nature of the interviewees and the emergent COVID-19 pandemic prevalent at the time.

Interviews were recorded and then transcribed verbatim. Illustrative interview transcripts (redacted as appropriate) are detailed below to demonstrate the scope and nature of the

interview process. All redacted transcripts are included in Appendix one of this thesis. All analysis was conducted on non-redacted transcripts.

In the results chapter the association of subjects' experiences is summarised. To assist in this process several case classifications were constructed to further understand the breadth of the data basis and these are described further in the next chapter.

### **3.6.2 Pilot study**

The approach taken in this pilot study is to assess the research questions of “How do we ensure that international approvals for imported medicines reach the same standards as those for local market approval and how expertise is applied, data is reviewed? Also is there inherent variability in the current process from different areas and what is needed to overcome these to ensure a safe pharmaceutical?”

A mixed methods research approach was selected. An online questionnaire as the qualitative component followed by selected semi-structured interviews, with the interviewees being selected on the basis of the responses gathered from the questionnaire. Participants selected for the interviews will be a broad spectrum across the roles selected to receive the initial questionnaire. The roles concerned were to cover experiences gained from the following:

- Industrial Research & Development
- Commercial Production
- Retail Pharmacy
- Hospital Pharmacy
- Country specific Regulatory Agencies

Figure 14 below demonstrated how a mixed methods approach will function for the author's proposed research question. The phase 1 questionnaire and the phase 1 Interviews are summarised in this thesis and conducted prior to the main body of research. These were designed in a manner consistent with that proposed by Clark and

Creswell (2008) as previously reported by the researcher (Cummings 2019).

### **3.6.3 Questionnaire**

A forty-three-question online survey was constructed via SurveyMonkey® for the pilot study and distributed to twenty volunteer participants. Prior to receiving the survey each participant was provided with an Ethics Board approved Participant Information Sheet and on receipt of a signed Participant Consent Form a link to the survey was provided.

The survey was sent to twenty participants with a response level to the survey of seventy-four percent, primarily due to the short notice given to complete the study and that time period corresponding to the UK holiday season. The questionnaire was developed on the SurveyMonkey® platform and designed as a simple data capture survey requesting information on the selected topics.

### **Survey Topics**

The following topics were all covered in the survey:

- Confirmation of consent
- Level of qualification
- Years of experience within:
  - Industrial
  - Regulatory
  - Or both
  - Including experience or eligibility as an EU Qualified Person\*
- International experience
- Knowledge and involvement in:
  - Serious Adverse Events (SAE)
  - Product Recalls
  - The root cause analysis of the above incidents and the level of

involvement in remediation

- Specific expertise in areas such as:
  - Pharmacology
  - Toxicology
  - Product formulation development
  - Phase of clinical trials including post marketing trials
- Industry process validation and oversight/review by regulators
- Drivers for sharing best practice
- Other drivers or hinderances such as political, geographical, or cultural (both corporate and country specific)

(\*An EU Qualified Person (QP) is a specific role within the pharmaceutical industry that is enshrined in EU wide legislation European Directive 2001/83/EC issued on Nov. 6, 2001. It is separate and superior to the role of a Head of Quality Control in the United States of America as details in US guideline 21.CRF210/211.)

## **Survey Structure**

The survey was constructed using a mixture of specific open-ended questions, closed-ended questions, and contingency questions as appropriate. As evidenced by the details in appendix 3 of this thesis. The questionnaire was created to cover the following topics:

- Identification of the key expertise and experiences of subject matter experts
- Areas of experience (such as agency or industry)
- Qualified Person status
- Differing geographic experiences
- Length of professional experience
- Academic background

In addition, the predetermined research questions: How is expertise applied?

- Parity of standards
- Communication barriers and best practice
- Process variability
- Validity of market approvals

### **3.6.4 Interviews**

On completion of the survey component individual interviews were scheduled with three participants (fifteen percent of the invited survey group) These individuals were selected based on the data they had already provided and the roles that they had experienced either within or in regulating the Pharmaceutical Industry to gain a cross section population.

The questions asked were to research deeper into specific responses given to open-ended survey questions, such as “specific international markets that give cause for concern” or “markets with unacceptable or elevated levels of serious adverse events” as perceived by their experiences, “the universal perception of the application of current good manufacturing practice (cGMP)”. It was important that the interviews were conducted in a fluid manner to allow open discussion and the opportunity for the interviewee to provide sufficient data. As new topics arose and new concepts were identified, such as specific market issues or illustrative product examples, these were discussed during the interview. These also contributed to the design of a modified questionnaire and interview for the main research study.

In the cases where new concepts were identified these were also researched via literature search prior to the main study.

## CHAPTER 4: RESULTS

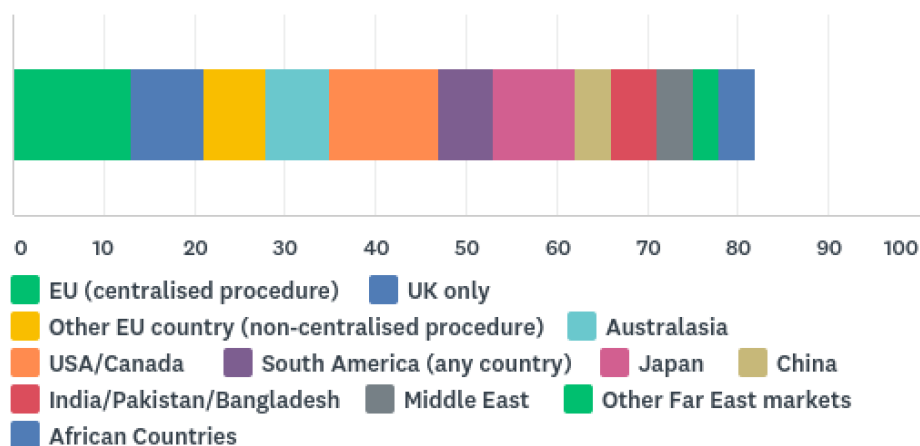
### *4.1 Pilot study results*

The results from this pilot study have been categorised into three groups, the survey questionnaire and then the subsequent follow up interviews conducted with a smaller subpopulation of the respondents and a concurrent review of data reported by regulatory agencies in the UK and USA.

The reporting of mixed methods generated studies has been well documented by Creswell and Clark (2011) and Bazeley (2009) amongst others and has been shown to be superior to single method approaches for some research questions by Bryman (2006). In relation to the data harvested in this pilot study the approaches initially taken with respect to integration and reporting is to validate the chosen methodologies as appropriate for the research question and to correlate where possible the experiences of professionals and agency personal with respect to the questions posed.

#### **4.1.1 Survey**

For this pilot study the researcher requested volunteer participants from a group of industry leaders, individuals who had held position of senior industry responsibility for a significant period of time within the industry or within a regulatory agency. In some cases, participants had served in both industry and regulatory roles during their careers. From the pool of respondents, the split across a wide range of international markets/manufacturers is shown in Figure 16 below.



**Figure 16: Distribution of primary fields of experience**

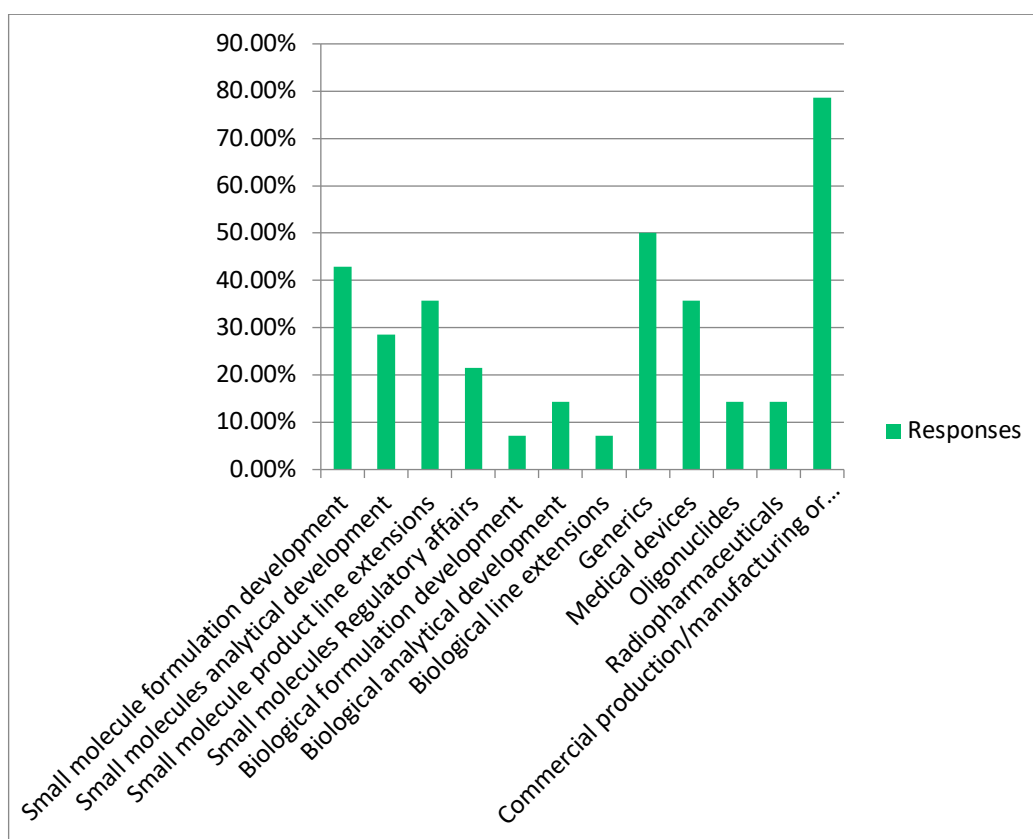
As previously highlighted the role of the Qualified Person (QP) is essential in the approval for sale of pharmaceutical products and requires a documented and examined body of evidence to enable an individual to be registered. For the pilot study participants sixty percent were eligible for QP status or were fulfilling the role of a QP at the time of the survey. In addition, sixty-five percent of the participants had in excess of thirty years industry and/or Regulatory Agency experience with the majority of thirty years experienced individuals also being the QP or QP eligible individuals demonstrating that the participants were both current with UK/EU regulations and approved as individuals to assess and if needed reject imported medicines.

#### 4.1.2 Qualifications

The majority of respondents held Bachelor's Degrees (fifty percent) as their highest scientific qualification. The remaining participants thirty-five percent holding Master's level qualifications and eighteen percent holding vocational qualifications. For the vocational qualification these are MRS, CBiol or MRSC, CChem via study and examination or BPharm. The latter vocational qualifications are recognised in the industry as equivalent to a Bachelor of Science (with Honours) degree. No Doctoral level educated individuals responded although one respondent does hold an honorary doctorate.

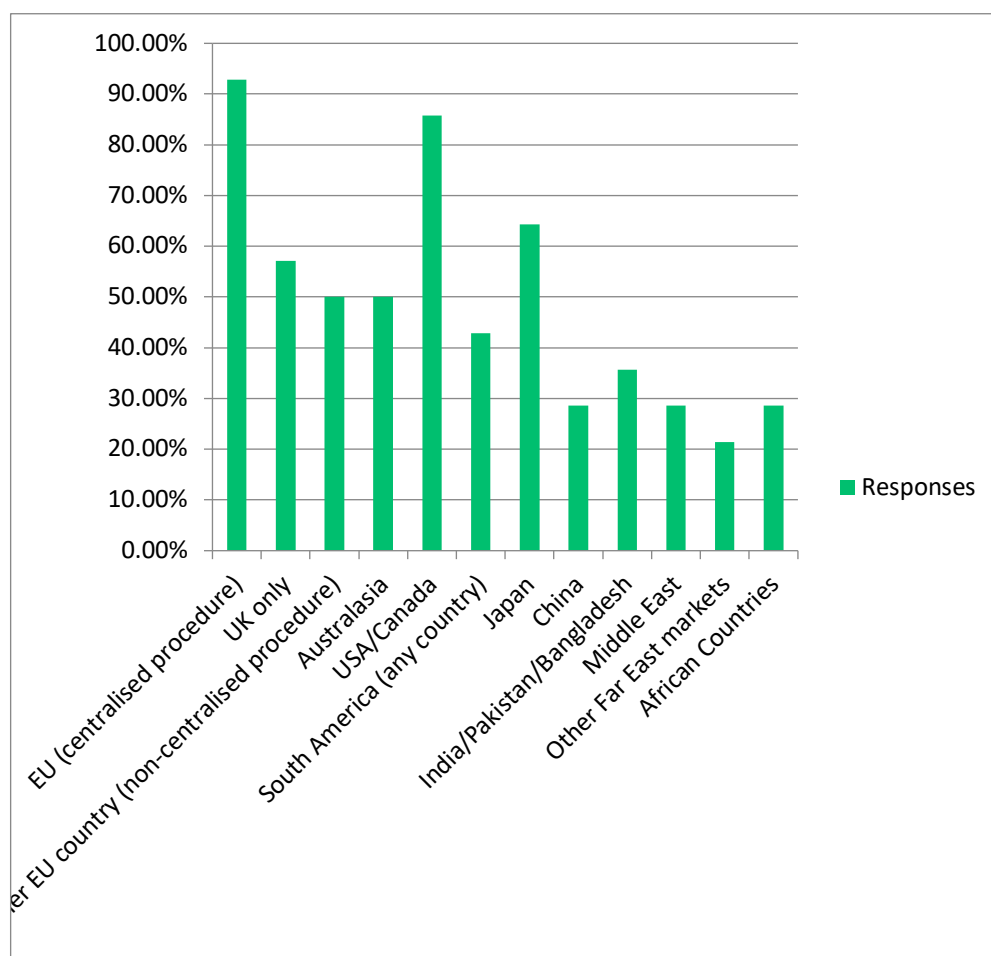
### 4.1.3 Professional experience

To understand the breadth of experience held within the respondents' pool Figure 17 below shows the diverse nature of the pharmaceutical industry and the breadth of experience gained by this relatively small pool of people. It should be noted that many individuals had experiences in multiple areas.



**Figure 17: Breadth of pharmaceutical product type experience gained by respondents**

To gain an understanding of the international experience the participants had gained is demonstrated by Figure 18 below. Between the individuals questioned they covered twelve distinct pharmaceutical territories including the main areas of UK/EU, USA, and China/Japan/Korea/Taiwan. This demonstrates the international nature of the pharmaceutical business experienced by the individuals (respondents in this small study) concerned with development, manufacture, approval, or oversight.



**Figure 18: Personal experience of specific market registrations for all product types**

(note: some respondents covered more than one territory)

#### 4.1.4 Pharmaceutical Quality

When questioned with regard the quality of pharmaceutical products only fifteen percent of participants supported the premise that pharmaceutical good manufacturing practice (GMP) was well understood in all markets that supply to the UK or USA, whilst the majority stated in their experience GMP was only sometimes applied.

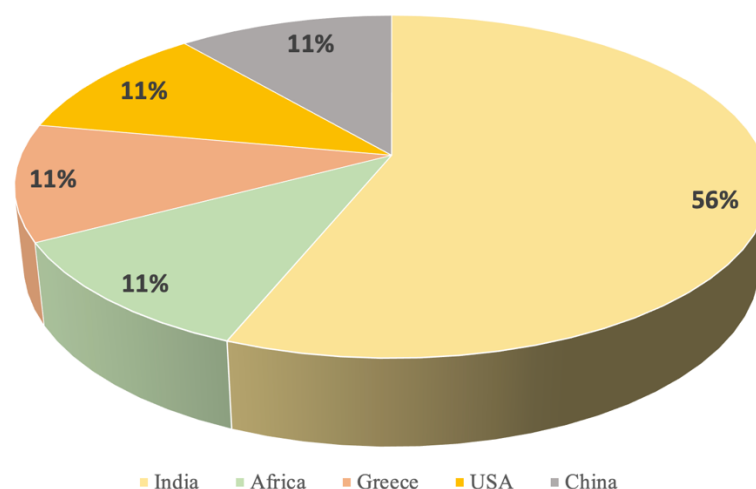
There was overwhelming support (seventy-five percent) for a far greater international role of the sharing of good practice and assessment as detailed within the International Congress on Harmonisation (known as the Q series) with the suggestion it should being applied globally to ensure an increased harmonisation to quality.

When considering the split between research and development, product development and manufacturing, one hundred percent of respondents replied that R&D was satisfactory whereas commercial production could not manufacture the robust and reproducible products that were being developed. When researching that response further there was an equal split between respondents that half of reported defects observed were caused from manufacturing issues with the remainder caused by distribution issues (for example between manufacturer to pharmacy to patient).

#### 4.1.5 Product recall and specific markets

Seventy-eight percent had experience of a product recall due to unsafe, non-efficacious or adulterated medicinal products. These were divided between seventeen percent in a role as a regulator and eighty-three percent as an industry professional, with twenty-five percent of recalls being initiated by the regulator, the remaining initiated by industry itself. Of recalls experienced within the participant group there was an equal distribution between recalls caused by poor manufacturing, failure on product testing and other (non-disclosed reasons).

When the participants were asked to consider individual markets they had experienced (captured in Figure 19 below) fifty-six percent indicated that products supplied from some markets gave concern shown in Figure 19 below:



**Figure 19: Manufacturing markets that give cause for concern to respondents**

Of the product recalls experienced by the study participants eighty-six percent felt that failures were not investigated, the respondent's opinion, in a satisfactorily robust manner such as root cause analysis utilising Failure Mode Effect Analysis, Ishikawa, five-whys or similar.

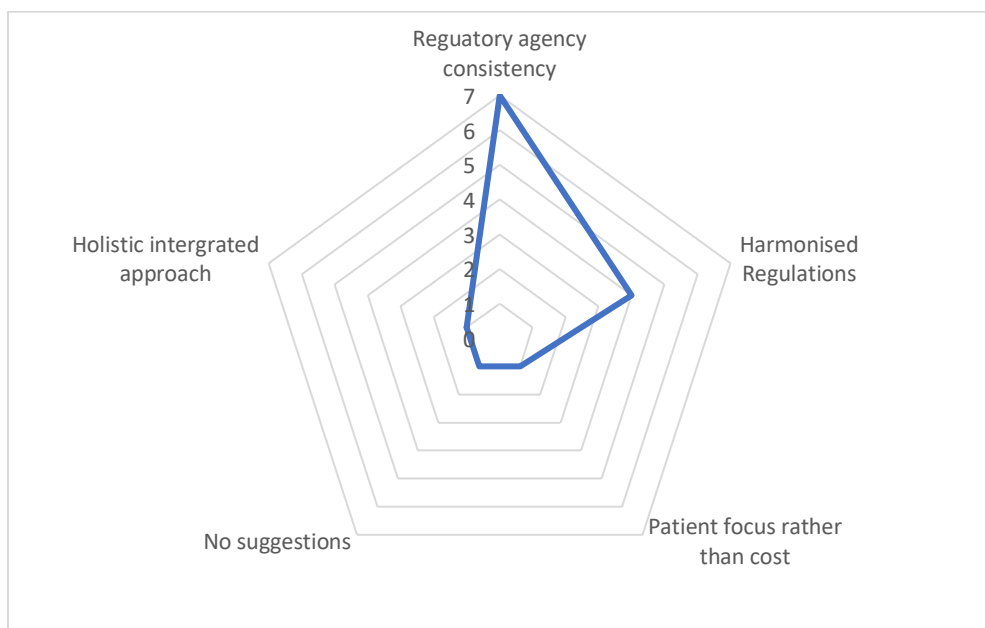
Eighty percent felt that products were not uniformly validated with the same level of diligence across all markets from which products are imported, whilst sixty-five percent also felt that country specific politics also impacted the application of science and good practice within the pharmaceutical industry.

#### **4.1.6 National agencies, constraints and other impacting factors**

The subject group were questioned on other constraints and drivers within the industry that may impact the production and supply of safe and efficacious medicines. All participants responded that all the regulatory agencies concerned do not work to a single, unified, or even equivalent quality standard and that there were additional pressures, both corporate and country specific, that impact pharmaceutical innovation and best practice. There was concern within the subjects that pharmacogenomics was poorly understood by many manufacturers and regulators and that this contributed to ineffectual or in some cases unsafe medicines being dosed. Although it should be acknowledged that due to the patient specific nature of pharmacogenomics the widespread application of this is still in its infancy.

#### **4.1.7 What can be done to improve the current process?**

All participants were asked to consider, based upon their own personal professional experiences, what could be done to improve the current process to achieve a truly global pharmaceutical market that had equivalent safety and patient-centric measures in place. The results of this question are shown in Figure 20 below:



**Figure 20: Radar plot indicating areas considered important for patient safety and improvements**

#### 4.1.8 Interviews

Participants selected for interview were assigned a random number as identification.

##### Participant 0560

Participant identified as 0560 was interviewed to elicit further insights to the feedback gained via the questionnaire. The following points were discussed and are presented below in rank order of concern (high to low) to the participant.

- “Countries vary hugely in their approach to manufacturing, and some have a history of repeat deficiency, repeat fraudulent activity and a poor-quality culture. In this participant’s experience one country was of particular concern.”
- “Regulatory agencies are not equal. There is a demonstrable lack of experience within some, a lack of application and a lack of will to embrace new or improved technologies. A risk averse approach to pharmaceutical oversight and control as opposed to a more pragmatic approach in the EU.”

- “Culture has a large impact on agency activities and the application and sharing of best practice. When considering more litigious societies or countries that have strict cultural interpretations of what a ‘satisfactory product’ should be has a roll-on impact on patients, decisions are not generally directed by good science. “

### **Participant 3124**

On interview participant 3124 was firm in the belief that countries were not all equal on quality and safety. Two particular countries were mentioned as areas that did not demonstrate a satisfactory level of quality commitment and oversight.

In line with the comments made by 0560 above the order of concerns were again:

- Individual countries and their application and quality knowledge being insufficient.
- The agencies being tasked with oversight being poorly funded and poorly educated for current expectations and emerging technologies.
- The impact of cultural influence on companies and agencies. The feedback was that some countries where the culture was very ‘deferential’ maybe contributing to deficient work and regulatory practices.

### **Participant 7690**

This participant stated that the unequal level of agency oversight and application gave the greatest concern due to the nature of the business and the importance of oversight and quality management.

Of least concern for this participant was the cultural impact. The feedback from 7690 was very similar to that gained from 0560, (of note when considering 7690 and 0560 is that one participant had spent the majority of their career in industry and the other in a regulatory Quality function.

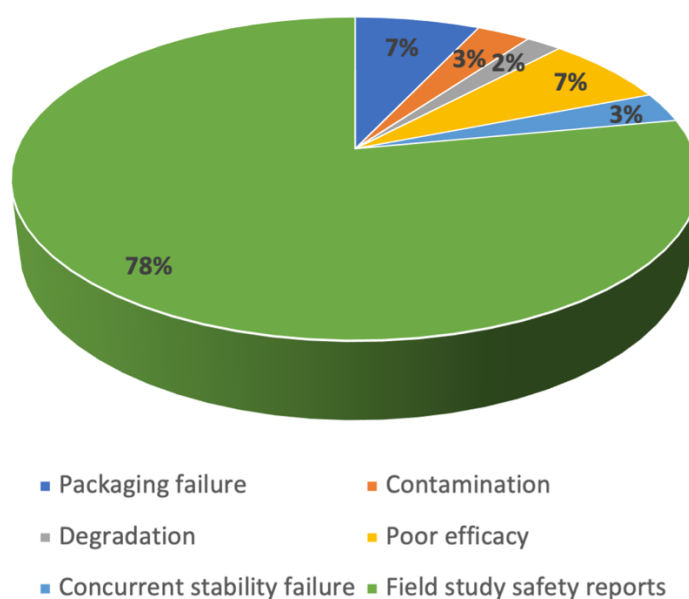
#### 4.1.9 Quality Incidents reported on commercial products

For the purposes of this pilot study only two markets were investigated with respect to reported quality incidents, product recalls and serious adverse events, these were the United Kingdom (UK) and the United States of America (USA). Both sources of information are the existing pharmaceutical data reporting systems already in place administered by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK and the Food and Drug Administration (FDA) in the USA.

In the UK for the period 01 January 2018 to 31 December 2018 a total of 120 products were recalled due to quality defects, the products did not meet the pre-approved quality measures for safety and efficacy (MHRA, 2019). Some of these products were manufactured within the UK or EU, many were imported from non-EU manufacturers. These can be summarised as:

- 120 incidents concerning licensed pharmaceutical product (non-biological derived drug products)

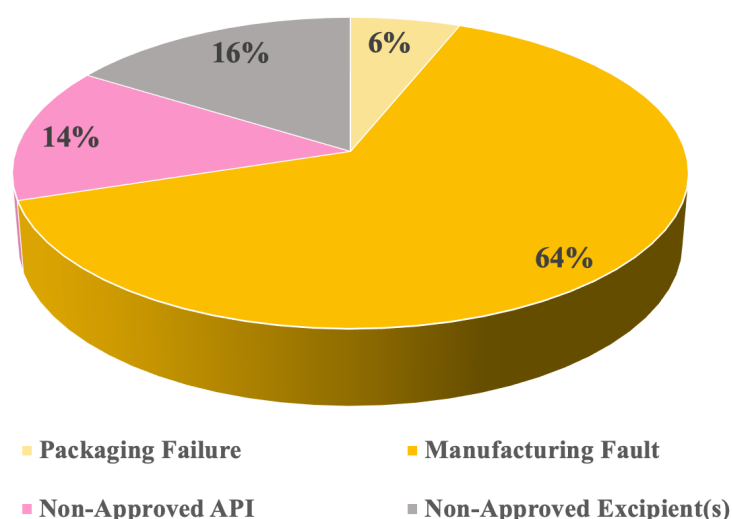
These incidents can be further categorised (by the author) as shown in Figure 21 below:



**Figure 21: Categorisation of UK Medicine and Healthcare Regulatory Agency notified product recalls January 2018- December 2018**

For 2019 January to June the US FDA recalled nineteen and a half percent of all *imported* products due to failure on repeat specification testing conducted by an agency appointed independent laboratory as reported by US Statistica (Anon., 2019). Each product batch recall had an average batch size of in excess of three hundred thousand doses, a substantial impact upon the availability of licensed medicinal products of acceptable quality within that specific market.

In the USA, across all marketed licensed products the equivalent monitoring system administered by US FDA Centre for Drug Evaluation and Research (CDER) listed one hundred and fifty-nine product recalls for January 2018 – December 2018. For the recalls under the jurisdiction of FDA the recalls can be further analysed US Statistica (Anon., 2019) as shown in Figure 22 below:



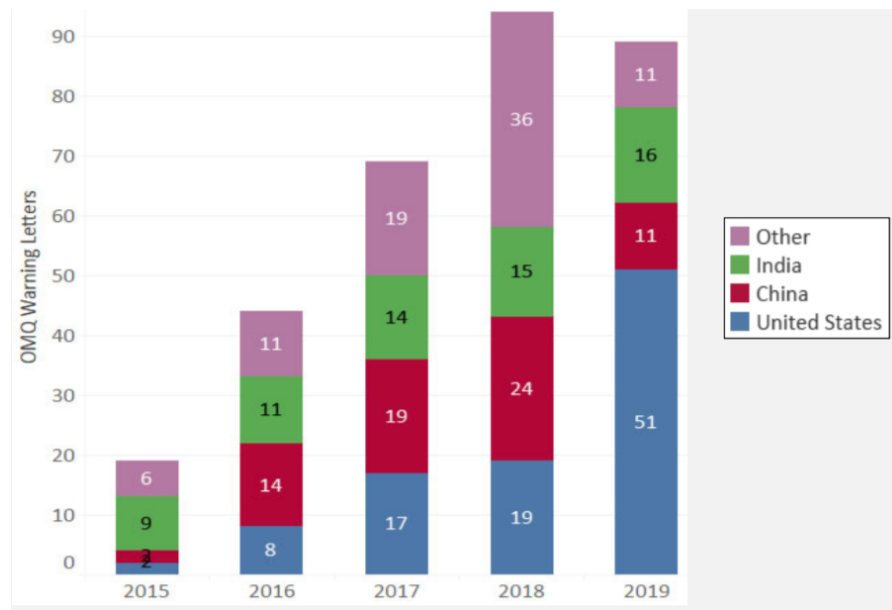
**Figure 22: Categorisation of US Food and Drug Administration notified product recalls January 2018-December 2018**

It is also noted that during the same period the number of US FDA recalls for biologics also appeared to track at a similar level of occurrence. US FDA Centre for Biologics Evaluation and Research (CBER) reported that the incidence of issuance of warning letters to companies for substandard products continues to rise (Anderson 2019). In the year-to-date formal warning letters have been issued covering the following deficiency categories:

- 21 CFR 211.113(b) –Control of microbial contamination
- 21 CFR 211.42(c)(10) –Design and construction features
- 21 CFR 211.100(a) –Production and process controls
- 21 CFR 211.160(b) –Laboratory controls
- 21 CFR 211.80(a) –Control of components and drug product containers and closures
- 21 CFR 211.166(a) –Stability testing
- 21 CFR 211.22 –Quality control unit

Whilst this is not a clear root cause analysis, and a detailed investigation into each deficiency letter may yield further insights for the purposes of further study, it can be deemed that the quality of medicinal products is not necessarily a given constant and is subject to variability. It cannot however be determined from this data if there is a clear causal link at this stage between the number of warning letters issued and defective or recalled drug products.

However, data recently reported by Friedman (2019) clearly demonstrates an increase in product defects being tracked for the past five years by the FDA as shown in Figure 23 below. This shows a clear increase in the number of USA deficiencies with a corresponding decrease in ‘others’. The overall the increasing trend overall is concerning. This maybe primarily due to a greater understanding in deficiencies allowing further classification into appropriate cause definitions. Effectively is the use of root cause analysis leading to this increased level of granularity.

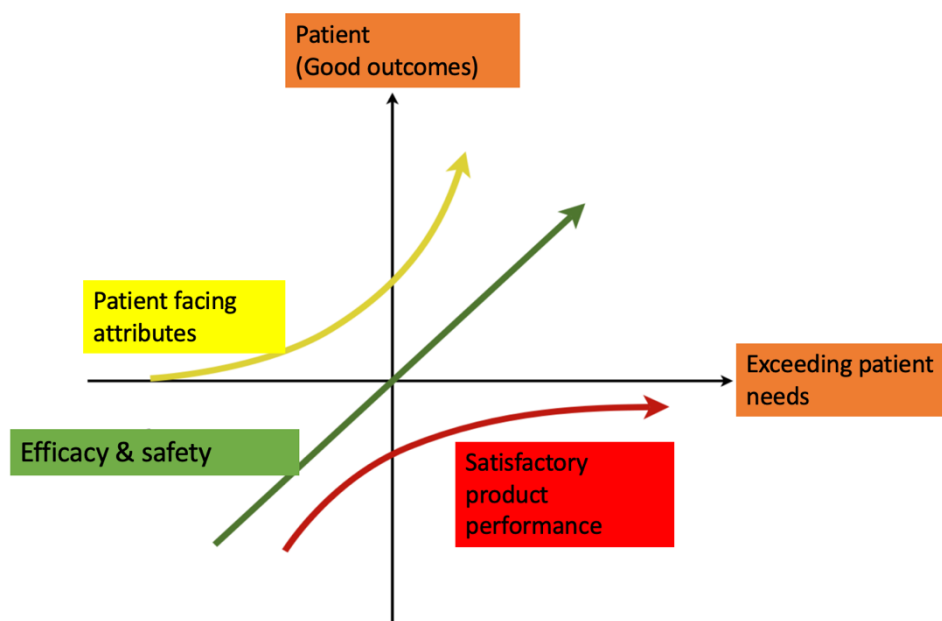


**Figure 23: FDA issued warning letters issued 2014- 2019 years as published (Friedman, 2019)**

#### 4.1.10 Comparative data analysis

The use of comparative data analysis during a research project was evaluated by Creswell (2013) and utilised in this study to direct the data interpretation with regards the interactions with the number or recalls observed across the industry sectors identified and also to guide further development of the mixed methods approach with respect to questions asked and interview specific topics.

During the data capture phase of review of the emerging data it became apparent that this research question could be considered in an interrelated manner. If we consider product quality attributes that relate to product efficacy and safety these can applied to a variant based on the Kano model (Mikulić, Prebežac, 2011). This is shown in Figure 24 below:



**Figure 24: Application of the Kano model to pharmaceutical safety and efficacy with respect to patients**

The above Figure 24 clearly represents the relationships between patient outcomes with respect to the medication they are receiving, the efficacy and how it impacts medical outcomes and the minimum expected standard for medicines. The application of medical outcomes should be considered when identifying key quality characteristics of medicinal products (Tarlov, 1989 and Bodrogi, 2010). The comparative data analysis conducted also led to the formation of the interview questions posed during this pilot study and these are discussed earlier.

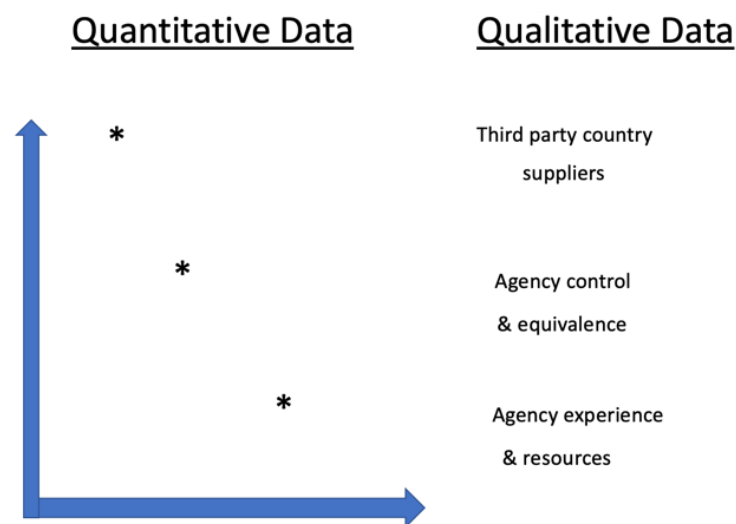
#### **4.1.11 Pilot Study Summary**

As identified by previous researchers such as Borg, et al., (2014) the importing of competitor or generic medicinal products is increasing in part due to the globalisation of the industry and also as part of corporate cost reduction strategies and healthcare reimbursement cost controls. The impact of substandard product on patients is obvious from a medical perspective. The financial impact to manufacturers and companies that are active in the same therapeutic area has also been discussed and assessed by Bala, et al., (2017). In addition, the commitment to regulatory agency education and advancement with regards to emerging technologies was first highlighted in 2016 by Fisher, et al.,

(2016).

The data captured in the pilot study has demonstrated that the primary research question of whether there is an issue with safety and efficacy of imported medicines does exist and requires further study. The data in this study is limited to a small defined pool of participants and a limited period of reported regulatory data. The study demonstrates that the processes selected, mixed methods approach, are satisfactory in capturing relevant information for further analysis. This should be conducted on a wider scale to facilitate further conclusions and recommendation for additional processes and controls to facilitate an improved method of ensuring safe and efficacy medicines.

To consider where the data correlates between the two methods described in this study, they could be expressed as a mixed methods integrated results such as shown in Figure 25 below:



**Figure 25: Integrated mixed methods representation of the pilot study data gathering**

There is limited data at this stage to make such a powered claim as shown in Figure 25, however additional data will add validity and weight to this type of analysis on further study.

This Pilot Study was conducted after ARU Ethics approval was granted. Copies of all Participant Consent Forms are retained by the Author.

#### **4.1.12 Pilot study Conclusion**

Considering the question “do the data gathered so far support the premise of the current modality that all drugs containing the same active pharmaceutical ingredient are equivalent with regards to safety and efficacy?” the data appears at this early stage to not support this premise at least within the context of the geographical areas considered in the pilot study.

When considering the methodologies utilised in this pilot study the conclusion is that the approach proposed to utilise a mixed methods of questionnaire and interview yields interesting relationships based upon senior individuals from the pharmaceutical sector. To roll this out to a much wider audience firstly requires some modifications to the questionnaire to yield further details such as:

- Segregation of industry sectors into:
  - Research and Development, Commercial Manufacturing,
  - Regulatory Affairs
  - Quality Assurance and Quality Control
  - Strategic direction of pharmaceutical investment.

This would diversify the data to add discrete breadth to the data collected and ultimately to consider each contribution as a potentially orthogonal view on the data collected with respect to the research question.

In future work there are some conclusions from this pilot study that should be adopted to assist in data capture and analyses. Further work could include:

- The use of a DMAIC type analysis (as used as part of a lean sigma or Kaizen analysis) could also prove beneficial once additional data is captured and

analysed.

- Application of Process Capability (Cp) and Process Capability Index (CpK), (frequently used statistical tools utilised in defining pharmaceutical manufacturing processes of varying complexity). This could be used to analyse specific product data to demonstrate the level of existing control and the scope to improve such control.

In addition, the interview questions will need to be more probing in the areas of root cause analysis, investigations, and outcomes.

The sequential mixed methods approach undertaken was a linear process as demonstrated in Figure 26 below, this facilitated an assessment of the data continually as it evolved.



**Figure 26: Sequential sampling process summary**

The actual questions to be covered during the interviews are summarised as:

- Personal professional experience summary
  - Range/breadth
- Personal knowledge
  - Professional background
  - Any changes and why?
  - Has their opinion changed regards regulation and if so, why?
- Behaviours & experiences
  - Personal
  - Third parts

- How did you deal with it?
- Opinion & belief
  - Do they believe in the current process?
  - Does the current process protect the common good?
  - Their opinion on Agency resourcing (meritocracy or autocracy)
- Feeling & perception
  - How do they feel about imported products?
  - Why, what evidence?
  - Are they safe or comparable to domestic products?
- Sensory inputs
  - Do they feel swayed by data or solely perception?
  - What evidence do they have for this?
  - How does this influence them?
  - Any specific examples that can be shared?
  - What can change?
  - What can they personally do to effect change?
  - Do they feel empowered?
  - To suggest the top three drivers for change in regard to regulation of pharmaceuticals
  - Their top three drivers for change in relation to the above
  - Who can effect change on this scale?

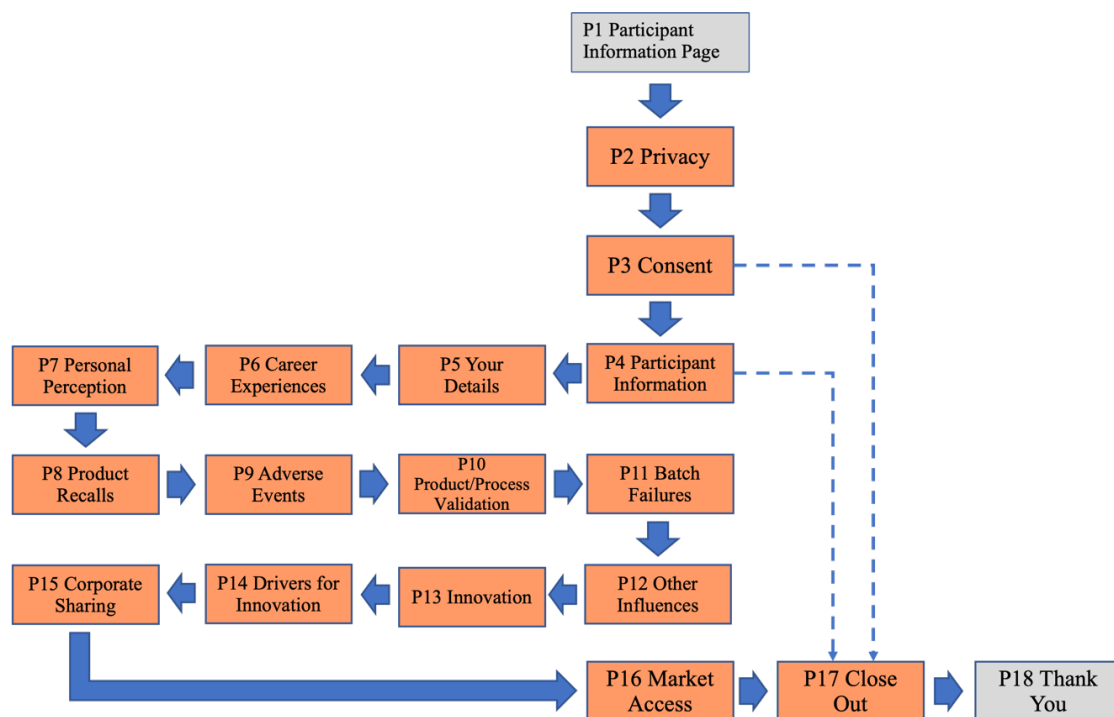
Whilst the language used during each interview, as seen by the transcripts in the appendix, varied depending upon the time and course of the interview and the interviewees use of English, all topics were covered.

## 4.2 Main research results

### 4.2.1 Population identification.

Building upon the knowledge and experience gained during the pilot study a fifty-two-question online survey was constructed via Online Surveys (previously identified as Bristol Online Surveys) and distributed to one hundred potential participants. In this instance the participant consent form was included in the survey and required a positive acceptance before the participant could continue. The consent form was aligned with that already approved by the ARU Ethics Panel.

The actual online survey was an enhanced version of that already utilised in the pilot study and the broad survey structure can be seen in Figure 27 below.



**Figure 27: Main study questionnaire flow**

The identification of the population to be questioned was conducted using purposeful sampling. This technique is recognised as a key tool in the identification of specific population, in this case subjects who are information and experience rich in this area,

namely pharmaceutical scientists and regulatory agency inspectors, or individuals who have fulfilled both roles in their careers. Purposeful sampling is widely recognised as suitable for mixed methods research and has been extensively discussed in papers such as Palinkas, et al., (2015) and Onwuegbuzie and Collins (2007) highlighted a few key parameters that clearly demonstrate the effective use of this sampling technique in research such as this. Onwuegbuzie and Collins are quoted as claiming *“to obtain insights into a phenomenon, individuals, or events (as will often be the case in the qualitative component of a mixed methods study) then the researcher purposefully selects individuals, groups, and settings for this phase that maximise understanding of the underlying phenomenon”*. These selected individuals are identified as being information rich (Patton, 1990). In addition, Onwuegbuzie, and Collins (2007) suggest methodologies for determination of appropriate sample sizes. For this type of research project, the sample size is key, both to determine analytic generalisations (themes) and also to avoid the use of unrealistic statistical tests of inadequate power due to the fact that the study and sample size, due to its niche role subject matter, is not sufficiently powered to provide robust statistical analysis. Varying levels of sample size have been suggested, such as this in Table four below.

**Table 4: Proposed Sample Sizes**

<b>Design/Approach</b>	<b>Suggested sample size</b>	<b>Reference</b>
Phenomenological	≤10 Interviews	Creswell (1998)
Phenomenological	≥6 interviews	Morse (1994)
Grounded Theory	15-20 Interviews	Creswell (2002)
Grounded Theory	20-30 Interviews	Creswell (2007)
Data Collection Interview	12 Interviews	Guest, Bunce Johnson (2006)

#### **4.2.2 Questionnaire Data**

The questionnaire was based upon a similar format used in the pilot study and enhanced in certain areas for this study. The study was conducted via online surveys (formerly Bristol Online Surveys).

The survey questions were structured as per the previous Figure 27.

Full survey data, redacting personally identifiable information is included in Appendix 2.

The survey questionnaire was structured to identify respondents' general experiences and to identify a subgroup for further interview.

Initial questions covered name, agreement to ethics and consent statements and are not included in this thesis but are retained by the researcher only.

#### **4.2.3 Data summary**

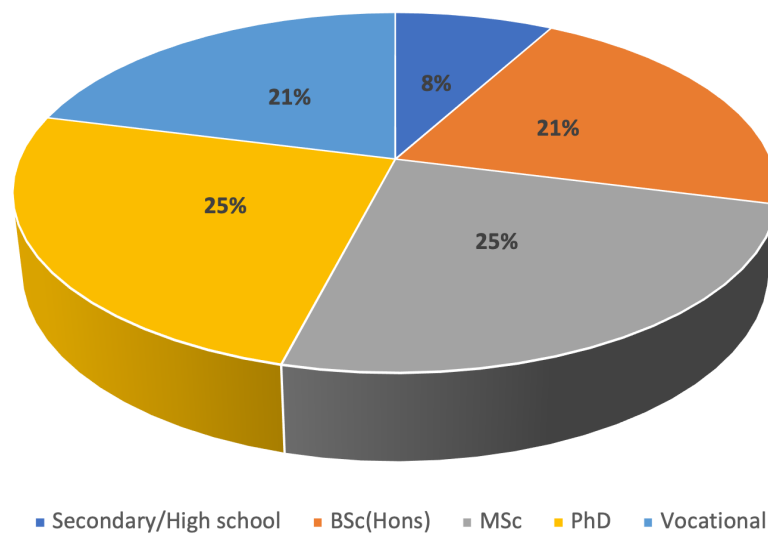
1. Respondents had experience of working in the following geographical areas (note some covered more than one area).

- United Kingdom
- India
- China
- Taiwan
- Canada
- USA
- Switzerland
- Israel
- Italy
- Denmark

- Australia
- Germany
- Estonia
- EU Member States
- Japan
- Belgium
- Croatia
- Eire
- Germany

## 2. Highest level qualification

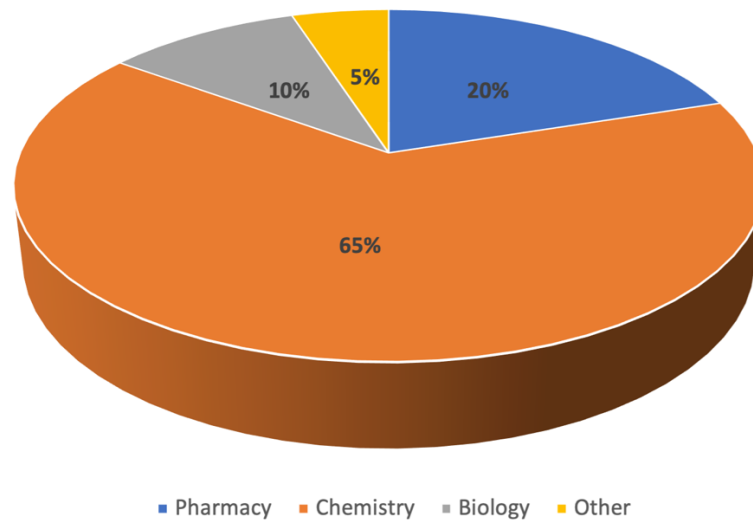
This is important to understand the professional's ability to critically assess a situation.



**Figure 28: The distribution of respondents and their highest level of qualification**

### 3. Primary discipline of qualification

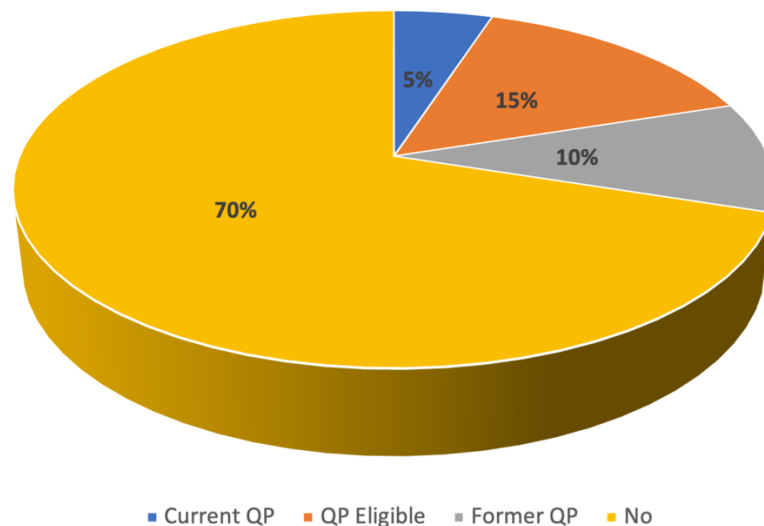
This information allows an interpretation of professional area.



**Figure 29: Respondents primary scientific discipline**

### 4. Qualified Person status, respondents were asked if they were eligible as an EU/UK Qualified Person.

The sub-population that has a defined legal responsibility is a key parameter. They also undertake specialist training for the role.



**Figure 30: Respondents eligibility for EU QP status**  
(under EU Directive 2001/83/EC)

5. Respondents were asked how many years of QP experience they had.

For all QP respondent's sixty-eight percent had been a QP for greater than ten years whilst the remainder had fulfilled that role for between six and ten years.

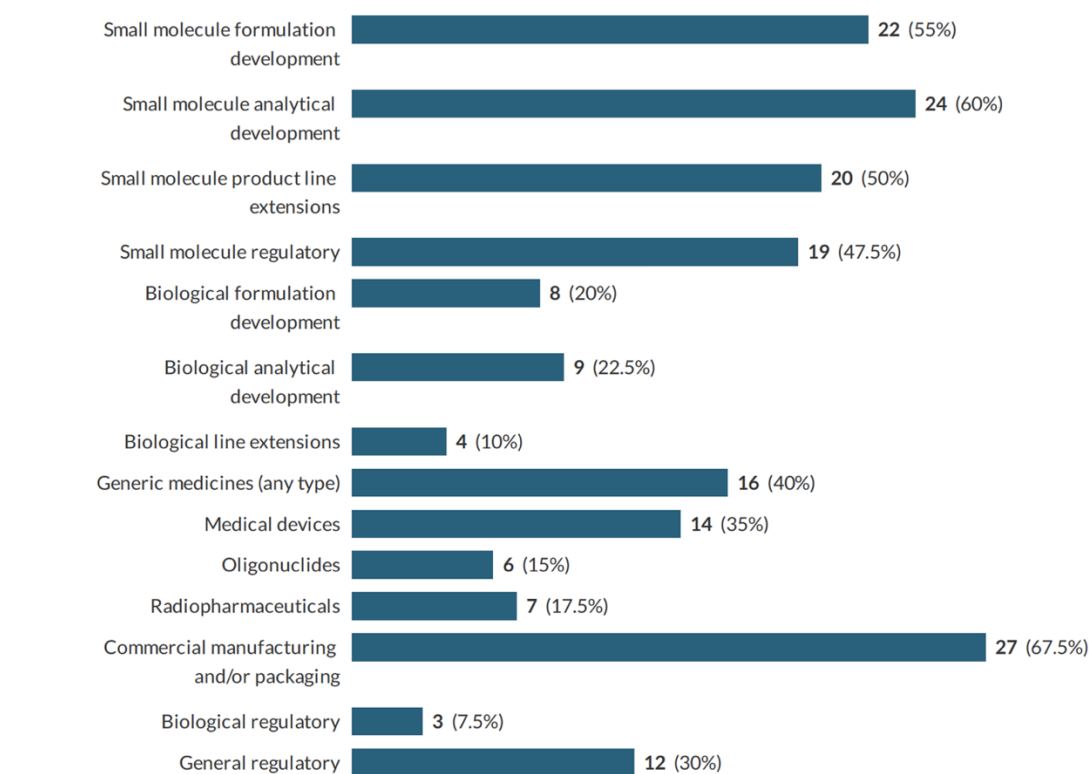
6. They were asked to describe their breadth of experience.

This is key to understand their perspective. From respondents all had industry experience of varying degrees with a third having current or previous agency experience.

7. To gain a perspective on the amount of experience as well as breadth they were asked how many years they had worked in their respective roles.

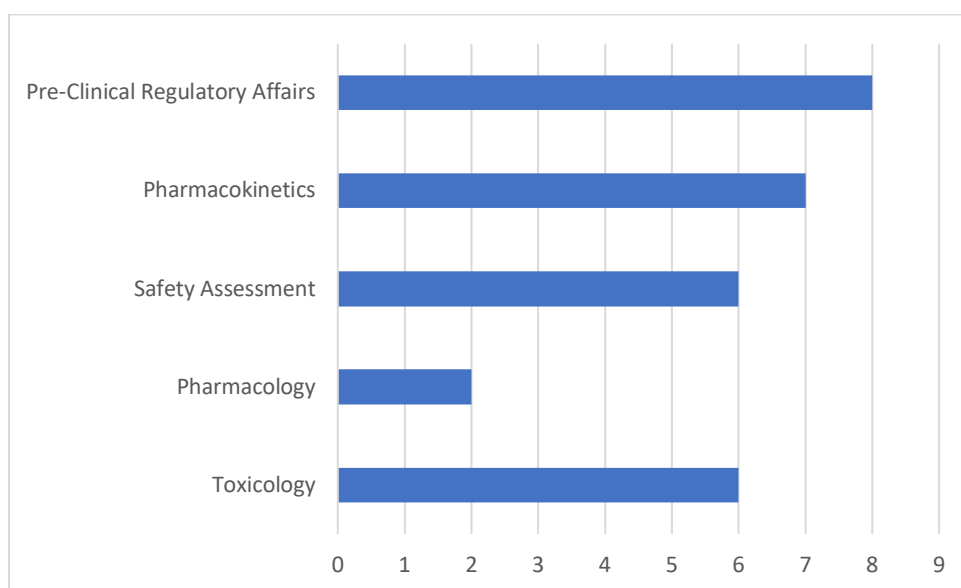
It is key to establish a claim to SME status the number of years performing that task. In this case over sixty percent of participants had greater than 30 years professional experience and twenty five percent having between twenty and thirty years of experience. An extremely experienced group of SMEs.

8. Respondents were asked to specify key areas they have worked within.



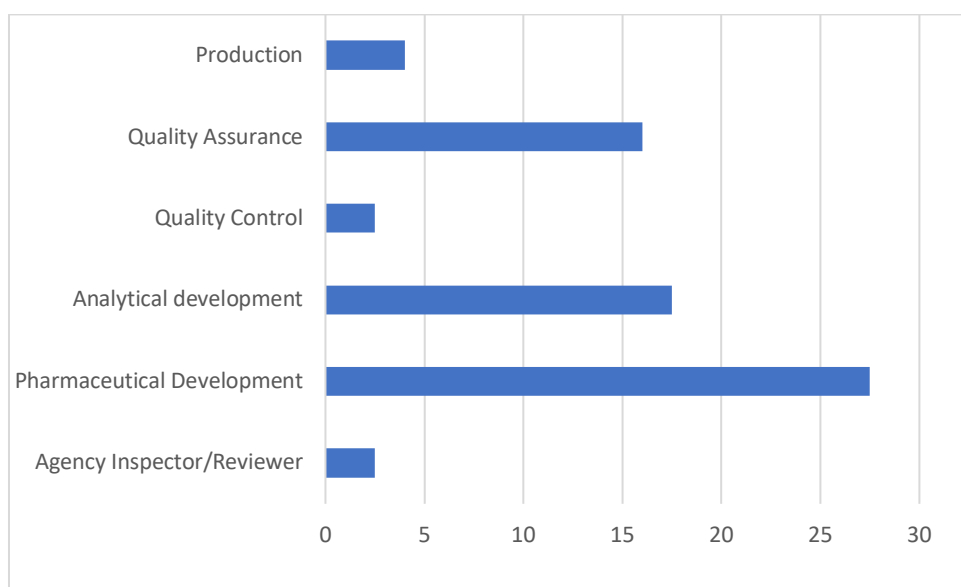
**Figure 31: Respondent's summary experience in product development**

9. Respondents were asked in addition to roles already questioned what experience they had in related areas.



**Figure 32: Respondent's summary experience in related areas**

10. What was their primary work area (the most time in their career)?

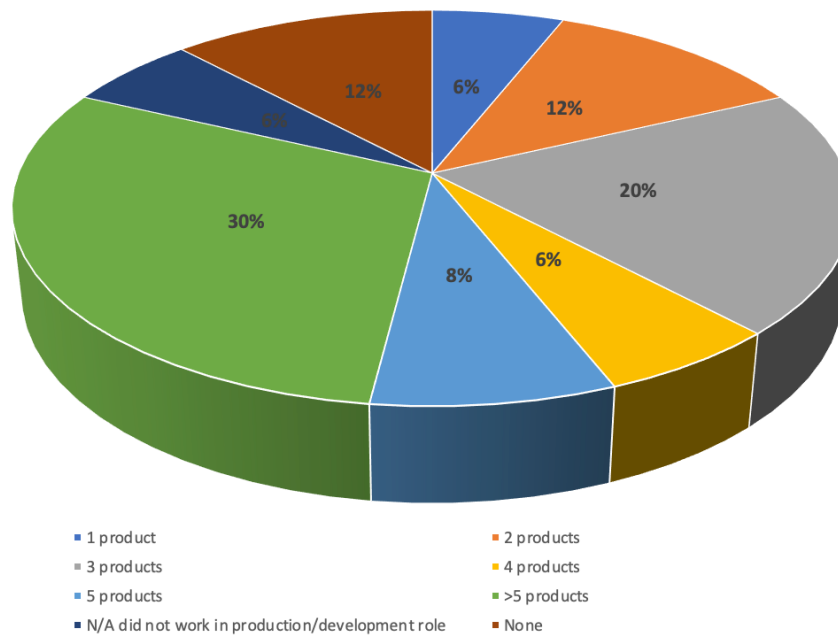


**Figure 33: Respondent's summary primary work areas**

11. Experience of clinical phase dosing, clinical phase I to phase IV.

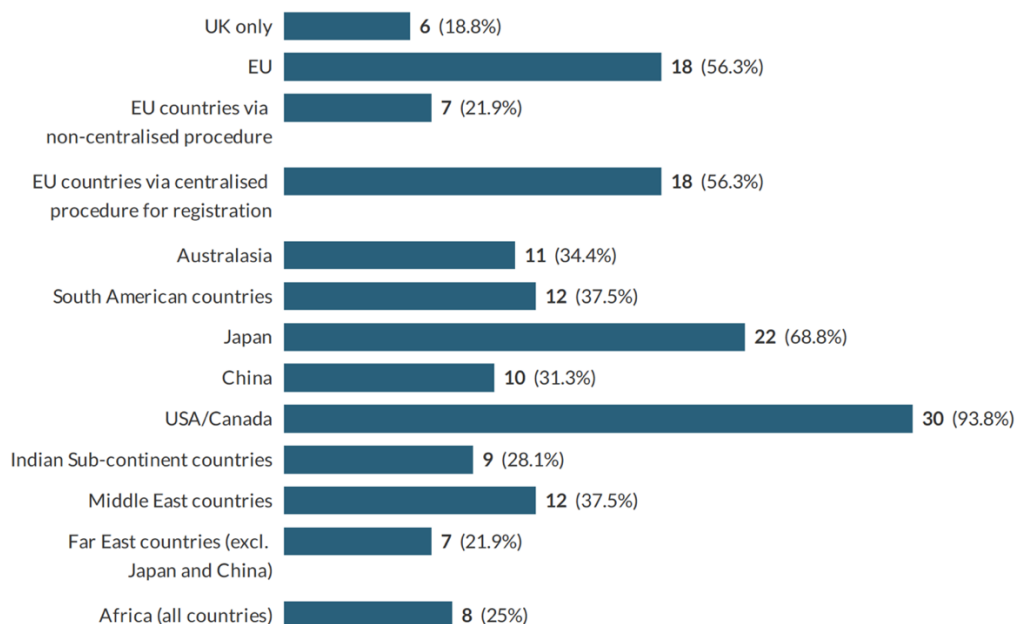
This data adds a different perspective to the experiences captured, the exposure to different areas of clinical trials will help define a SMEs point of view. In this population it was equally split between all four phases.

12. To understand commercial product perspectives respondents were asked how many products they had worked on that had been commercialised.



**Figure 34: Respondent's experience of commercialisation**

13. In what markets were the above products registered?



**Figure 35: Respondent's scope of product registrations by country/region**

14. When asked whether they had been involved in product importation and/or the testing of imported products, only seventeen (of sixty-two) respondents stated they had.

15. When asked if they had worked in a patient facing role (hospital/pharmacy etc.) only two had served that role.

16. Of those that replied they had served in a patient facing role only one replied that it had changed their perspective of drug product development or manufacture.

17. The same respondent from the previous question who stated it had changed their perspective also added that it had changed their awareness of patient needs and developed a greater interest in patient benefit.

18. All respondents were asked whether the concepts of cGMP are sufficiently understood and demonstrated in the markets they had worked within? Sixty-five percent replied it had been understood.

19. Respondents were also asked if any markets/areas give them cause for concern, as a professional, with regards to delivering safe and efficacious products? Fourteen replied that they did indeed have concerns.

20. Respondents were asked if certain countries/markets gave cause for concern and ranked the following as examples (in rank order, highest first).

- China
- India
- EU
- Japan
- USA
- Eastern Europe
- Egypt
- Saudi Arabia
- Colombia
- Sierra Leone
- Uganda
- Guinea
- Brazil
- Central sun-Saharan  
Countries

21. When asked if they had been part of a product recall process, eighteen replied that they had.

22. When asked what event initiated the recall it was summarised as below:

- Poor packaging 23.1%
- Stability failure 25.6%
- Poor manufacturing 25.6%
- Other reason 20.5%
- Product adulteration (tampering) 5.1%
- Unknown 53.8%

23. When asked if they had investigated a serious adverse event caused by or suspected to be caused by poor GMP and/or poor GDP only seven responded that they had been part of such an investigation.

24. Respondents were asked, in their experience what were the most common reasons for recalls. They responded as:

- i. Product quality failure/GMP failure (91%)
- ii. Unknown or undefined reason not linked to quality or GMP (9%)

25. Respondents were then asked regards their experience of ICH and whether the principles of ICH were being used to their full potential? Fifty-one percent of respondents replied that it was being used to its potential.

26. For those that replied that ICH was not being utilised fully a free text response was permitted for further details, these comments are shown in Table 5 below. The comments can be summarised as a diverse range of experiences from respondents from a minority that felt that their experience was that they/ their company already adhered to these standards on an almost international basis to others whose experiences were that either ICH was at worst poorly understood or at best was translated into internal procedures that were either ambiguous or poorly structured. The latter to allow personal interpretation and therefore poor adherence to ICH ideals. Overall, a lack of a driver for implementation as the benefits were not clear. (These responses have been allocated into appropriate categories based upon the research questions.)

**Table 5: Respondent's response to lack of ICH implementation/compliance**

Although not always understood completely, ICH is a benefit to country regulators
It is Routinely referenced with audit reports and associated documentation
Practical Interpretation of ICH Guidelines.
<b>Parity of international standards</b>
Global Regulatory Standard
<b>Inherent variability</b>
Many are not well translated into company policies and procedures
Some companies unaware of ICH
The principles are general enough to open to interpretation, I've not witnessed any specific issues.
<b>Validity of other market approvals</b>
I believe that in many markets, BRIC, ASEAN that additional testing is part of the political landscape e.g., importation testing, 300C/75%RH stability testing, new stress testing guidelines (ANVESA)

27. When asked whether there would be a benefit to expand ICH application to other countries not yet aligned ninety seven percent of respondents replied that it would be beneficial.

28, When asked why it would be beneficial, the following free text responses were provided as shown in Table 6. (These responses have been allocated into appropriate categories based upon the research questions.)

**Table 6: Respondent's responses to benefits of ICH increased roll out**

(Verbatim text)

**The application of expertise**

Personal experience during inspections in various countries. Albeit limited to just a few of the ICH standards.

I work more in GCP and our clients follow ICH GCP guidelines closely

In countries who are members of ICH, they generally apply when assessing their products and the requirements are embedded into their regulatory requirements.

**Parity of international standards**

ICH is a guidance document and manufacturers do not need to follow it to the letter.

Not all (non ICH) countries in the world formally follow all ICH guidance

Most of the markets I've worked in or with are highly regulated or operate to PIC/s standards

ICH could/should be implemented more with generics before approval to ensure alignment with innovator product.

I audit under those principles and as a rule they are adhered to

I work within a regulated environment whereby we use ICH M7 to steer our regulatory submissions with regards to mutagenic impurity control. These strategies have been widely accepted across all agencies with only minor questions.

Harmonised pharmacopeia and regulatory requirements.

**Communication barriers**

Some markets do not understand ICH Q9

There are still too many local guidance documents which interpret the ICH documents differently, A good example of this is ICH Q3D, where different territories interpret the guidance very differently.

**Inherent variability**

A lack of true desire for continuous improvement e.g., Q10 is still poorly adopted/implemented in most organizations I deal with.

ICH barely known and rarely understood

Potential for improved compliance in China.

**Validity of other market approvals**

ICH is used more readily in recent years particularly in established markets, but I think it could be more widely used.

Brazil are developing their own regulations that in some cases far exceed ICH requirements.

29. To gain insights to respondents' experiences of pre-commercialisation activities, they

were questioned whether they had worked on product validation on the basis that they would then have a personal perspective on product robustness and reproducibility and key product characteristics that drive efficacy and safety. Of all respondents seventy-two percent claimed to have experience in this area.

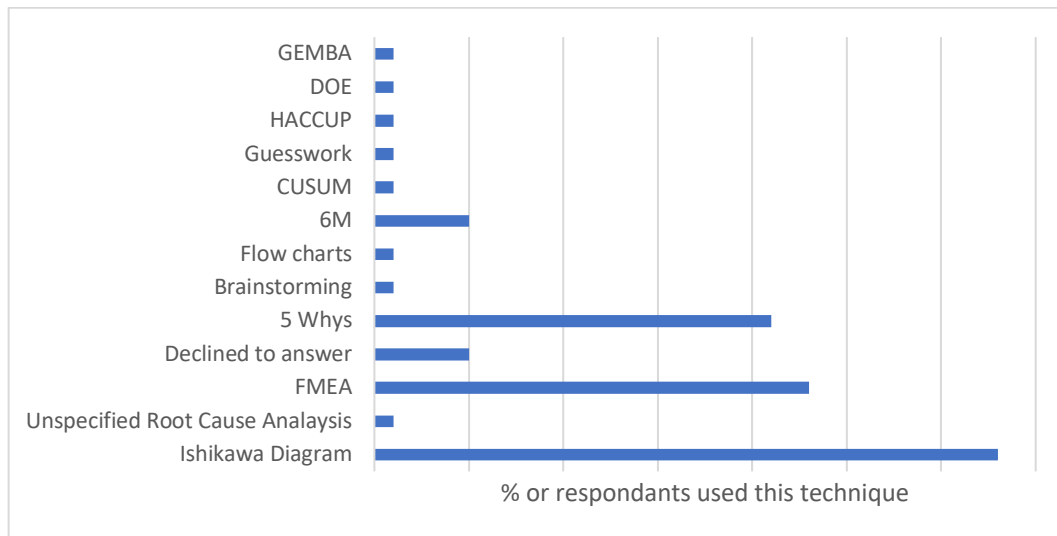
30. To gain further clarity on those who had experience in product validation they were then asked if in their experience the same level of validation was applied to each supply market (i.e., domestic, or overseas) that they have experience in. Forty-one percent claimed no there was no equivalence whilst thirty-one percent claimed there was equivalence and twenty-eight percent declined to answer.

31. When asked to cite reasons for the difference seen in question thirty above a range of replies were forthcoming.

- Not expected by local regulatory agency (twenty-four percent)
- Lack of market understanding of the benefits of robust validation (thirteen percent)
- Insufficient resource (three percent)
- Other reasons – unspecified (one percent)
- Declines to answer (fifty-nine percent)

32. Respondents were asked about batch failure investigations and whether companies evaluated batch failures in sufficient detail to prevent future failures, and therefore increase of severity in the supply chain. Forty-three percent claimed that companies did investigate sufficiently whilst thirty-five percent claimed they did not, the remaining respondents declined to answer.

33. Building upon the responses in question thirty-two respondents were asked what the most common investigative tools were used to determine root cause analysis in batch failure investigations.



**Figure 36: Chart to summarise respondent's use of root cause analysis tools in batch failure investigations**

34. Respondents were then asked to consider pharmacogenomics and the potential impact on new product development. When considering if sufficient effort was made to consider pharmacoeconomics thirteen percent responded that it was considered, twenty-five percent claimed it was not and sixty-two percent had no view on it.

35. When asked if pharmacoeconomics had a detrimental effect on innovation the response was more defined with thirty-eight percent claiming it did, thirteen percent claiming it didn't have an impact and the remaining respondents had no view on the topic.

36. Asked to consider whether there were other drivers that impact innovation, sixty-six percent claimed there were other drivers, three percent claimed none and thirty-two percent didn't know.

37. Respondents were asked to offer supporting statement to the above reply and these are detailed in Table 7 below. These comments can be summarised as primarily driven by cost, but budgetary expenditure and manpower/resources, this was the primary response from the majority of respondents. A small group felt agency knowledge and applicable expertise was an impacting factor with the cost of innovation trumped as the primary concern. These have been divided into research question alignment categories.

**Table 7: Respondents detailing why they believed there were other drivers to product innovation (verbatim text from 32 individuals)**

**The application of expertise**

Impact on quality of the product will be significant

The industry is truly global and as such global. Harmonised standards should be developed

Over time ICH standards do become a defacto global standard e.g., ICH Q7

Enhanced uniformity of consistency of regulatory expectations.

The principles are sound and well documented

Expansion of globally recognized standards

Unification of guidance's is always a good thing.

**Parity of international standards**

Should lead to greater harmonisation of expectations.

Sensible move

To achieve further harmonisation

More consistent global approach

Harmonisation and less country specific burden

Full adoption of ICH in all markets would benefit both patients and the pharmaceutical industry

Drives up standards and consistency

It would help standardize and provide a common language of understanding

**Inherent variability**

Greater harmonisation globally can help with potential reduction of costs if all countries would accept the same standards

Common Knowledge and understanding

To bring other territories up to a higher standard. 2. To harmonise further, making the regulatory burden more manageable.

To improve the quality of medicinal products being developed and manufactured across the globe to an internationally approved level.

The more the WHO world can standardise the better all-around as we can all work to the same guidelines

Great believer in standardization in the industry

**Validity of other market approvals**

Level playing field for all markets and equivalent standards of quality for all patients

Global harmonisation of quality processes

Raising the quality 'bar' through the application of common standards.

Helps to standardise approach to certain aspects of development across more markets.

It is harmonised well across the countries where it is adopted, this can be beneficial to those who do not currently follow. An aligned process steers further collaboration and consensus.

Potentially one global file leading to improved access to medicines and a marginal reduction in R&D costs

It would be best if all countries in this global economy adhered to the same standards.

Would enable a more consistent standard worldwide

ICH provides a solid framework and guidance for consistency in drug development

Common standards

It provides an effective benchmark for quality

Simplifies process to file same marketing applications globally

38. Questions then moved onto pharmacoeconomics (an individual's genetic attributes affect a likely response to therapeutic drugs and whether it had a detrimental impact on product quality. Twenty-six percent of respondents claimed it did and twenty-nine percent claimed it had no impact. Forty-five percent had no perspective on pharmacoeconomics impact.

39. Respondents were then asked what other drivers impacted quality and these responses are shown in Table 8 below. The responses generally fell into a category of culture, both staff training, education, and management engagement. The level of demonstrable management engagement with quality ideals is a key aspect as this influences both staff recruitment and staff training. There was no distinction visible from the replies between company or country culture. A small group of respondents felt cost was an issue in contrast with cost being a primary concern for innovation.

**Table 8 Respondents views on other drivers impacting product quality**

(verbatim text from 30 individuals)

**The application of expertise**

Companies focus on specific therapeutic areas

Training and efficient use of resources

Cost and resources/expertise available drug,

Cost can potentially always be prohibitive to innovation as if it not seen as commercially viable then innovation is often halted.

The larger the company the less likely it is to innovate. Overly powerful Quality Groups in big Pharma.

Data analysis, government initiatives like Patent Box, support for antibiotic development, regulatory exclusivity for orphan drugs and similar schemes, enabling technologies like CRISPR, continuous processing. Single Use Technology – things that make manufacturing cheaper and therefore make product available at viable cost.

**Parity of international standards**

Fear of regulators perceived or actual costs of product development.

How regulations are interpreted and therefore companies afraid to change

**Communication barriers**

Cost of goods and willingness of industry to explore new treatment pathways. Big pharma is very money focused and will not buy in readily for treatments that may be expensive to develop.

Corporate rules and micromanagement

**Inherent variability**

Compliance rather than quality, no incentive to change/improve/innovate

Regulatory divergence e.g., Continuous manufacturing

Innovation can be adversely affected by corporate culture, senior management focus and operational environments e.g., before, during and after major merger and acquisition processes.

Cost containment and short-term financial targets stifle innovation aimed at long-term product improvement. e.g., continuous manufacturing not supported, process robustness and process understanding not fully implemented in manufacturing.

Choice is limited by available budget to less risk is taken often leaving the tried and trusted approach.

**Validity of other market approvals**

Data analysis, government initiatives like Patent Box, support for antibiotic development, regulatory exclusivity for orphan drugs and similar schemes, enabling technologies like CRISPR, continuous processing. Single Use Technology – things that make manufacturing cheaper and therefore make product available at viable cost.

39. Respondents were then asked what evidence they had to support the previous response; the replies are detailed in Table 9 below. The responses covered a very wide spectrum from just “experience” to being willing to leave a company due to a perceived lack of commitment to product quality within the existing company. Some respondents also cited resource and budgetary constraints as supporting evidence, but no single overriding theme was evident.

**Table 9: Respondent's evidence to support their views on quality drivers  
(31 individual responses)**

Company culture as driven by senior management
Personal position in hierarchy and threats, real or implied
Question is too broad to answer!
Special Cause variation and Uncertainty ignored
Company culture, resources, training
Training of staff
Attitude of senior and middle management
Lack of process understanding and trending and analysis of manufacturing data
We standardise our GMP and processes to an expected format and often stick to what we know.
Training and Patient Focus
Senior management lack of interest/understanding of GMP and quality. Globalisation and outsourcing, loss of oversight of the supply chain. Conflicting business priorities between the different organisations in the supply chain.
A failure to follow instructions
Lack of understanding of risk, complicated systems within some companies, poor root cause investigations.
Lack of true understanding of regulations, e.g., why not just what is required.
Cost of goods
Poor training in organisations
Lack of quality culture in organisations
Humans
Company Culture, leadership, people, training
Budget, lack of experience, lack of resource including manpower

Staff attitude and understanding of why GMP/GDP is necessary and important – human factors messaging by management (Sometimes inadvertent) can adversely impact quality. Automation has the potential to improve quality by removing variation and human intervention.

The drive for lower costs/higher profits in some companies and in some markets

Timelines, particularly in generic where it feels sometimes quality comes second to meeting timeliness.

Time restrictions, attitude of staff and complicated processes

Corporate values and reputation

Cost and speed to market drives many Pharma companies. This often results in minimization of proper development and product understanding

Operator Error

Aiming for impurity specification limits rather than striving hard to produce a purer product.

Poor Training, Lack of single point accountability.

Understanding and organizational culture.

40. Asked to consider whether there were additional constraints on the pharmaceutical industry that prevent innovation and use of best practice that had not already been considered, sixty-three percent claimed there were other constraints, thirty-seven claimed there were none in their experience.

41. They were then asked why they believed that there were or were no other constraints, the range of replies is shown in Table 10 below.

This data was also very broad in its scope, whilst cost and speed to market were slightly predominant responses there was also a number of respondents who alluded to conservative approaches to development and manufacturing being a constraint.

**Table 10: Responses from questionnaire respondents as to why they believed there were or were no other drivers constraining the pharmaceutical industry**

(Verbatim text)

Because I've witnessed it.

Inherent in complexity of raw materials and complexity of products into which they are formulated

Too many instances of job cutbacks, sacking experienced people and management claiming we can do the same (or more) with less resource ... "without impacting quality!"

In my experience staff respond well to appropriate training and support from management.

Management need to demonstrate their personal commitment to maintaining or improving product quality

Trying to make change places you in a position of difference and unless you are a very large company with sufficient backing, you are different and seem as not conforming.

If you understand the end user, the significance of quality will automatically come into play.

Complex supply chains hinder effective QP oversight. Problems remain hidden, commercial penalties prevent contractors from admitting openly errors and issues.

The cultures of an Organisation (set by Sr Management) underpins and determines the way the company does everything.

Frequently seen.

Experiences gained in inspecting various pharma companies.

I have seen many people just cut and pasted regulations into local SOPs and when asking for an explanation they are unable to clearly explain.

Pressure on CMO's, generics to manufacture with limited resource and new equipment.

Quality starts at the top. If management simply pays lip service to quality, it will never become embedded in the culture of an organisation.

Humans are prone to errors, which can occur for a wide number of reasons.

Fundamentally quality will be built into successful organisations as an established way of working.

A review of regulatory sanctions (483s, Warning Letters) and product recalls – type and source.

Experience in this industry both personally and from discussions with colleagues.

The people are not given time to complete things appropriately they rush, cut corners and try to meet all the deadlines that are demanded. Staff attitude also plays a part in that, if they want cut corners there's opportunity to do so. Processes that are overly complicated will lead to people making mistakes.

You can't codify everything.

I left a company due to their unwillingness to fix process to minimize potential harmful results. The product was launched but has since resulted in severe eye infections and blindness in patients. This did not happen

in the clinical trials. Several changes were made to the commercial process to make it less costly, and even though we knew they had bad implications to the product, the managers refused to delay the timeline. The fix process would have required a 1 year delay launch.

My experience. It is self-evident

These two items work in both a positive and negative way, I have seen companies get this very right and very wrong.

42. In starting to wrap up the questionnaire respondents were asked to consider what they felt, in their experience, was the most important driver for product innovation and quality.

- Unmet medical needs (42%)
- Company budgets and targets (18%)
- Improved side effect profile (16%)
- New chemical entities (12%)
- Improved patient compliance (9%)
- Other reason (3%)

43. When asked if country specific politics had a hindering effect on innovation thirty-five percent thought it did hinder, five percent claimed it helped innovation and the remaining respondents had no view on it.

44. When asked why they believed their response to the previous question the following information was offered, as shown in Table 11. The range of why they believed this was very broad, many expressed personal experience of political hindering combined with cost and also a significant country specific contribution as a hinderance.

**Table 11: Respondents beliefs on political interventions impact**

(Verbatim text)

Company Culture

Failure to understand the cost of poor quality

Regulatory agency expectations can restrict innovation,

Territory specific differences

Cost

Compliance > Quality

Regulatory conservatism, particularly in fast-track projects. Whereas EMA and FDA have indicated that fast track projects i.e., new antibiotic will be supported: they are in clinic with new dosing regimens

(Adaptive trials) but in CMC you never see submissions being supported with less QbD or less data.

In big pharma corporate culture often is at odds with an innovative environment. This can be due to disregarding local practices or decision-making procedures that may differ from site to site or territory to territory Harmonisation of approaches can lose the element of thinking “out of the box” which has resulted historically in new innovative products being developed.

High Profit margins in the US mean efficiency and effectiveness is not a priority. For example, Pharma manufacturing is mostly in batch mode which is primitive compared to most other industries.

Fear of the regulator’s reaction – often misplaced fear.

Cost – lowest bids tend to win business.

Business cost considerations

Inertia/bureaucracy in regulatory agencies to adapt to emerging trends

Complicated systems (e.g., PQS elements)

Fear of regulatory censure

Lack of understanding of risk

The regulatory processes for making changes to registered details.

The lack of harmonisation of approaches to variation across global regulatory authorities.

The Cost of changes e.g., Validation, filling variations etc.

Regulators not familiar with new technologies

Regulatory Barriers/constraints perceived or otherwise.

1 conservative culture in pharma and lack of interaction with other industries e.g., Pharma lags chemical industry in continuous processing development by about 30 years.

I am sure there are but haven’t thought about it in any detail

Pharma companies sometimes to not introduce something innovative as there is unknown and risk of not being accepted by health authorities due to lack of knowledge.

Corporate aversion to business risk

Corporate aversion to avoidable regulatory consultation

Egotism on the part of big pharma

Lack of qualified people in their positions

Lack of integrity of upper management

Innovation and best practice are determined by the likelihood of a financial return.

Budgetary, focused approaches.

I think the industry for too long has aligned Quality with caution and has held itself back from innovation

45. Respondents were asked if they agreed with the following statement:

“The pharmaceutical industry is too insular and is not sharing or learning best practice across international markets. Companies internalise processes and systems rather than proactively sharing common best practice to achieve the best possible product in all markets for the benefit of patients”

In reply twenty-eight percent fully agreed, fifty-eight percent partially agreed and fourteen percent did not agree with the statement.

46. All respondents were asked whether they were comfortable with products from all markets being interchangeable from a quality perspective, the majority (seventy-four percent) were not comfortable with all products.

47. Penultimately respondents were asked if they believed that national regulatory agencies are all of the same level of competence with regards to diligence to quality and efficacy assessments. Eighty-eight percent of respondents were not happy with agency parity in this regard, only eight percent were comfortable with five percent preferring not to answer.

48. Finally when asked, in a free text field, what they considered could be done to achieve a truly global pharmaceutical market, parity across all markets for product development, manufacturing and quality, various suggestions were proffered, these are shown in Table 12 below. These suggestions ranged from harmonisation of regulation (guidelines) as the predominant response, to international country cooperation leading to global standards and globalisation of approach.

**Table 12: Respondents views on what can be done to improve product quality in a global market**

For a Global Company innovation can be blocked by backward looking regulators
Some countries perceived as too difficult/ too expensive/ too slow
Meeting all the requirements constrains manufacturing sites, it created unmanageable costs and introductions inefficiencies.
ANVESA in Brazil is a prime example
Take the UK Tax breaks to stimulate innovation. FDA initiative on “Quality for the 21 <sup>st</sup> Century”
Certain agencies within countries help drive change and allow it to be a lower bar for change: for example, FDA in USA through the annual product review.
Poor Recognition of patent regulation by developing countries.
I have worked in areas were the poorest in the world do not have access to drugs because of price.
Innovation to drive costs down for the most venerable.
We need a truly global standard of GMPs applied with the same degree of diligence by all regulators to ensure equal quality products for all.
In multi-national companies the teams work together and try to rise above national politics.
Depending on country, may help or hinder.
Local Politics will always cause potential issues. Taking Medical devices as an example some commonly used materials are outlawed in some territories on the basis of politics alone.
I’ve had experience of a centralized EU application being blocked as a member state had a competitor product that would be damaging by commercialization
I believe unless Brexit is negotiated sensibly in terms of IMPs then it could be very detrimental on the supply of IMPs.
Additional costs due to requirements for local development, clinical trials and /or manufacturing.
An Innovative product may be not acceptable globally by all health authorities. Companies will not develop different products for different markets where possible and will fall back to most accepted.
US behaviour in the COVID-19 pandemic. US did not work with the EU to come up with a concerted, unified response and effort to this pandemic.

Organisations like ICH, ICMRA and PIC/S to drive standards

Global Legislation and guidance, harmonisation of inspection practices

Quality culture and global standards

More international standards and mutual recognition between government agencies to increase efficient use of global government resources.

Ensure all agencies are accredited to a united common body which would make all standards equivalent.

Good Adherence to the ICH or Global guidelines on product research/development/validation. Better audit trail in manufacturing/quality control.

The Gap between the wealthiest and the poorest countries is far too wide. Getting the large pharma countries to invest such poor regions and to seed manufacturing there.

Global Standards and global regulator. The EMA for example does not ensure consistent standards across the EU, the subcontracting of EMA work to individual member states regulatory bodies resulting in a very inconsistent application of standards. The EMA should directly employ the regulatory staff and the national regulatory bodies should be abolished.

Expanding ICH guidelines globally, but this would not solve things

A global Regulator

International Standards for regulators, true international code GMP (e.g., ICH?), more even costs across countries.

I am not sure, something like the MHRA accredited ICH, that each member has to pay a fee, the money in return will be used to monitor and inspect the countries involved on a regular basis, If a country fails, they are struck off the list and import testing will be required from that country will be required.... Which could be a nightmare for distributors, but that is always a risk for a non ICH Country. The failed country will then have to 're-gain' their membership by implementing corrective actions and maybe needs to pass x amount of import testing.

ICH of medical product quality (similar to ICH Q7)

A global regulatory authority to approve all products.

True harmonisation of regulations

Expanding the ICH process to incorporate more of the regulatory filling process.

A global healthcare regulatory body with the ability to align and harmonise standards across territories which in return will bring products made in those territories to an equivalent standard.

It is hard enough for the EU to all agree never mind globally but it would take a global organisation to set, guide and enforce standards which I cannot see happening.

One single international body governed by same regulations.

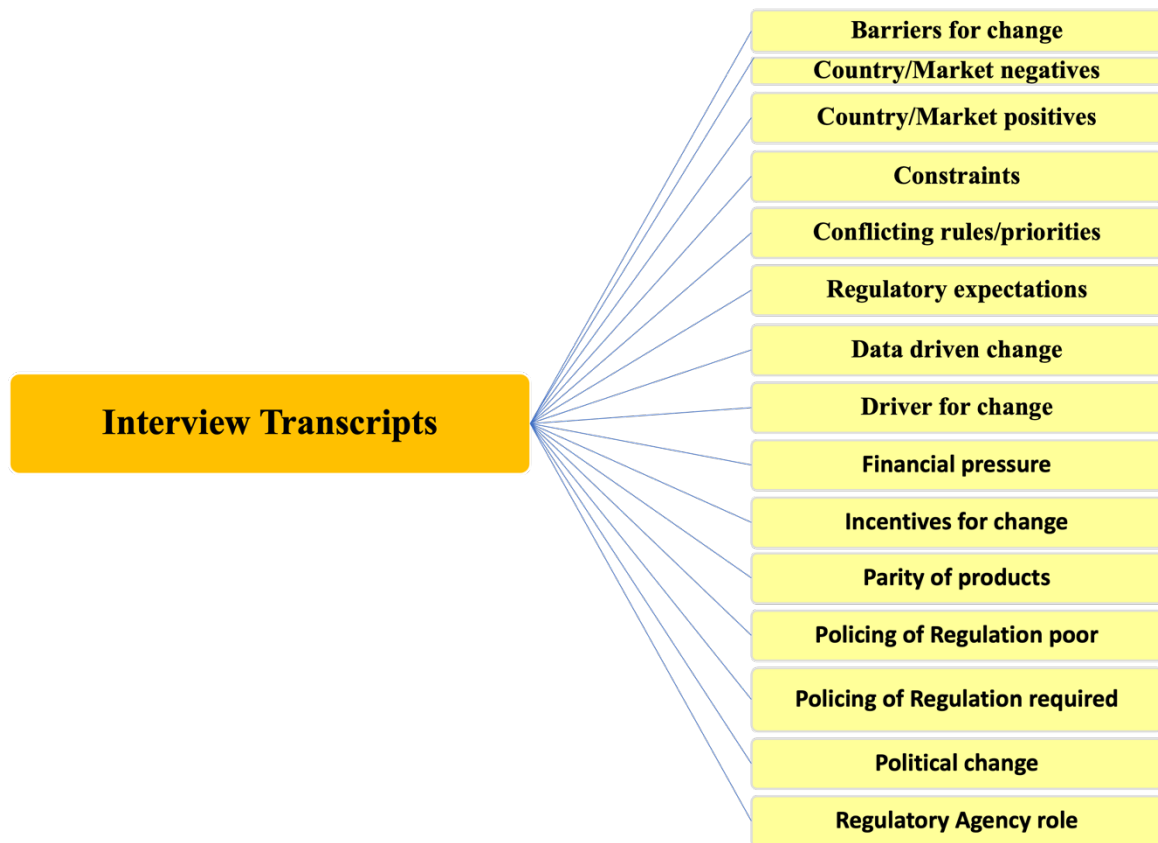
#### **4.2.4 Interview Results**

On completion of the interview component of this research the interview transcripts were entered into NVIVO (version 12) to facilitate researcher coding of the interview responses.

Construction of a coding manual was undertaken to facilitate a robust and defined framework to analyse the interview transcripts. Note that the transcripts in the appendix, where appropriate, were redacted to remove company/agency/country or personal information that may have inadvertently been shared as part of the interview dialogue, these include company and or drug product names as well as personally identifying information.

#### **The coding manual**

The generally adopted approach to thematic analysis was proposed by Braun and Clarke (2006). In this research the researcher, based upon the position of Braun and Clarke (2006), developed a deductive coding model. This deductive model was based on the existing literature already outlined in this thesis and the researcher's own professional practice. The determination of predefined codes and the implicit use of these deductive codes based on professional experience aids in the initial interpretation and context of the interview data, subsequent coding utilising emergent codes adds richness to the analysis. The devised coding manual is represented in Figures 37 and 38. Figure 37 demonstrates the inductive codes already highlighted in previous chapters of this research whilst Figure 39 shows the evolution of the coding process to include inductive codes determined during data review, transcription, and coding.



**Figure 37: Initial coding structure (coding manual I)**  
 (as derived from the mind maps described in chapter 3 of this thesis)

As previously discussed much of the initial codes were deductive codes however additional coding levels and merging of sub codes was enacted. After initial coding the formation of a second level of inductive codes was developed to complete the coding process. The merging of these deductive and inductive code is demonstrated in Figures 38 and 39 below:

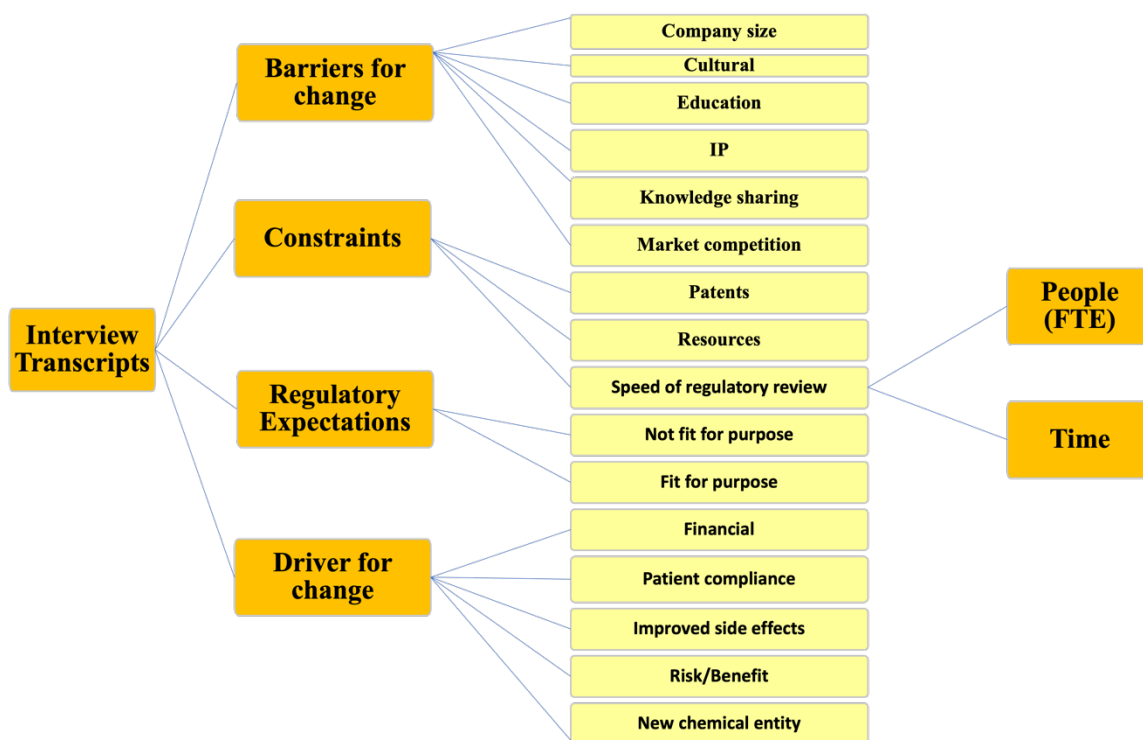


Figure 38: Sub-coding structure and inductive codes (coding manual II)

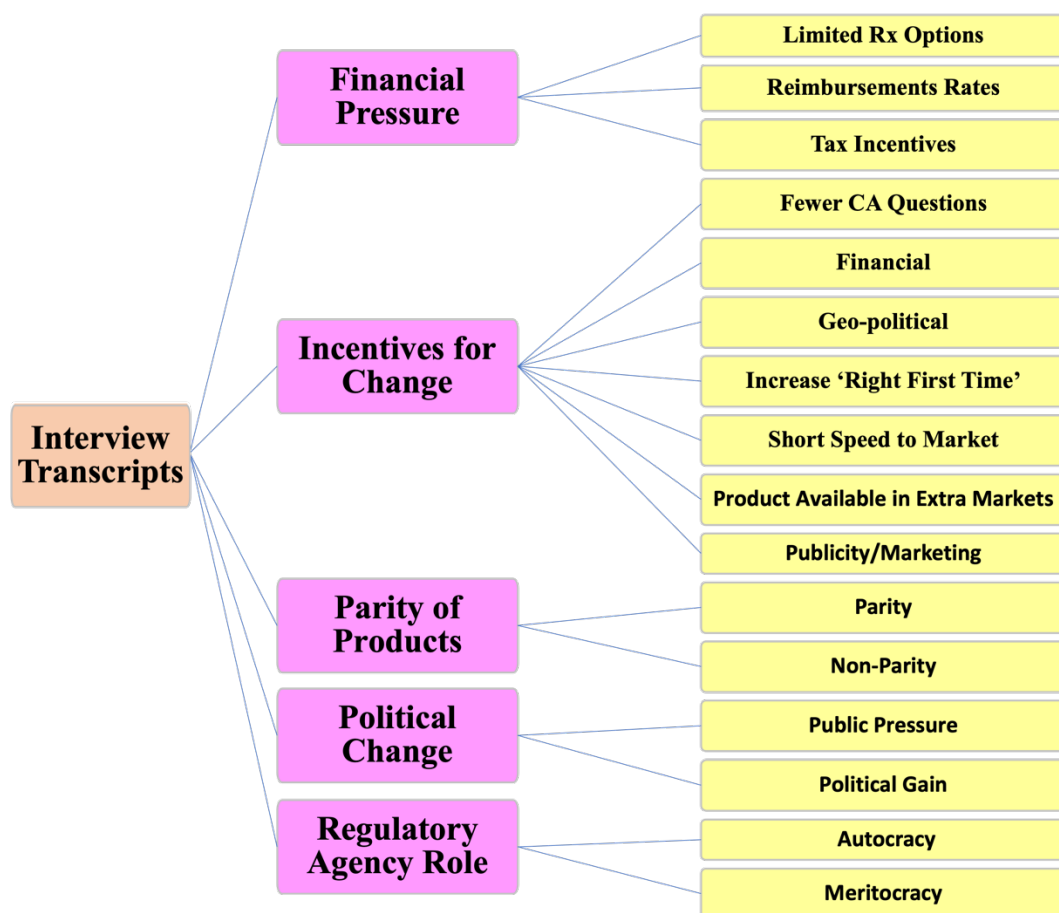


Figure 39: Sub-coding structure and inductive codes (coding manual III)

In addition to the above coding manual the researcher sought to assign a level of confidence and robustness to the coding process by determination of inter-coder reliability. The type of research undertaken, and the small sample size makes determination and reliability of Cohen's kappa an unreliable measure (Sun, 2011).

Reliability of the coding process was determined via the assessment of three sample transcripts by a similarly experienced pharmaceutical industry professional (the comparative coder) who had not previously been involved in this research and the use of a simple and effective percentage correlation measure as shown below:

% agreement = 
$$\frac{\text{The number of times the researcher and the comparative coder agreed}}{\text{The total number of times correlated coding could be possible}}$$

To determine this, three transcripts were each individually coded using the criteria defined by the research questions raised in this thesis and the coding manual as previous discussed.

Each transcript was coded by the researcher and a second coder independently and the results compared via NVivo summary data. The second coder was similarly experienced in the pharmaceutical industry and hence fully conversant with the requirements, structure, and nomenclature of the processes under discussion. The comparison measure used was the number of times a particular code was selected in a transcript rather than exact sentence correlation due to the variations in language use in each transcript.

In the above exercise initial correlation was a minimum of eighty-six percent across the coding under each code selected. To increase robustness a second review of coding of all transcripts was conducted by the researcher and the comparative coder. They independently verified another three transcripts and the second correlation matched a minimum of ninety-two percent correlation. This latter correlation was acceptable as a measure of robustness.

## Theme identification

The codes developed and utilised were combined into themes, the analysis and impact of these themes is detailed below.

### *Barriers to change*

When asked about barriers that inhibit or totally prevent positive change in product or processes this was one of the highest ranked codes utilised in responses, a large proportion of respondents felt there were significant barriers to change, and it became clear that, whilst there were often other contributing factors, the perceived existing of a barrier led to a more conservative and potentially local or parochial approach. Interviewees felt this was the highest contributing factor in poor product quality.

“I think in our industry we don't actually get close enough to the patient in terms of the real requirements”

“that's very bureaucratic, rather than thinking about the real purpose of things, you know, the patient focus, the science focus, rather than has this document got all the 'i's dotted and 't's crossed, then I think if we get too much of a sort of bureaucratic focus, we lose that science and patient risk element”

“a very different sort of playing field in terms of cultural acceptance, cultural norms of what people will and will not accept”

“You see very little in the way of umm science-based pro-active risk management. It is used largely to justify inappropriate behaviour, inappropriate results “

“there is a difference in terms of the culture between many different parts of the world and I'm not sure the regulators fully account for that culture and I think as a regulator from one part of the world visiting another part of the world, that culture can take some time to get used”

It is important to understand what these barriers are and if these are real or perceived and if so where do these barriers exist, on an industry, country, or company level. It is clear

that respondents felt that there were significant barriers to change either self-inflicted (within industry via procedure, resource or budgetary means) or imposed via regulators or political machinations.

### *Conflicts*

To understand interviewees perceptions of conflicts in legislative or cultural conflicts. These were some of the least utilised themes for the interview cohort. A very small group, both industry and regulators thought that conflicting rules or cultural conflicts led to a lack of quality

“what the medics do versus what the pharmaceutical industry does, there's a real gap with the communication there”

“a high turnover of staff and that's the biggest challenge we have because with that turnover of staff “

Cultural impact was an impacting factor in this and other categories both country cultural or company cultural. The latter culture being very hard to describe as a target rather it is the impact and working environment often instilled by senior and line management.

### *Constraints*

The interviewees were asked about their thoughts on constraints they had encountered in their respective roles, either resource (manpower FTE, financial (budgetary or cost of goods or expertise) or other constraints such as lack of facilities. Physical or legislative constraints was one of the least identified themes in responses.

“So, I think the review process definitely needs another look at, no doubt about that. In terms of inspections it's been amazing really that the agencies have not adopted some form of remote inspection sooner, you know, we've had the best part of nearly 15 16 months now haven't we with almost no enforcement action whatsoever and we all know, over the last 15 months or so, there's been a lot of staff turnover, there's been a lot of stress, there's been a lot of additional risks I'm sure “

“we have European Medicines Agency the level of equality between European states is very subjective. Sometimes it's a real challenge to convince one state to let you market a drug as being safe because another country has approved it and that interaction can be very hard to understand at least at face value”

“in big pharma there is a level of arrogance and a level of secrecy which is hindering product development or at least hinders development of the best possible product but then we have to remember this is a commercially sensitive environment. Small pharma is often more reactive because it doesn't have the resource sometimes doesn't even have the established procedures with which to develop products”

A large number of constraints were identified during the interviews, these can all be viewed independently and sometimes often linked or have a cascade impact. It must be recognised that constraints or an individual's perception of constraints is by its very nature a person perspective. In this research it is clear that commonality exists in the areas of variation in regulation and enforcement of pharmaceutical regulation.

### *Regulatory processes*

Many cited regulatory frameworks as an area of concern that hinders parity but also showed a few areas of positivity. They were questioned on the disparate processes they had personally dealt with, from both a regulator's and industry perspective. Such systems included US NDA and ANDA, UK MAA and EU centralised processes.

“I have seen much closer liaison with the U.S., European and other agencies going on and that seems to go on more and more, which is great.”

“the Western regulators fall down is thinking about what they're trying to do in a global context and what I mean about that is safety transcends what country or what continent you live in and the nature in which regulators apply safety to Canadian citizens, to American citizens, to European citizens, I just think is somewhat arbitrary,”

“I have a personal concern because we have brought in risk-based. My experience of it is it's inherently dangerous and I am, as an ex-regulator, having seen really poor practices in many places, I am worried about it”

“It was terrible and you know that's a company that we knew was dodgy as hell when it comes to it. That would always use the letter of the law rather than the spirit of the law to get out of things. “

“one of the strengths I believe of the European system, with the centrally authorised products is that the hi-tech products have to go through the centralised route and that allows Europe to pull on the expertise from around the whole of Europe so that they would give it to the / they would appoint the rapporteur and the co-rapporteur based on expertise”

This variation in regulatory processes is a key concern, the breadth of responses and the examples generated during this research clearly demonstrate that whilst some processes are indeed satisfactory and, in some cases, exemplary, others are sorely lacking. For the deficient process, these can be due to many reasons however the result is still a sub-standard product for patient usage.

#### *Data driven changes*

As a scientific community data is at the forefront of many decisions, certainly in a science-based industry such as pharmaceuticals. Interviewees were questioned on the role of data in triggering change or, in some cases, lack of data and subsequent impact. This was the least used category for impinging on quality.

“I would like it to be based upon data most pull science based upon process understanding and clear quality and efficacy goal. I joined the industry not just to make tablets I joined the industry to make medicines to help people. That's what drives me and if I can do anything to make that simpler make that process better that can only be a good thing. I think this also applies to the agencies certainly within Europe there's a lot of movement between industry professionals and agencies and vice versa and I can only be a good thing but we must concentrate on the science.”

“we should be addressing science; product knowledge and medicine we should be driven by data we should be driven by innovation we should not be held back by things gone before. One of my early mentors told me that even when we develop a drug and it fails is still not totally a failure because we learn from that and the next drug may improve

because of that. we have to develop knowledge base and technologies; this innovation is hugely important let's bring it back to the science!”

Given the researcher’s previous assertion that “data is at the forefront of many decisions”, that should now be described as “data *should be* at the forefront of many decisions”. It is evident from the interviewee pool that in many cases this is not the case. Most interviewees stated examples of poor decision making based on a lack of data or poor interpretation, this can and does have a major impact on patient safety.

### *Drivers for change*

When asked what drivers exist for support to a change of product or process, a positive change mentality, as opposed to change control, there were a moderate number of responses. The aim was to understand the separate and often invisible drivers that exist with industry and agencies.

“Developing a rating system to incentivise drug manufacturers to invest in quality management”

“we should be addressing science; product knowledge and medicine we should be driven by data we should be driven by innovation we should not be held back by things gone before.”

It should not be underestimated the impact that a driver for change can have, ranging from tax incentives to offset resource or budgetary constraints or an expedited product review leading to a potentially faster speed to market and hence a return on product investment and development. The impact of these will vary depending upon the company, country and even the product in question.

### *Financial measures*

When questioned on financial interests whether overall costs to develop and manufacture or the costs to sell and subsequent reimbursement in certain markets, this was reported as having a small impact across both the industry and regulatory groups interviewed.

“We expect them to do things for us, then they feel that they might feel they might lose the business for the next project or something like that, it's the fear of loss, of business, maybe.”

“the financial and the differential in the expertise and understanding,”

“particularly with generic products money is such a big driver,”

“Cost and also available resources. Sometimes there just isn't the sufficient number of people to review dossiers or to generate data”

Financial measures will always have an impact on product quality, whether in respect to the R&D process or the depth of understanding in product manufacture, such as the financial commitment required for a ‘Quality by Design’ product development and manufacturing approach. It is therefore not surprising that many individuals cited this. It was interesting to note that this response was not as widespread in the respondents pool as would be expected. The pharmaceutical industry, as discussed earlier in this thesis, is a for-profit business, all projects have budgets and a return is expected on sales, it was expected that this would be a response of a larger proportion of the interviewee pool.

### *Incentives*

This theme was to determine what incentives, if any, exist to support change and positive parity of drug products, this was one of the highest ranked themes after barriers for change and general parity considerations. Incentives can be tax (relief) based, guaranteed product reimbursement or purchase costs from national or managed health schemes or even just R&D investment subsidies.

“although the sponsor is always accountable and responsible for designing the development plan, it is a partnership with the regulators”

“I do feel that the smaller companies are more responsive they can move faster and be more engaged with requirements.”

“organisations with broad support, like PICS“

The use of incentives, as distinct from tax or cost incentives, previously mentioned, was an interesting category. Many cited regulations and non-financial or intangible benefits to companies. A few discussed the incalculable cost of failure and avoiding failure as an incentive. Whilst it is hard to model the cost of failure it does have a substantial cost implication, through lost sales, lost company image etc.

### *Parity*

The assessment of the perception of parity between domestic and international products was a more direct question as can be seen from the transcripts and majority responded that disparity did exist. Whilst a few felt that there was trust in the various agencies oversights that existed globally, this was a minority view and primarily held in non-western markets.

“once you start to get that breakdown in the culture and it's not just about the science it's actually about the way people interact”

“Japan is an interesting one isn't it, because very sophisticated healthcare systems, but they are a country, again, which is absolute about having Japanese citizens and being very wary about taking alien data”

“if my Procurement Department suddenly said I've got this API that I'm going to purchase from India or China, we would not want to receive that without doing some additional work to understand that facility, where it's coming from and its quality management system”

“there is a lot of history and just what we see data that's come out of agencies and problems in say challenges in countries like India and China”

“maybe some agencies aren't as rigorous as others in ensuring that they've got the appropriate subject matter expertise in place”

“Across the globe there's a lot of differences in interpretation of things, umm, you get countries like India where umm you know I'm assuming there are some rules but I don't think they are really effectively enforced at all”

“It would be nice to have equivalents within the E.U. alone wouldn't it”

“it's not a level playing field at all”

Parity was, not unexpectedly, an area that prompted most discussion. A very small minority felt parity was not an issue whilst the vast majority felt that there was no product parity across markets, between countries, not only with respect to quality of the products manufactured but also the level of detail and understanding that went into not only their development and the regulation but country competent authorities. The impact of non-parity has the potential for substantial impact on patient health and economics.

### *Regulatory policing*

The impact of regulatory enforcement was seen by many as an influencing factor and the majority perceived it as a required component of product quality.

“compliance versus science debate”

“I think they are largely reactive. I think there might be pockets of pro-activity but I think they are largely reactive”

“they are far more concerned about a GMP inspection from an E.U. or a U.S. inspector than they ever would be from one from their national competent authorities”

Regulatory policing was an emotive topic, the variation experienced by respondents from different country agencies was extreme. This variation can by its very nature allow sub-standard products to slip through the oversight net leading to impacts on patient safety. In addition, in these situations it allows for a claim that the regulatory agencies are not fulfilling their statutory duty of care with regards to pharmaceutical oversight.

### *Political change*

To assess the impact of political drivers both domestically and internationally on product quality interviewees were questioned on political influences on the pharmaceutical industry and if they were a hindrance or a positive influence.

“with anything related to healthcare there is always had political component because people use it to want to gain trust, they want to gain support, it’s a football against pushed and kicked around”

“there was obviously a dimension of politics, as there is with any organisation”

“there definitely is a political dimension that perhaps the protectionism”

“the political will to fund regulators is relatively limited”

“we live in a political world so it's only obvious the politics will impact regulation and policy and therefore impacts our work”

“sometimes politics has too much of a role and sometimes we also play it too safe”

“Politics always wins whether that's country politics or even internal company politics.”

“Politics trumps pragmatism” a useful and accurate description agreed by many respondents. Political interventions will have an impact via legislation or budgets, the role and level of influence that politics plays is almost impossible to assess or mitigate. It should be noted that it can have a significant impact.

### *Regulatory agency*

To gain an understanding from industry and regulator interviewees on the allocation of suitable resources respondents were questioned on the resourcing of agency roles. On questioning the role of the regulatory agencies, a small percentage, across both industry and agency experienced personal perceived they functioned as an autocracy rather than a meritocracy.

“you get somebody that's very bureaucratic, rather than thinking about the real purpose of things, you know, the patient focus, the science focus, rather than has this document got all the 'i's dotted and 't's crossed, then I think if we get too much of a sort of bureaucratic focus, we lose that science and patient risk element”

“more of a meritocracy in the established agencies in my experience”

“probably more autocratic in some of the / like in China,”

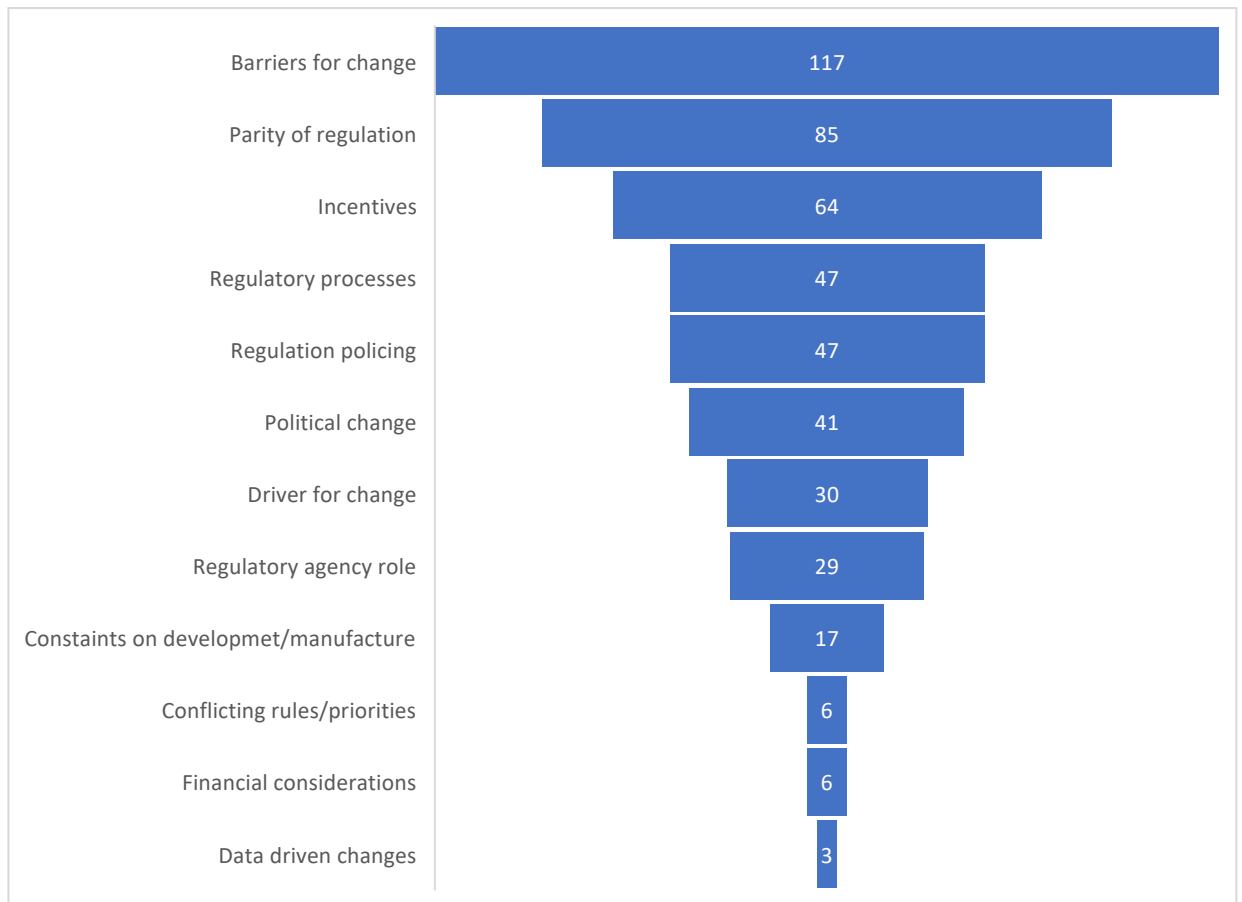
“I don't think they want to admit they don't know everything. And that is a worry”

“applies to industry and some / you know some inspectorates, so they just in case, we're just going to do this, do that, and before you know it that's the expectation and before you know it the whole of industry is doing it. The thing now with Grade D solid dose you know all of a sudden tablets have to be made in Grade D and / you know new facilities are a Grade D. I mean it's just ludicrous”

“the other thing / the showboating, I think there's a bit of showboating umm amongst some inspectors and also in the industry,”

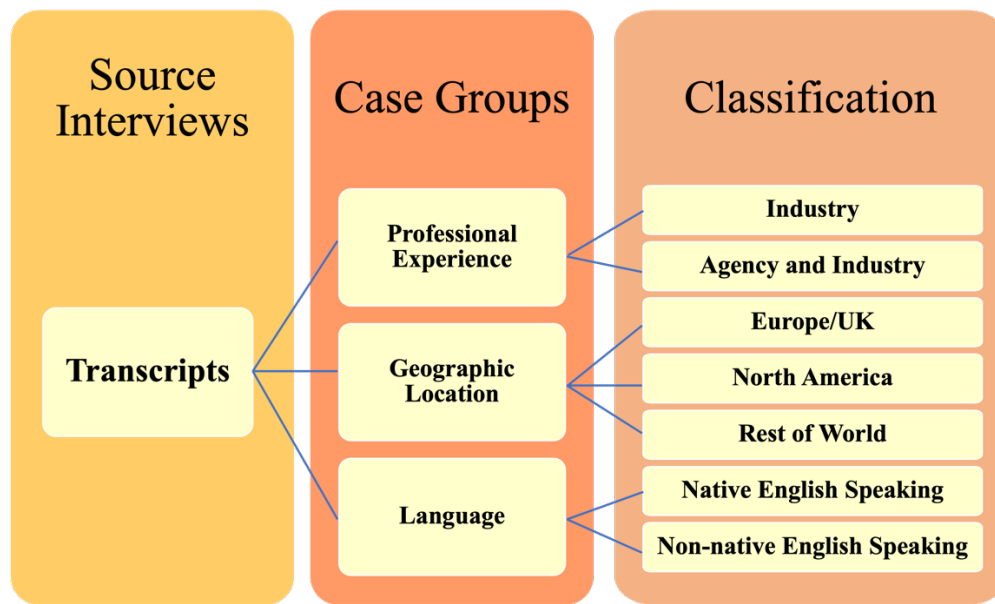
Regulatory agencies, again unsurprisingly, do have a significant impact on pharmaceutical quality, these come from either leadership, industry engagement or enforcement. All three often working in tandem to fulfil a pivotal role that accordingly to respondents is often not only challenging but, in some cases, poorly fulfilled, whether for resource, expertise or other reasons. The role of the agency is key to a successful high quality pharmaceutical product.

The rank order of major theme references is shown in Figure 40 below:



**Figure 40: Rank order of coding themes assigned to interview responses**

Before further analysis and correlation of data can be discussed it is worth outlining the process via which data received was categorised into general categories, or themes. This is shown in Figure 41.



**Figure 41: Composition of case classifications**

In summary, the assembly of deductive and inductive codes facilitates analysis of the interview transcripts, the assembly of codes and child codes is best summarised by the tree map in Figure 41 above.

### **Coding summary**

The summary of coding references and number of items coded can be seen in Table 5.

- After coding against the inductive and deductive codes it was apparent that some of the deductive codes were not utilised in analysis (not referenced by the interviewees in context) these were therefore removed from further processing. Table 13 shows the number of times a code was assigned against a transcription section during the completed coding process.

(Note: The full interview transcripts generated during this research and analysed in this thesis will not be made publicly available primarily due to the sensitive and identifiable nature of the research topic and subjects therein).

**Table 13: Frequency of utilised codes from interview coding**

<b>Primary Node/child node</b>	<b>Number of coding references*</b>
Barriers for change	3
Barriers for change/Company size	1
Barriers for change/Cultural	52
Barriers for change/Education and existing expertise	22
Barriers for change/Intellectual property	5
Barriers for change/Knowledge sharing	26
Barriers for change/Market competition	8
Conflicting rules and priorities	6
Constraints	2
Constraints/Resources	5
Constraints/Resources/People (FTE)	6
Constraints/Resources/Time	1
Constraints/Speed of current review process	3
Current Regulatory processes	0
Current Regulatory processes/Fit for purpose	14
Current Regulatory processes/Not fit for purpose	33
DATA driven change	3
Driver for change	7
Driver for change/Financial	12
Driver for change/Improved patient compliance	3
Driver for change/Improved side effect profile	2
Driver for change/Medical need (risk-benefit)	4
Driver for change/New active moiety	2
Financial pressure	5
Financial pressure/Reimbursement rates	1

<b>Primary Node/child node</b>	<b>Number of coding references*</b>
Incentives for change	12
Incentives for change/Fewer regulatory questions	17
Incentives for change/Financial	6
Incentives for change/Geo-political	6
Incentives for change/Improved chance of first time approval	11
Incentives for change/Improved speed to market	7
Incentives for change/Product available in external markets	5
Parity	23
Parity/Non parity	53
Parity/Parity	9
Policing bad	16
Policing required	31
Political change	7
Political change/Political pressure induced by public pressure	15
Political change/Pressure for political gain	19
Regulatory agency role	5
Regulatory agency role/Autocracy	13
Regulatory agency role/Meritocracy	11

The interviews were coded and repeat coded until no additional code identification was possible from the texts. Examples text and code assignment are shown in Table 14.

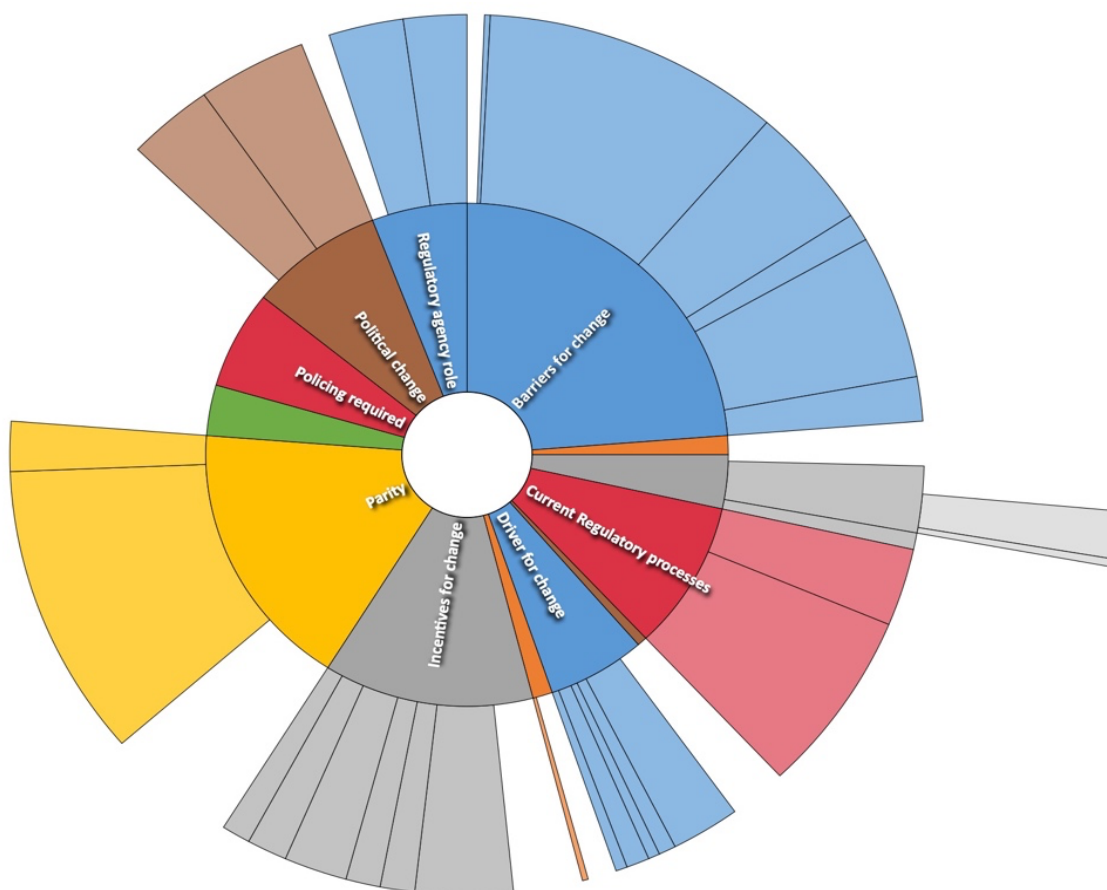
**Table 14: Illustrative coding texts**

Node (code)	Test example
Driver for change	<p>“Equality of standards in quality, equality of oversights and equality in approach and structure how we develop products why redeveloped products what we developed for us for how prescription medicines how they compare to the regulation for say homoeopathic medicines how do I compare to in the Far East to traditional medicinal approaches these are all areas that I think all lead to equality of systems and I think we need to be very firm on that.”</p> <p>“So, I think from that perspective we do need to have a proper look at the way licenses get approved, so that you know, therapeutics going to address unmet medical needs are approved, the licenses are reviewed and approved far quicker than what they have done before.”</p>
Political change	<p>“Politics always wins whether that's country politics or even internal company politics.”</p> <p>“there's no transparency there's nothing clear about how they review and assess documents you are not allowed to challenge the reviewer to ask why they came to that conclusion in many agencies and in the ones where you are allowed to do it completely so scared to be answering one problem creating another it's very hard to understand what the main drivers are. Like I said it's not transparent.”</p> <p>“I also think it's different in different countries and to try and tease those apart is very difficult. As I said before politics always has a role to play and as you mentioned patient safety when patient safety is questioned or at-risk politics even comes to four even more”</p>
Political change continued	<p>“we live in a political world so it's only obvious the politics will impact regulation and policy and therefore impacts our work”</p> <p>“sometimes politics has too much of a role and sometimes we also play it too safe”</p>
Incentive for change	<p>“A single quality standard! One standard for countries for all agencies can only be beneficial.”</p> <p>“the quality / patient”</p> <p>“A single point of registration with a single process”</p>

Node (code)	Test example
Policing regulation	<p>“I think they are largely reactive. I think there might be pockets of pro-activity, but I think they are largely reactive”</p> <p>“Across the globe there's a lot of differences in interpretation of things, umm, you get countries like India where umm you know I'm assuming there are some rules, but I don't think they are really effectively enforced at all,”</p> <p>“they are far more concerned about a GMP inspection from an E.U. or a U.S. inspector than they ever would be from one from their national competent authorities.”</p> <p>“the Brazilians are a case in point. They first started doing overseas inspections must be nearly 20 years ago now and very much you felt it was kind of GMP tourism at the time”</p>
Parity	<p>“No, I / no, my experience would suggest it's very variable and I think there's / for me there's far too much variability in the rigor of application standards across Europe and umm you know I have been saying for a number of years now I think it's time for the sort of EMA to man-up and have a European-wide inspection you know team of inspectors as opposed to each member state has its own and you get too much variants”</p> <p>“I think it is weaker and I think the overseas sites certainly are under less threat of an unannounced inspection”</p>
Party continued	<p>“there is a difference in terms of the culture between many different parts of the world and I'm not sure the regulators fully account for that culture and I think as a regulator from one part of the world visiting another part of the world, that culture can take some time to get used”</p>
Policing inspections	<p>“routine regular inspections keep management on top of the compliance aspects of work. And when you let it go it is always going to fall to the bottom of the list of customer service, profit, quality, those three are compliance, not quality”</p> <p>“they are really trying to use it to minimise the amount of work that they have to do, rather than appropriately targeted necessarily.”</p> <p>“I am concerned about the focus to risk-based and the weaknesses that that will engender.”</p> <p>“It was terrible, and you know that's a company that we knew was dodgy as hell when it comes to it. That would always use the letter of the law rather than the spirit of the law to get out of things.”</p>

Node (code)	Test example
Agency role	<p>“From an agency perspective yes, they are very risk averse, very conservative in nature and they have political masters it would be I to think otherwise”</p> <p>“I think it’s a mixture. I’ve really seen some good ones you could engage with, and I’ve also had issues with some who are a lot more difficult to work with however that said that’s probably not the agency that’s the individual concerned so I think in in some cases their autocracy in some cases they are meritocracy”</p>
Financial pressure	<p>always a drive to reduce cost of goods, but in my experience, certainly in development, if a product gets in to a clinical trial, well, if a molecule is shown to have efficacy and has the promise of being develop-able (that’s not a word but I’ve made it up) if there’s a chance of getting that to market, for the most part, in my experience, money is always found to do work</p> <p>“We expect them to do things for us, then they feel that they might feel they might lose the business for the next project or something like that, it’s the fear of loss, of business, maybe”</p> <p>“the financial and the differential in the expertise and understanding”</p> <p>“I think you have to change the finance model for regulators”</p>
Data driven change	<p>“You see very little in the way of umm science-based pro-active risk management. It is used largely to justify inappropriate behavior, inappropriate results and from a regulatory point of view you only have to look at financial services and what risk-based oversight did to that, to know that this is a terrible mistake.”</p> <p>“I think efficacy and safety are totally different items as far as agencies in India and other countries are concerned. In many markets is purely cost based. Wouldn’t it be nice to see I science and data-based assessment and understanding”</p>
Constraints	<p>“it comes from the leadership, yes.”</p>

On completion of the above coding the summary of highest ranked codes is displayed below in Figure 42.



**Figure 42 Sunburst representation of the top level codes extracted from Nvivo 12  
(for Mac)**

All redacted transcripts are contained in appendices of this thesis.

### *4.3 Published Regulatory Agency Data*

This section contains summary data from published regulatory agencies such as FDA and MHRA and also consolidated data reports from Organisation for Economic Co-operation and Development aligned countries (OECD). OECD, whilst not a single unified regulatory body does not track and trend key pharmaceutical data across member states however by inclusion of the European Union, Australia, the United Kingdom, and the United States of America in this thesis this covers a substantial part of the OECD community. OECD at the time of this thesis is a group of thirty-eight member countries detailed in Table 15 below:

**Table 15: OECD Membership countries**

Australia	Finland	Spain	Slovakia
Austria	France	South Korea	Slovenia
Belgium	Germany	Latvia	Spain
Canada	Greece	Lithuania	Sweden
Chile	Hungary	Mexico	Switzerland
Colombia	Iceland	Netherlands	Turkey
Costa Rica	Ireland	New Zealand	United Kingdom
Czech Republic	Israel	Norway	United States of America
Denmark	Italy	Poland	
Estonia	Japan	Portugal	

All regulatory agencies collect similar data and yet report in differing formats, the pertinent parts of each data set are summarised in this section, full reports from each agency are referenced accordingly.

#### **4.3.1 United States Food and Drug Administration**

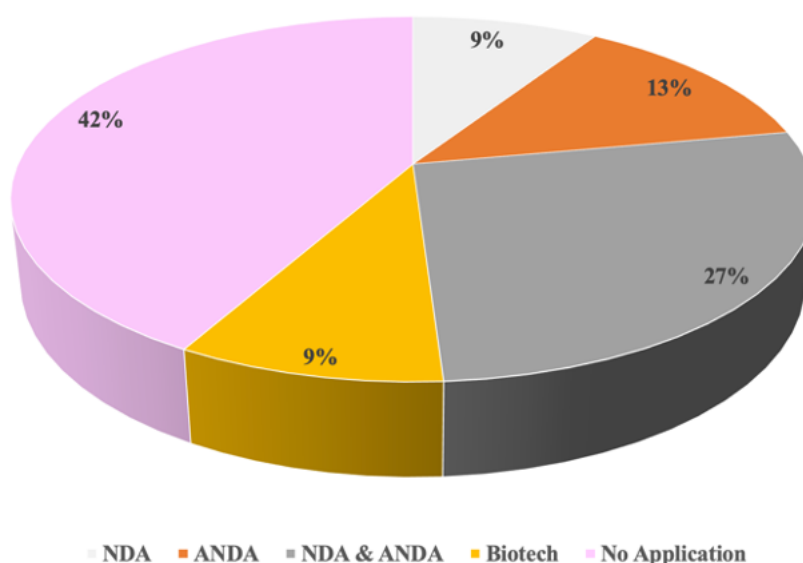
The United States Food and Drug Association Centre for Drug Evaluation and Research publish annual quality metrics for each fiscal year (these run from October to September, the most recent at time of this review was 1<sup>st</sup> October 2019 to 30<sup>th</sup> September 2020), a summary of the highlights for the past three published periods is summarised below, a reference to each source report is also provided.

##### **Covering the period 2018-2019**

Report on the state of pharmaceutical quality, Centre For Drug Evaluation and Research office of Pharmaceutical Quality [online] Available at:

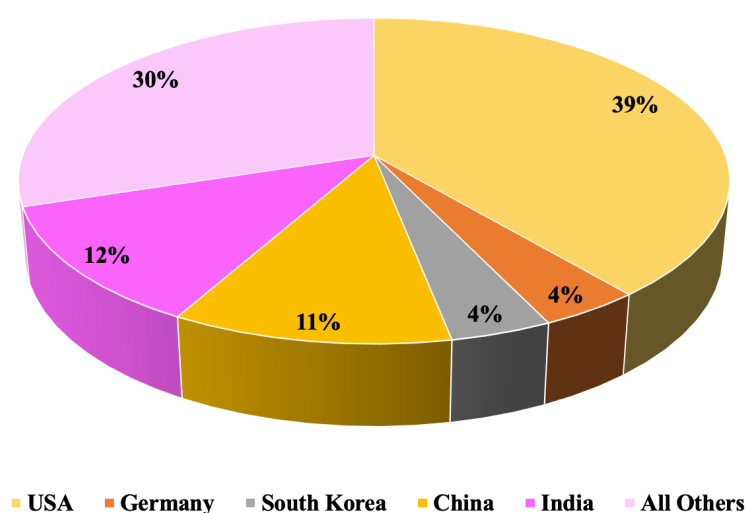
<https://www.fda.gov/media/125001/download> <[Accessed 19 September 2021].

The FDA identified all drug manufacturing sites that manufacture pharmaceutical drug products for the United States of America market by marketing application type. This is summarised below:



**Figure 43: FDA site manufacturing divisions by regulatory application type**  
 (data extracted from Report on the state of pharmaceutical quality, Centre For Drug Evaluation and Research office of Pharmaceutical Quality [online] Available at: <https://www.fda.gov/media/125001/download> <[Accessed 19 September 2021].

In addition, the identification of all US bound drug manufacturing sites was presented by country as shown in Figure 44.

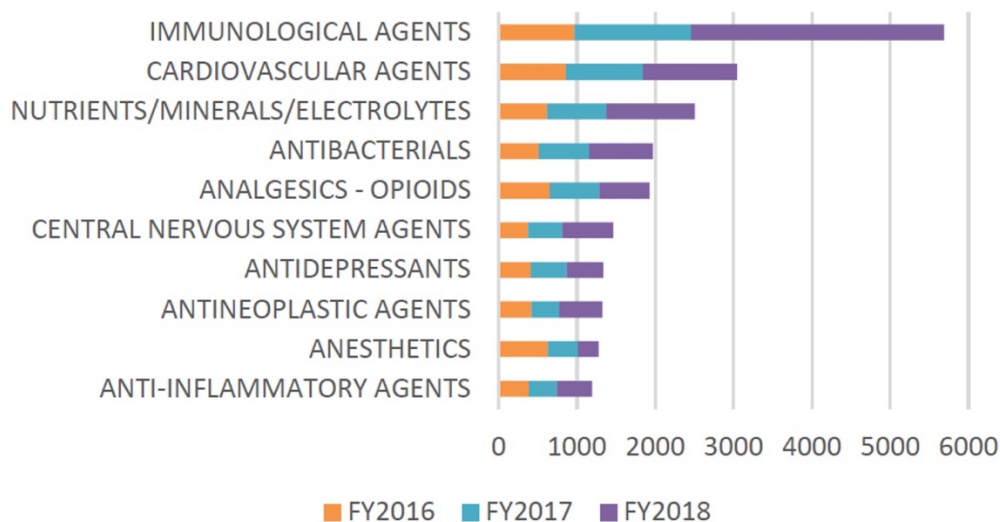


**Figure 44: Originating country of USA bound drug products this reporting period**  
 (data extracted from Report on the state of pharmaceutical quality, Centre For Drug Evaluation and Research office of Pharmaceutical Quality [online] Available at: <https://www.fda.gov/media/125001/download> <[Accessed 19 September 2021].

It was noted that for this reporting period there was a wide range of countries inspected by FDA for drug product quality assurance, the division by country was as follows~:

1. United States of America (47%)
2. India (13%)
3. China (9%)
4. Germany (4%)
5. Canada (3%)
6. Japan (3%)
7. Italy (2%)
8. France (2%)
9. South Korea (2%)
10. Switzerland (2%)
11. All other countries combined (12%)

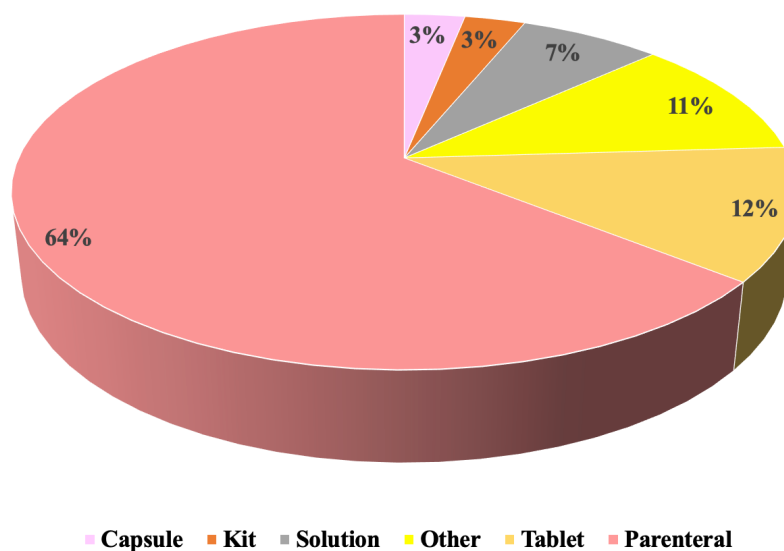
The FDA also classified all pharmaceutical product quality defect reports into therapeutic areas for those reporting period, this is shown Figure 45 reproduced from the FDA report. This demonstrates the breadth of products included.



**Figure 45: FDA identified drug product quality defects by therapeutical area for reporting period 2016 to 2018**

(reproduced from Report on the state of pharmaceutical quality, Centre For Drug Evaluation and Research)

FDA summarised the shortage of dosage form by drug product type and this is shown in Figure 46 below.



**Figure 46: FDA site manufacturing divisions by regulatory application type**  
 (data extracted from Report on the state of pharmaceutical quality, Centre For Drug Evaluation and Research office of Pharmaceutical Quality [online] Available at: <https://www.fda.gov/media/125001/download> <[Accessed 19 September 2021].

### **Covering the period 2019-2020**

Report on the state of pharmaceutical quality, Centre For Drug Evaluation and Research office of Pharmaceutical Quality [online] Available at:

<https://www.fdanews.com/ext/resources/files/2020/06-10-20->

[StatePharmaceuticalQualityReport.pdf?1591804532](#) > [Accessed 19 September 2021]

[Accessed 19 September 2021].

FDA acknowledged that at the time of this review seventy-two percent of sites manufacturing active ingredients for drug products destined for USA consumers are manufactured outside the USA.

The following key aspects of the breakdown of manufacturer demographics was presented in the FDA report:

- In this reporting year the Food and Drug administration identified an 8.6% decrease in the number of drug manufacturing sites that were listed as approved by the agency in the previous reporting period. 4676 sites were reported in this reporting year it was only 4273 this is also allowing for the fact today was in addition of 382 newly registered sites filed with the agency.
- It was noted the majority of this change was due to a reclassification of products moving from registered pharmaceutical products to requiring no registration at all for example moving to over the counter drugs and homoeopathic products.
- There was a commentary that the FDA believes that this decrease is indicative of an industry change to increasing consolidation, coupled with the FDA being more accurate in how it records the number of sites registered.
- In fiscal year 2019 42% of sites were located in the United States of America 20% of registered sites were located within the European Union, 12% of registered sites in India and 8% of registered pharmaceutical manufacturing sites in China.
- The FDA investigators performed 1258 drug quality surveillance inspections in fiscal year 2019 this was a decrease from the 1346 conducted in the previous fiscal year. It is worth noting here there is apparently no external drivers for this decrease such as it was seen in the years 2019-2020 due to the global pandemic

that arose at that time

- Within the European Union member countries 109 drug manufacturing site inspections were carried out on behalf of the FDA by European Union competent authority members under the existing mutual recognition agreement that was in place at that time.
  - A report from the office of pharmaceutical quality acknowledges that it was able to decrease by 25% its own European Union inspections due to the presence of this mutual recognition agreement.
- Within those inspections carried out by European Union competent authority investigators on behalf of the FDA 58% of inspections were for facilities located outside the United States of America.
- On reviewing the consolidated inspections conducted by European Union inspectors on behalf of FDA and also FDA staff inspectors the overall coverage of total global manufacturing sites listed in 2019 resulted in only 32% of sites being inspected.
  - Anecdotally it was noted that in the period 2017 to 2019 the FDA was able to decrease inspections within the US and the European Union and increase inspection efforts in India China and the rest of the world although no definitive justification was given for this switch of resources.
- The FDA utilised a 10 point inspection score as part of their site review process and in 2019 the overall score was 7.4 with average scores in European and United States of America based sites slightly higher than the rest of the world at 7.7 and 7.6. Scores in other parts of the world were significantly lower with 7.0 for manufacturing sites located within China and 6.8 for sites in Latin America and India.
  - Using the same 10 point score on review of homoeopathic products and over the counter products as a comparison recorded 6.5 and 6.2 respectively
  - Three quality categories accounted for 58% of all quality deficient observations and these are subdivided into: records and reports 23.9%, product controls 19.3% equipment efficiency is 14.8%, personnel 13.6%

and production in process controls at 12.4%

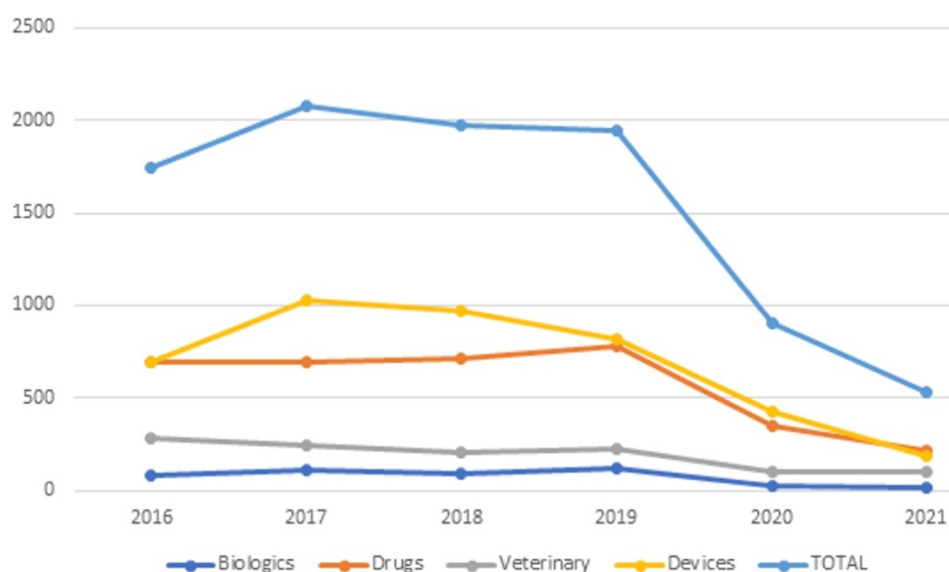
- Most common citations for deficiencies fell under the following federal regulations
  - 21 CFR 211.192 documentation
  - 21 CFR 211.22 quality control
  - 21 CFR 211.160 sound scientific judgement
- The lag time for FDA issuance of warning letters to manufacturers was decreased from one year to six months duration with manufacturers (domestic and international) receiving inspection reports within ninety days of inspection for the latest period.
- This reporting period identified a large increase in defects associated with cardiovascular and gastrointestinal drugs primarily associated with the increased surveillance on the presence and generation of nitrosamines in ranitidine and angiotensin II blockers. This was an emerging issue not based primarily on product defects but rather driven by the increase in knowledge and application of nitrosamine potential impacts on health.

In summary FDA conducted around 2,400 new drug applications and abbreviated new drug applications for small molecule pharmaceuticals and biologics in addition to 2000 investigative new drug meetings with the pharmaceutical industry.

### **Covering the period 2020-2021**

Extracted from report: Report on the state of pharmaceutical quality, Centre For Drug Evaluation and Research office of Pharmaceutical Quality [online] Available at: <<https://www.fda.gov/media/135046/download> [Accessed 19 September 2021].

The summary of observations for each regulated medicine type is shown in Figure 47 reproduced below.



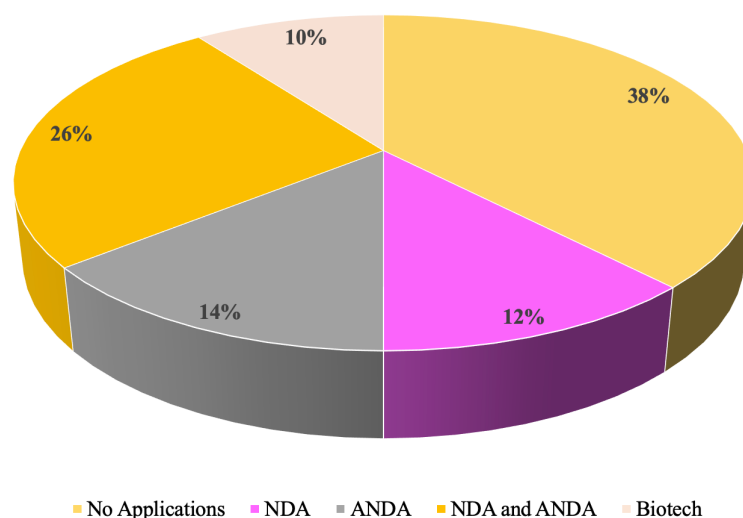
**Figure 47: FDA observations data for regulated medicines**

(extracted from Report on the state of pharmaceutical quality, Centre For Drug Evaluation and Research office of Pharmaceutical Quality [online] Available at: <https://www.fda.gov/media/135046/download> [Accessed 19 September 2021].

The data is also sub-divided across the manufacturing sites based upon the type of submission they have presented to the agency, the categories are:

- NDA (New Drug Application)
- NDA (Abbreviated New Drug Application)
- NDA & ANDA
- Biotech (Biological)

The division of sites is shown in Figure 48 below.



**Figure 48: FDA site manufacturing divisions by regulatory application type**  
(extracted from Report on the state of pharmaceutical quality, Centre For Drug Evaluation and Research office of Pharmaceutical Quality [online] Available at: <<https://www.fda.gov/media/135046/download>> [Accessed 19 September 2021]).

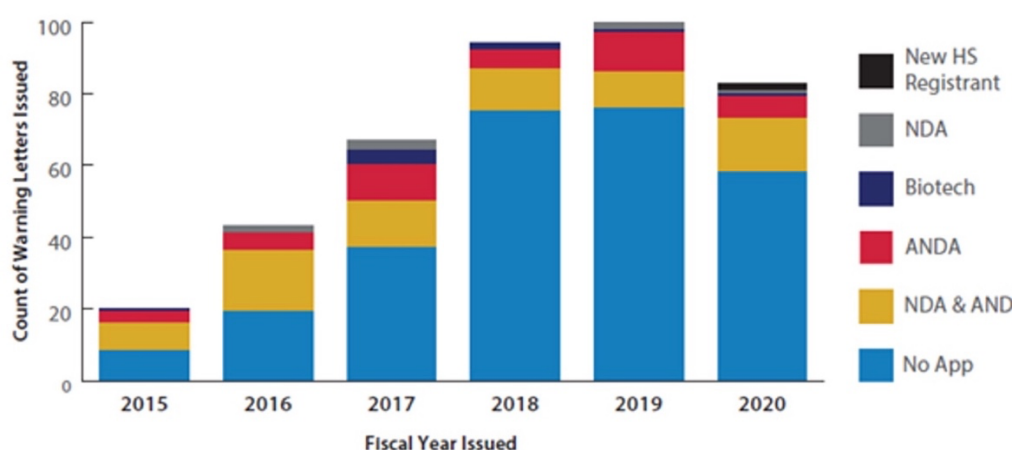
Table 16 below shows the rate of change in key pharmaceutical manufacturing sites supplying the USA market at that time in the fiscal year summary and their respective rates of site changes (for example the number of new sites and the number who are no longer licensed).

**Table 16: Rate of change in manufacturing site inventory approved by FDA**

Country	Sites in fiscal year 2020	Sites maintained	Sites removed	Sites added	% removed	% added	% net change
USA	1780	1644	286	136	-16.1%	7.6%	-8.4%
India	502	457	53	45	-10.6%	9.0%	-1.6%
China	367	334	70	33	-19.1%	9.0%	-10.1%
Germany	160	150	26	10	-16.3%	6.3%	-10.0%
Canada	146	137	19	9	-13.0%	6.2%	-6.8%
All others	1266	1152	170	114	-13.4%	9.0%	-4.4%
TOTAL	4421	3874	624	347	-14.8%	8.2%	-6.6%

Unique in these fiscal year reports is that this reporting period also covers the first part of the COVID-19 pandemic. The pandemic had huge restrictions on travel and therefore on site regulatory agency oversight. The FDA completed five hundred and sixty-two audits during this period the vast majority were prior to the COVID-19 outbreak.

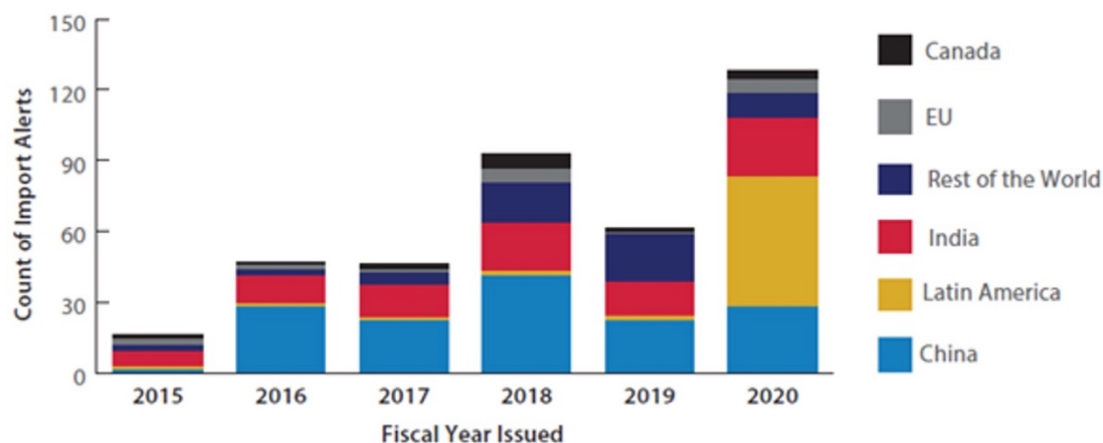
When compared to 2018-2019 the number of agency deficiency warning letters during the fiscal year 2019-2020 was slightly lower than the same periods in 2018 and 2019. They were over four times higher than those issued in 2015 as demonstrated by the image below extracted from the FDA report.



**Figure 49: FDA deficiency warning letters issuance rates 2015 to 2020**

(extracted from report on the state of pharmaceutical quality, Centre For Drug Evaluation and Research office of Pharmaceutical Quality [online]) Available at: <https://www.fda.gov/media/135046/download> [Accessed 19 September 2021].

The number of imported product alerts rose dramatically in this period primarily due to hand sanitiser from Mexico. Of the fifty-five sites that had import alerts in this period in Latin America eighty-nine percent were for hand sanitiser (registered as a pharmaceutical) from Mexico and caused FDA to issue a countrywide product alert. The breakdown of imported product alerts is highlighted by the extracted Figure in Figure 50 below.

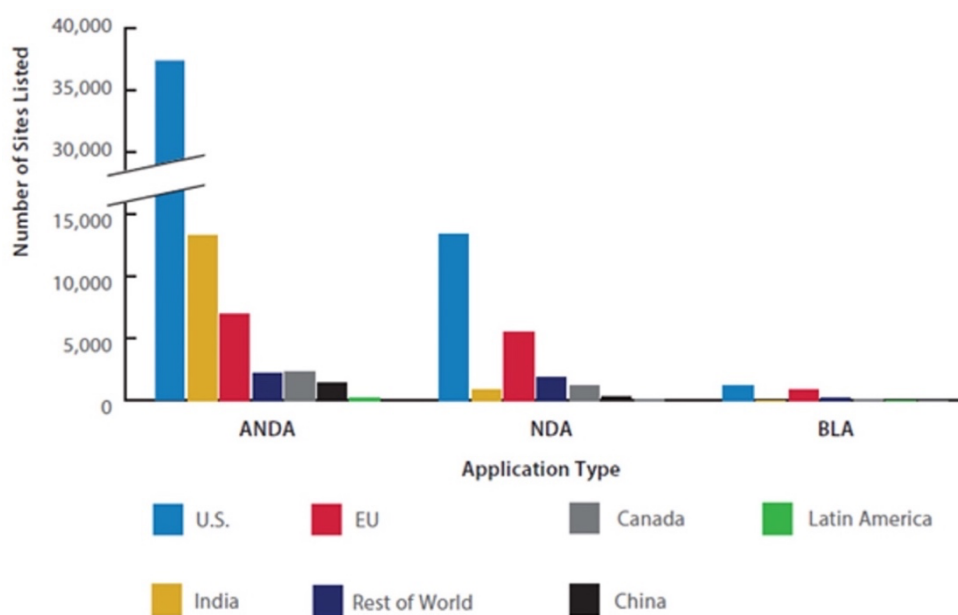


**Figure 50: FDA issued import alerts for 2019-2020**

(extracted from report on the state of pharmaceutical quality, Centre For Drug Evaluation and Research office of Pharmaceutical Quality [online] Available at: <https://www.fda.gov/media/135046/download> [Accessed 19 September 2021].)

In this reporting period there were more USA located (domestic) manufacturing sites referenced in drug product applications than previously. In addition, the number of applications per site is two files whereas sites in India reference sixteen point five applications. Therefore, the Indian sites have more products under a common QMS as opposed to the lower USA domestic ratio for this period.

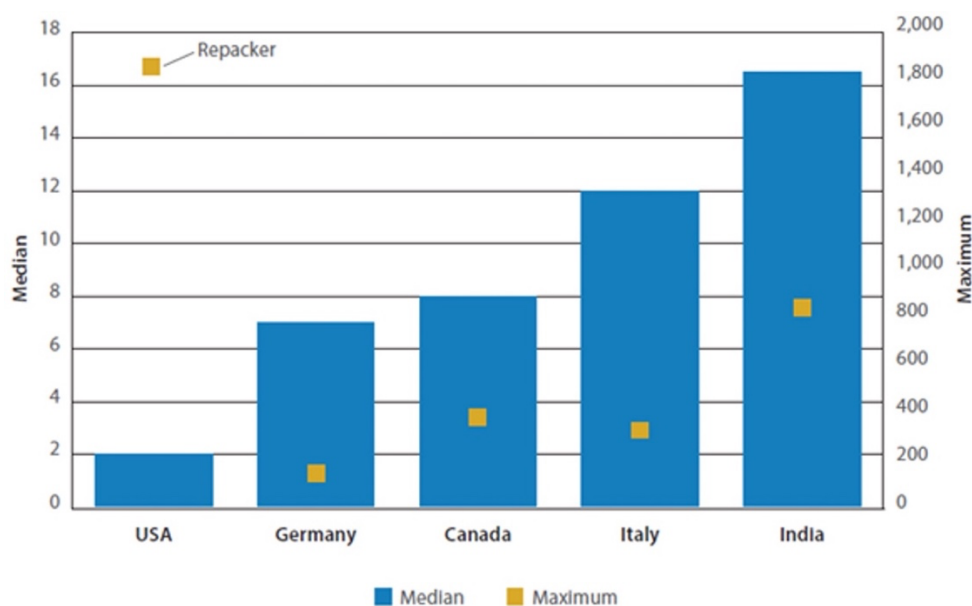
A further analysis of sites listed in regulatory applications is shown in Figure 51 below.



**Figure 51: Number of sites listed in a regulatory submission by region in 2019-2020**

(extracted from report on the state of pharmaceutical quality, Centre For Drug Evaluation and Research office of Pharmaceutical Quality [online] Available at: <https://www.fda.gov/media/135046/download> [Accessed 19 September 2021].)

The agency also broke down the number of times a site was referenced per application and this rate demographic is extracted below in Figure 52.



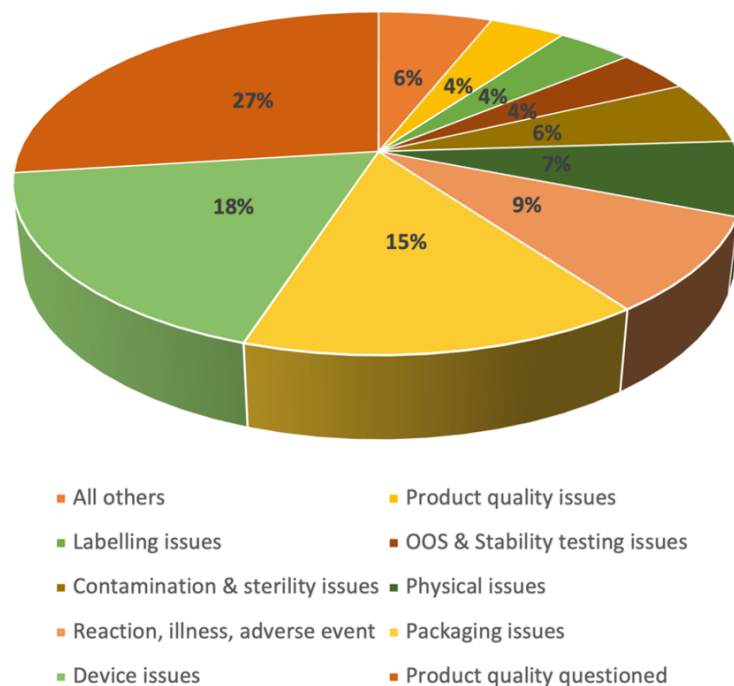
**Figure 52: Number of sites listed in a regulatory submission by country in 2019-2020**

(extracted from report on the state of pharmaceutical quality, Centre For Drug Evaluation and Research office of Pharmaceutical Quality [online] Available at: <https://www.fda.gov/media/135046/download> [Accessed 19 September 2021].)

Specifically, regarding drug quality causes, and discounting any further root cause analysis activities, the FDA identified that three defect categories accounted for sixty percent of defects. These were:

1. Overall product quality questionable
2. Device issues
3. Packaging issues (does not distinguish between primary or secondary packaging)

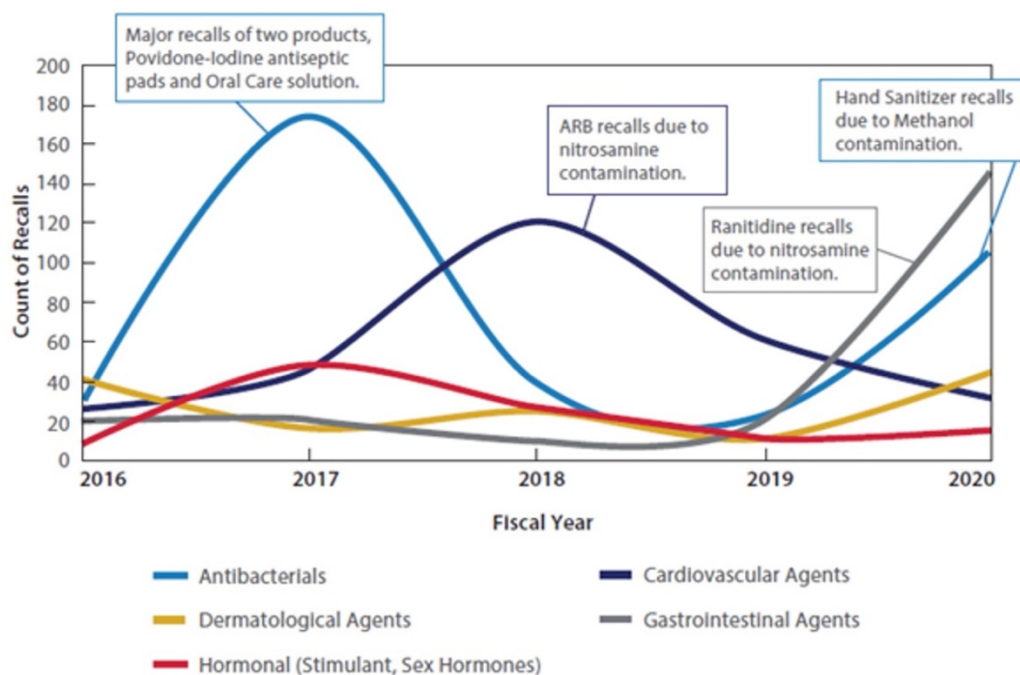
The data summary is extracted from the report and reproduced below in Figure 53.



**Figure 53: FDA identified top defect types in year 2019-2020**

(extracted from report on the state of pharmaceutical quality, Centre For Drug Evaluation and Research office of Pharmaceutical Quality [online] Available at: <https://www.fda.gov/media/135046/download> [Accessed 19 September 2021].)

In summary for this fiscal year the five most recalled products (by product type) are shown in Figure 54 extracted and reproduced below, the recalls being initiated by product contamination (Nitrosamine and Methanol contamination).



**Figure 54: The top five FDA recalled products by volume, expressed as product types, in 2019-2020**

(extracted from report on the state of pharmaceutical quality, Centre For Drug Evaluation and Research office of Pharmaceutical Quality [online] Available at: <<https://www.fda.gov/media/135046/download>> [Accessed 19 September 2021].)

In addition to the above the top ten FDA inspection findings for this fiscal period were not greatly different from previous recent reporting periods are details as:

1. QC Unit failed to meet its responsibilities
2. Failure to adequately investigate OOS results and other deviations
3. Absence of written procedures for production and process control
4. Lack of adequate controls in laboratories
5. Cleaning, maintenance, and sanitising of equipment
6. Lack of controls for authorisation of personnel to access master production and control records
7. Use of equipment that was not appropriately designed, of adequate size or suitably located
8. Failure to establish, write and follow procedures for preventing microbiological

contamination of sterile drug products

9. Failure to routinely calibrate, inspect and check equipment

### **4.3.2 United Kingdom Medicines and Healthcare Products Regulatory Agency**

#### **Covering the period 2015 to 2016**

Data extracted from extracted from MHRA Report on GMP Inspection Deficiency Data Trend 2015 [online] Available at:

<[https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/582841/MHRA\\_GMP\\_Inspection\\_Deficiency\\_Data\\_Trending\\_2015.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/582841/MHRA_GMP_Inspection_Deficiency_Data_Trending_2015.pdf)> [Accessed 01 September 2021].

In addition, defect data was taken from the following report. <MHRA GDP Inspection Deficiency Data 2016 [online] Available at <

[https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/667494/GDP\\_2016\\_Deficiency\\_data.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/667494/GDP_2016_Deficiency_data.pdf)> [Accessed 01 September 2021]

- During this. The UK agency conducted a total of 303 inspections
  - UK inspections (223)
  - Overseas inspections (79)

The MHRA use a classification system of critical, major and others during this time period. These classifications can be summarised as:

#### *Critical findings*

A critical finding is assessed as a significant departure from current European & FDA cGMP expectations. It may result in harm to patients and would result in regulatory action by an agency. A series of related Major deficiencies may be grouped together to form a Critical finding.

### *Major findings*

A significant finding but progressively less severe than a Critical finding. A departure from cGMP expectations however will not immediately result in harm and is easily detected from the product stream. A series of related Minor findings may be grouped together to form a Major finding.

### *Other findings*

Another finding is a minor infraction of cGMP expectations however the severity is mitigated by existing processes and procedures.

The rank order of deficiency classifications is shown in Table 17 below:

**Table 17: Rank order of cGMP deficiencies identified by MHRA in 2015-2016**

<b>Rank order</b>	<b>Classification</b>	<b>Critical</b>	<b>Major</b>	<b>Others</b>
1	Quality System	27	293	555
2	Complaints and Recall	10	25	94
3	Documentation	9	138	372
4	Quality Control	4	26	136
5	Computerised Systems	1	21	19
6	Production	0	161	357
7	Premises and Equipment	0	107	311
8	Validation	0	93	128
9	Personnel	0	41	95
10	Materials Management	0	19	134

MHRA in addition to the above analysis also provided a group of illustrative examples for each deficiency observed in these categories in this reporting period, the source reports wide ranging examples all cross linked to chapters in the Eudralex guideline to GMP manufacture key summary examples are detailed below:

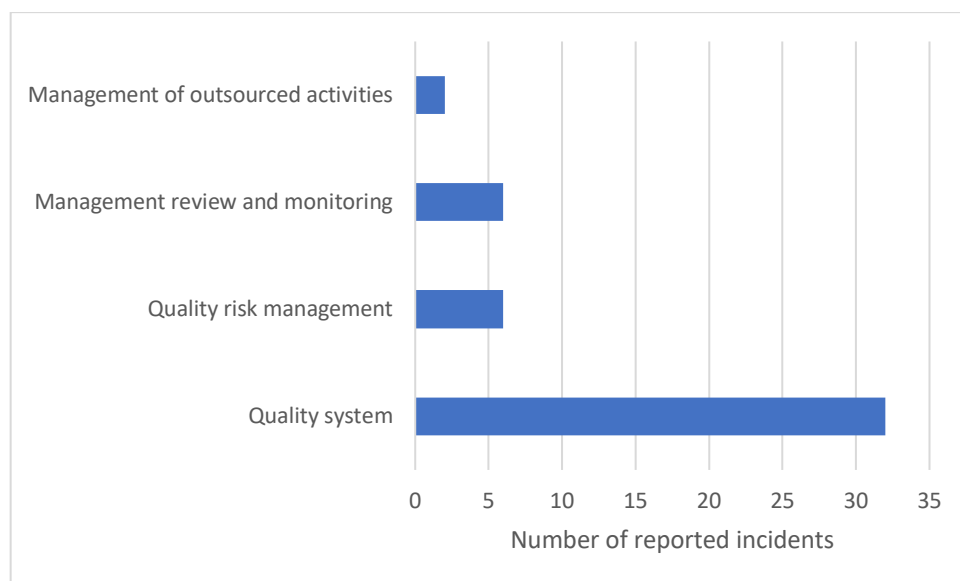
- Chapter One
  - Lack of training
  - Poor change control
  - Insufficient documentation
  - Poor CAPA control and effectiveness assessments
- Chapter Two
  - Insufficient training in key roles such as QP and Managing Director
- Chapter Three
  - Facility degradation
  - Appropriate facility areas being used for key activities
  - Poor QC sampling control
- Chapter Four
  - Poor good documentation practice
  - Procedures not adhered to
  - Primary records destroyed
- Chapter Five
  - Cross contamination control was poor or non-existent
  - Lack of validation on multiple systems
  - Poor control of materials
- Chapter Six
  - Poor laboratory control and failure to follow GLP expectations
- Chapter Seven
  - Quality and Technical Agreements were either incomplete or not existent
  - Poor control of contracts
- Chapter Eight
  - Recall records were incomplete

- Failure to follow root cause analysis
- Poor complaints procedure
- Non robust product impact assessments
- Chapter Nine
  - Audit training non-existent or incomplete internal audit program

Further detailed deficiencies were listed for Eudralex annexes 1 to 19 and these are detailed in the full report references above.

The deficiencies for Good Distribution Practice are summarised below, these are important to assess as they also have a critical impact on product efficacy and safety.

Deficiencies in Quality Management (GDP Chapter one) is shown in Figure 55 below:



**Figure 55: MHRA identified GDP deficiencies in 2016**

(extracted from <MHRA GDP Inspection Deficiency Data 2016 [online] Available at <[https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/667494/GDP\\_2016\\_Deficiency\\_data.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/667494/GDP_2016_Deficiency_data.pdf)> [Accessed 01 September 2021])

The summary top GDP deficiencies for this period were:

1. Quality Systems (22%)
2. Transportation (13%)
3. Responsible Person (12%)
4. Supplier Qualification (10%)
5. Equipment (9%)
6. Documentation (9%)
7. Temperature Control (9%)
8. Storage (5%)
9. Customer Qualification (5%)

### **Covering the period 2018**

Data available as raw excel data file. Available at:

<[https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/845170/2018\\_Deficiency\\_Data.xlsx](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/845170/2018_Deficiency_Data.xlsx)> [Accessed 01 September 2021].

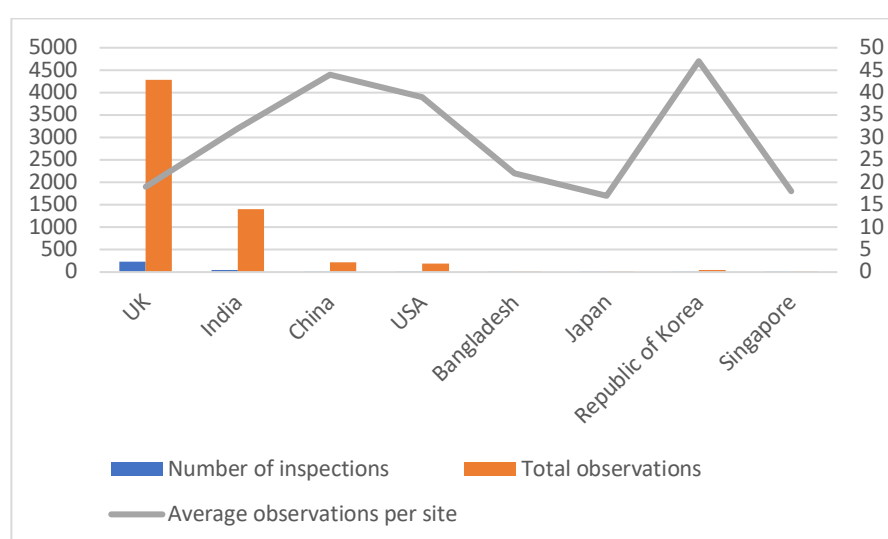
In summary the highlights from the 2018 GMP Deficiency data is as follows:

- MHRA conducted 286 inspections globally in 2018
- Of these inspections 228 were in the UK and 44 were based in India, 15 were in the rest of the world
- 6209 cGMP deficiencies were noted in these inspections, an average of 22 deficiencies per inspection ranging from critical to others classification
- Of the all the countries audited:
  - Korea had the highest incident rate of deficiencies at 47 deficiencies per inspection
  - Japan had the lowest incident rate at 17 deficiencies
  - However only one site was audited at each country therefore this data is not a robust representation of compliance

Table 18 shows the countries inspected and the frequency of deficiencies. Figure 56 graphically represented the countries inspected considering the number of inspections and the frequency of deficiencies.

**Table 18: Rank order of cGMP deficiencies identified by MHRA in 2015-2016**

Country	Number of inspections	Total observations	Average observations per site
UK	228	4287	19
India	44	1408	32
China	5	219	44
USA	5	191	39
Bangladesh	1	22	22
Japan	1	17	17
Republic of Korea	1	47	47
Singapore	1	18	18



**Figure 56: Countries inspected by MHRA in 2018 and the number of sites inspected with the frequency of deficiencies noted**

On analysis of the actual deficiencies identified, these are broken down as the following:

- Critical deficiencies 17
- Major deficiencies 432
- The remaining were minor cGMP infractions. However, they were till recorded as observations
- The number of critical deficiencies per inspection is an incidence of 0.1
- The number of major deficiencies per inspection is an incidence of 1.5

The top seven deficiencies categories when noted against specific EU GMP requirements (cross referenced to specific chapters are the following:

1. Chapter 1 Pharmaceutical Quality System
2. Chapter 3 Premises and equipment
3. Chapter 4 Documentation
4. Chapter 5 Production
5. Chapter 6 Quality Control
6. Annex 1 Manufacture of sterile medicinal products
7. Annex 15 Qualification and validation

Table 19 below shows the top 10 deficiency categories and incidence.

**Table 19: Top 10 MHRA identified deficient categories**

<b>Rank order</b>	<b>EU-GMP Reference Chapter or Annex</b>	<b>Title</b>	<b>Number of Deficiencies</b>
1	Chapter 1	Pharmaceutical Quality System	1519
2	Chapter 4	Documentation	757
3	Chapter 5	Production	655
4	Annex 15	Qualification & Validation	611
5	Chapter 3	Premises & Equipment	567
6	Annex 1	Manufacture of Sterile Medicinal Products	448
7	Chapter 6	Quality Control	349
8	Chapter 8	Complaint, Quality Defect & Product Recall	285
9	Chapter 7	Outsources Activities	256
10	Chapter 2	Personnel	219

In summary for this reporting period:

MHRA reported 1519 deficiencies related to the quality management system, nearly a quarter of the overall deficiencies noted by the agency.

### **Covering the period 2019**

Data extracted from extracted from MHRA Report on GMP Inspection Deficiency Data Trend 2015 [online] Available at:

<[https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/927085/2019\\_Deficiency\\_Data\\_Top\\_10\\_s.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/927085/2019_Deficiency_Data_Top_10_s.pdf)

> [Accessed 01 September 2021].

Additional raw data was sourced from the following raw data sets:

1. Data extracted from excel file MHRA Report on GMP Inspection Deficiency Data Trend 2018 [online] Available at: <  
[https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/845170/2018\\_Deficiency\\_Data.xlsx](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/845170/2018_Deficiency_Data.xlsx)> [Accessed 01 September 2021].
2. Data extracted from excel file MHRA Report on GMP Inspection Deficiency Data Trend 2019 [online] Available at: <  
[https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/927085/2019\\_Deficiency\\_Data\\_Top\\_10\\_s.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/927085/2019_Deficiency_Data_Top_10_s.pdf)> [Accessed 01 September 2021].

These latter raw data sets, whilst too large to be reproduced here, are referenced as they are used in the overall analysis and discussion in this thesis and copies are appended on an attached CD.

In summary, the MHRA data from 2019-2020 highlight the following trends:

- MHRA conducted a total of 258 inspections, this was a marginal reduction compared to the previous reporting year.
  - The top ten identified cGMP deficiencies noted by the agency were as follows:
1. Quality Management Systems were deficient in the vast majority of cases. This has been the top deficiency for 2019-202 and the previous five years. It was also noted that due to COVID-19 travel restrictions at the latter part of this reporting period the vast majority of inspections were UK based.
  2. cGMP documentation deficiencies were noted as the second most frequent deficiency. Although good documentation practice is part of an overall QMS it is also a standalone GMP requirement and hence is reported separately. This was also number two rated in the period 2018-2019.
  3. Issues in production, whilst a vague catch all category this primarily relates to the issues encountered during routine production that were handled incorrectly and

could not be associated with any other quality deficiency category. This was also number three rated in the past three years.

4. Process and product related validation, this was also highlighted as deficient in previous years.
5. Deficient premises and equipment were the fifth ranked deficiency observed by the MHRA.
6. Sterility assurance of parenteral and sterile products
7. Complaints and recalls effectiveness or polices were deficient
8. Quality Control Laboratory role was in adequate
9. Computerised systems and data integrity
10. Vendor selection, qualification, and oversight

Further to the above top deficiencies the following points are noted from the data.

- In 2019-2020 the majority (>90%) of inspections were conducted in UK and India
- Other overseas audits were reduced compared to previous years, also the number of UK on-sites audits were reduced, both primarily due to COVID-19 restrictions and risk assessed auditor visits. (Auditor visits were included as essential travel. Each visit was risk assessment before being deemed appropriate hence the reduction in numbers.
- There was an increase in virtual/live streamed audits during this period, this was a new approach for the agency.

MHRA assessed that there was an increased threat from counterfeit medicines and medical devices and also an increase in poor quality drug products and medical devices failing quality standards due to inadequate sourcing, manufacture and/or testing due to personnel and material shortages due to the COVID-19 pandemic and increased product demand.

### 4.3.3 The Australian Therapeutic Goods Administration

#### Covering the period 2019-2020

As with the previous reported agencies, FDA and MHRA, the TGA inspect their own domestic manufacturers and international manufacturers, the pertinent 2019-2020 domestic manufacturers data is summarised below in Table 20.

**Table 20: Number of domestic TGA inspections and results of inspection 2018-2020**

<b>TGA Inspections</b>	<b>2018-2019</b>	<b>2019-2020</b>
Number of TGA Inspections	195	163
Acceptable compliance	152 (78%)	99 (60%)
Marginal acceptance	29 (15%)	32 (20%)
Inacceptable compliance	8 (4%)	5 (3%)
Number still under assessment at end of reporting period	6 (3%)	27 (17%)

The TGA use a slightly different reporting structure to the previous agencies, although the overall aim remains the same. TGA inspection criteria are:

- Compliance Level A1 (Good), few deficiencies were found, all minor in impact.
- Compliance Level A2 (Satisfactory), A few major deficiencies (<5) and a larger number of minor deficiencies were observed, no critical)
- Compliance Level A3 (Basic). a large number, >5 and <10 minor deficiencies were found and no critical.
- Not Rated (Unacceptable), one or more critical deficiencies and/or many major deficiencies were observed.

For the reporting period 2019 -2020 the following highlights were extracted from the domestic data and reports:

- Domestic Australian inspections conducted by TGA were reduced on previous

years primarily due to the COVID-19 pandemic and resultant travel restrictions. In addition, the TGA took 6 weeks to generate a domestic virtual audit platform to allow them to conduct remote or hybrid audits.

- Increases and decreases overall in compliance categories for any given year are a response to the reinspection timeframes for manufacturers due in a certain year. Repeat inspections are based upon the previous classification on a risk-based basis. The data for this period showed that 60% of manufacturers had a compliance rating of satisfactory (A1 and A2 on the TGA scale), 3% had an unacceptable compliance

**Table 21: Number of international TGA inspections and results of inspection 2018-2020**

<b>TGA Inspections</b>	<b>2018-2019</b>	<b>2019-2020</b>
Number of TGA Inspections	75	51
Acceptable compliance	64 (85%)	31 (61%)
Marginal acceptance	11 (15%)	13 (25%)
Unacceptable compliance	0 (0%)	3 (6%)
Still under assessment at end of reporting period	0 (0%)	4 (8%)

For the reporting period 2019 -2020 the following highlights were extracted from the domestic data and reports:

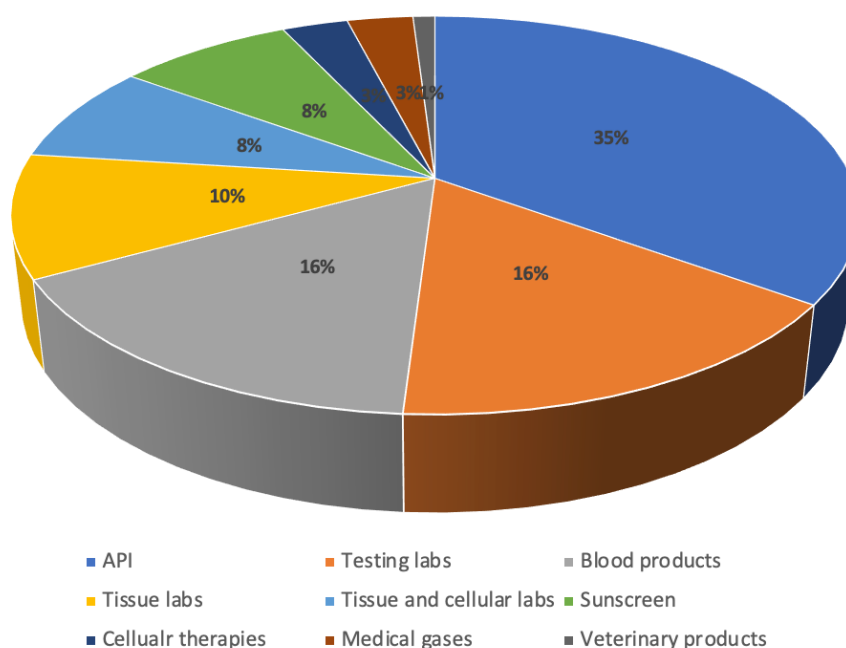
- In this reporting period the last international inspection was conducted in March 2020.
- In a similar approach to the domestic inspections, increases and decreases overall in compliance categories for any given year are a response to the reinspection timeframes for manufacturers due in a certain year. Repeat inspections are based upon the previous classification on a risk-based basis. The data for this period showed that 61% of manufacturers had a compliance rating of satisfactory (A1 and A2 on the TGA scale), 6% had an unacceptable compliance.

An analysis on the countries audited and their respective status is shown in Table 22.

The TGA, as with other agencies cover more than drug products and it is worth highlighting the scope and division of work, they undertake within the same resource pool. Figure 57 shows the breadth of inspections undertaken by TGA.

**Table 22: Number of international TGA inspections and results of inspection 2018-2020**

Regulatory status (compliance)	Country	Type of product manufactured
Satisfactory	USA India China France	Sterile drug products Non-sterile drug products
Marginal	USA India Canada South Africa	Sterile drug products Non-sterile drug products Biologicals (large molecules)
Unacceptable	USA India	Sterile drug products Non-sterile drug products



**Figure 57: Types of manufacturers inspected by TGA in 2019-2020**

Key points from this data are as follows:

- Drug products constituted the majority of TGA inspection in this period, 60.8%)
- Drug substances were 13.5%
- Blood testing laboratories were 6.3%
- The remaining inspection were for other testing laboratories, sunscreen, cellular therapies, and human tissue analysis

This breakdown is represented graphically in Figure 69.

From the data published by TGA it can be determined what the most common GMP deficiencies are, and these are shown in table 23.

**Table 23: Most common TGA identified GMP deficiencies in 2019-2020**

<b>GMP Category</b>	<b>Identified deficiency</b>
Deviations	Poor investigations Poor root cause analysis Poor corrective actions (CAPA) plans and effectiveness checks
Computerised systems	Audit trails in sufficient Data back-up and restore deficient QMS electronic systems not validated Access and procedural control deficiencies
Validation	Poor cleaning qualification and validation Poor process validation Insufficient equipment qualification

## TGA Recalls

This section summarises the recalls processed by TGA during the 2019 to 2020 period. In 2019-2020 TGA coordinated 790 regulated product recalls, this was an increase from the 768 in the previous reporting period.

Considering these recalls by product type the breakdown can be seen in table 24.

**Table 24: Most common TGA identified GMP deficiencies in 2019-2020**

Product type	Recalls in 2018-2019	Recalls in 2019-2020
Drug products	41	60
Medical devices	596	614
Blood products	102	100
Biologicals	29	16
TOTAL	768	790

Key points from this data are as follows:

- The total number of drug recalls rose by 3%
- The number of recalls for drug products only rose by 46%
  - This was primarily driven by ranitidine and newly detected nitrosamine contamination, a point referenced previously in this chapter for similar agency findings
- Recalls for biologicals decreased, these were similarly related to a particular product type

Table 25 highlights the reasons for recall actions on drug products.

**Table 25: Most common TGA identified GMP deficiencies in 2019-2020**

<b>Recall justification</b>	<b>2018-2019</b>	<b>2019-2020</b>
Adverse patient reactions	2 (5%)	1 (2%)
Foreign contamination	5 (12%)	0 (0%)
Illegal supply chain	2 (5%)	2 (3%)
Impurities and unexpected degradation	4 (10%)	13 (22%)
Labelling and packaging	14 (34%)	18 (30%)
Microbiological issues	2 (5%)	4 (7%)
pH	0 (0%)	0 (0%)
Potency/assay	1 (2%)	4 (7%)
Sterility assurance	0 (0%)	7 (12%)
Other <sup>1</sup>	11 (27%)	11 (18%)
<b>TOTAL</b>	<b>41 (100%)</b>	<b>60 (100%)</b>

<sup>1</sup> Other includes dissolution, physical attributes, variability, bioavailability, efficacy, and general non-compliance issues

There appears to be no impact of COVID-19 on the recall process and timings and this is consistent with previous reporting periods.

## CHAPTER 5: DISCUSSION

As with all research involving individuals, the information collected is interpretative. The individuals questioned sharing their personal truth, furthermore on collation and analysis of the data garnered the researcher will likewise exhibit contextual interpretative analysis. In summary the use of a purposeful sampling design is a well-recognised and effective use of limited resources, utilising individuals who are skilled or knowledgeable in the phenomenon under investigation (Patton, 2002), (Creswell, Plano, Clark, 2011), (Bernard 2002), in this case pharmaceutical science professionals who have worked in industry and/or regulatory agencies.

It is also important to consider a post-positivistic stance. Knowledge, even the researcher's experience, and the combined experiences of the population questioned, can be and should be challenged. It is certainly not unchallengeable. In this chapter the data gained from this qualitative exercise will be rooted in the quantitative data to provide an interpretation of holistic reality.

The completed questionnaire and interview data was subjected to thematic analysis, also known as interpretative phenomenological analysis, a process as described by Miller, Chan and Farmer (2018). This chapter discusses the data, emergent trends and the importance of the data captured in relation to the research question and sub question posed at the start of this thesis. To commence this discussion, it is important to understand the regulatory framework within which the pharmaceutical industry resides and the views and findings of key regulatory agencies. To that purpose we will discuss the findings of the United States of America Food and Drug Administration (FDA), the United Kingdom Medicines and Healthcare Regulatory Agency (MHRA) and Australia's Therapeutic Goods Administration (TGA).

### *5.1 The United States of America/FDA*

The regulatory agency data summarised in this thesis is part of the ongoing data capture required by the cited regulatory agencies to demonstrate a state of control over the products regulated within their sphere of influence. The United States of America FDA is often regarded as one of the most important pharmaceutical regulatory agencies for various reasons, not least being it is the agency that regulates one of the largest and most profitable pharmaceutical markets in the world. The FDA regulates two completely different product streams, namely pharmaceuticals and foods. Pharmaceutical products include prescription medicines and over the counter medicines, within the prescription medicine domain this includes classic small molecule drug products, large molecules, such as proteins and peptides (biologicals), and those drug products which fit into the category of medical devices in addition to registered pharmaceuticals. The bulk of analysis and discussion will concentrate on the trends in compliance seen in small molecules. Recognising that the balance between small molecules and large molecules is ever changing, with the latter becoming more prominent over the past five years, there will be discussion of the emerging trends in these areas as well.

During the period 2018 - 2019 the majority of applications to the FDA, for regulated drug approvals, either new drug applications or abbreviated new drug applications constituted around 60% of the agency's application workload. The remaining portion being concerned with non-regulated<sup>1</sup> products. Of primary note during this period is that 61% of all drug products approved for use in the United States of America during this came from international markets and therefore were not subject to domestic FDA office inspections. Whilst considering the majority of products came from overseas it is interesting that only 47% of FDA inspections were for drug products manufactured in international locations compared to domestic locations. This clearly shows a potential imbalance in the application of available inspectorate resources to ensure the overseas manufacturers were working to the same level of compliance as those subject to domestic inspections. Those international inspections were global in nature, and it was identified that the largest single supplier country to be inspected outside of the United States of

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<sup>1</sup> Regulated in this context means prescription only medicines as opposed to over-the-counter medications.

America was India, supplying over a third of imported drug products to the United States. This was closely followed by South Korea at 30% and China at 11%. It is worthy of note that during this period there was not a fully effective mutual recognition agreement (MRA) between the FDA and European regulatory agencies. An effective MRA could potentially exclude European manufacturers from that inspection process at FDA discretion. It is important to also consider the breadth of products which fall under the umbrella of drug products. In this reporting period there was a huge increase in the number of immunological agents submitted to the agency compared to previous reporting periods of 2016-2017 and 2018-2019. Other products remaining at comparable levels for the two previous years included products such as analgesics and cardiovascular drug products. The increase in immunological agents at this point is the start of the trend of increasing development of large molecule based therapeutic agents. Also, during this time there was a reported shortage of parenteral products, and the vast majority of immunological agents are parenterally based. This also coincides with additional actions by European regulators on the enforcement of revised annex one requirements for parenteral manufacturers and therefore it is logical to conclude that these two data sets are linked.

Given the resource allocation to international audits detailed above it is key to identify that the following reporting period of 2019-2020 resulted in an increase in inspections from 61% overseas drug products to 72% [the subsequent reporting period]. There was a drop in inspections from 1346 to 1258. However, that is an artefact of the prominent usage of the USA/EU mutual recognition agreement that resulted in 109 EU inspections being conducted on behalf of the FDA, in consideration of that number the overall number of inspections is comparable.

2019-2020 only 32% of sites were inspected on a risk-based selection process. The FDA had increased the inspections of sites in China and India throughout these reporting periods leading to the conclusion that, via their own internal FDA matrices, these are higher risk facilities. The disproportionate number of cardiovascular and gastrointestinal drugs reported as defects during this does skew the data. This is not a true reflection of all product defects due to poor manufacturing, quality control or other associated deficiency. Rather this represents the increased identification of nitrosamine formation during manufacture or on subsequent storage. This became a regulatory hot topic during this

period due to its potential as a human carcinogen on lifetime dosing extrapolation. The identification of nitrosamine in these two product groups was a particular concern given the likely chronic dosing involved with both drug product types. Therefore, there were a number of nitrosamine related product recalls during this period that may otherwise have been not reported and for the purposes of this analysis these particular recalls and defects are not included in this analysis. The researcher considers the presence of these contaminants as part of the knowledge gaining process and indeed it does demonstrate the effectiveness of regulatory agency responsiveness to emerging data as this occurred in Europe as well as in the United States of America and other markets.

The subsequent reporting period (2020-2021) covers the emergence of the COVID-19 pandemic and therefore this data, whilst interesting, is not representative of routine manufacture and routine regulatory oversight, this applies to the FDA as well as all other regulatory agencies. It is worth discussing this period of time as it does reflect an evolution of the regulatory oversight process and the movement from on-site inspections to virtual inspections utilising online platforms. When looking at the data for the period of 2018 - 2019 it is clear to see the majority of FDA resources were applied to initial review or further reviews of either new drug applications (NDA) or abbreviated new drug applications (ANDA, the latter being applications that reference and use substantial amounts of data that exist within the original new drug application, for example a product line extension. This amounted to 60% of the applications received by FDA for action. In parallel to this 61% of all applications came from overseas manufacturers. The majority of supplies coming from international manufacturers and requiring detailed review and assessments of suitability by their very nature put a strain on the existing FDA resource pool. It is interesting to note that inspections during this time period, when assessed for the number of inspections that were conducted for overseas manufacturers, was less than half of the overall amount (47%). This obvious imbalance between domestic and international inspections is of concern considering that international manufacturers would by their very nature have a poor frequency or even no history with the FDA. Domestic manufacturers would have cultivated, over time, a relationship with their local FDA office and inspectorate team and therefore it is expected that the FDA would have a better grasp on activities at those domestic sites than those conducted by most international manufacturers.

India was and remains as the largest single international manufacturing country supplying

the United States with drug products, as demonstrated by the data in chapter 3. It is also worth noting the FDA tracking of product defects showed an increase during this time period. What cannot be determined is whether that is due to increased diligence or truly a reflection in a decrease in product quality. There is clearly a trend of increasing importation of pharmaceutical products into the United States increasing from 61% in 2017 - 2018 to a level of 72% in 2018 - 2019, that is a significant proportion of the United States of America pharmaceutical market. At current market value about 72% would represent approximately a market value of US\$ 350 billion. Put into further perspective the United States market represents 40 percent of global pharmaceutical sales (the largest single pharmaceutical market in the world). This then represents a significant financial share being imported.

These trends continued into 2020 - 2021, during this period the COVID-19 pandemic commenced and like any other industry during this time major impacts were felt across the industry not least of which was a development of numerous COVID-19 vaccines which will be discussed elsewhere in this thesis. Nevertheless, when considering the number of applications to the FDA there was unsurprisingly a drop in the number of NDA and ANDA applications for regulated pharmaceutical reviews during this time, a total 12% drop in NDA and a total of a 14% for ANDA applications, there was also a significant drop in the number of combined NDA and ANDA applications amounting to 26%. The drop in the number of biotech applications amounted to 10% of all regulated work however this does not distinguish from 'routine' biotech applications and the reactive response to proposed COVID-19 vaccines. In addition to this out of trend number of applications there was significant variation in the number of sites approved by the FDA over the course of this reporting period. The number of registered sites located within the continental United States of America decreased by 8.4% to 1780 whilst the number of sites approved by FDA in India also decreased but by a much smaller magnitude of 1.6% to 502 sites. This data clearly demonstrate the potential impact India based pharmaceutical manufacturers continues to have on the United States of America pharmaceutical market. It is believed that the primary driver, at least in America, for the decrease in sites is due to pharmaceutical company consolidations as this metric represents approved sites and not necessarily approved manufacturers. For the periods reviewed in this research most of these number of site decreases were the highest during these periods. There was also a global decrease in the number of sites monitored by FDA,

of 6.6%, which fits with the assumption of consolidation being the primary root cause, as there were no corresponding decreases in the number of regulated pharmaceutical drug products that were manufactured and supplied based on the data reviewed during the same period.

At this time there is no data on the specific impact of COVID-19 on site opening, closing or consolidation. Likewise, no data on any new product applications that may have been delayed during this period because of a lack of resource, for example, driven by a lack of resource for pivotal stability testing or even application authorship and/or review. Further to this point the researcher has noted that the number of deficiency observations (FDA Form 483s) issued by FDA decreased when compared to the previous reporting period, most likely driven by the decreased number of inspections. The number of deficiency observations that were raised were still 400% more than those raised in the reporting year of 2015. This metric alone clearly demonstrates a perceived decrease in quality and/or an increase in regulatory oversight. From the period of 2015 to 2021 this increase, and recorded deficiencies, is significant. A significant number of these deficiencies were noted to be driven by the continuing presence and detection of nitrosamine in certain product types and also related to the importation of mouthwashes and alcohol scrubs that were imported from Latin America to assist in the American response to COVID-19 and were deemed deficient. Therefore, whilst this increased level of deficiencies is concerning it could be considered that this represents an atypical reporting year.

The supply issues from Latin America notwithstanding, India still provides the second biggest number of deficiencies after Latin America, clearly demonstrating the vulnerability of American pharmaceutical consumers to international pharmaceutical supply chains.

The rate of new product registrations, that is registrations that were reviewed and approved as acceptable, rose on previous years approvable submissions across the continental United States of America. There was an average of two new applications per manufacturing site compared to an average of 16.5 new USA applications turn manufacturing site in India. One positive result of the increase across Indian applications would be that each site would have a quality management system and therefore for each 16.5 new applications per site they would at least be under a single QMS and therefore

have some level of reproducible consistency with respect to quality. However, if the quality standard they are adhering to is deficient the impact on products and ultimately patience will be significant.

There are three main product defect categories identified with the latest reporting period, these categories were:

- Overall product quality
- Device issues (medical devices and may include medical devices that include a pharmaceutical drug product component)
- Re packaging (this can include both primary and secondary packaging configurations)

On reviewing the non-quality management system related quality deficiencies identified other major topics included the following:

- Serious adverse events
- Adverse events
- Out of specification and out of trend data, due to product failure and not attributable to a failure in quality culture
- Labelling and packaging issues

As can be seen from the above these aspects, in conjunction with the quality management system, represent either a failure or sensitivity for an entire product supply chain. That remains true despite the data for this reporting period being heavily influenced by the nitrosamine issues identified previously.

In rank order the defects identified that give cause for concern for patient safety and compliance can be summarised as the following:

1. Poor quality control
2. Poor out of specification investigations

3. Poor process control
4. Inadequate cleaning
5. General procedural failures
6. An overall ineffective quality culture

## *5.2 The United Kingdom / MHRA*

As discussed previously in this thesis the regulatory agencies, acting as country wide competent authorities, all have a common aim. The manner in which they achieve that aim varies from state to state and as a result, the data is captured in slightly different formats. In this next section I will discuss the data captured by the MHRA and how this aligns or differs from trends seen in data captured by the FDA.

During the reporting year 2015 to 2016 the MHRA conducted 223 inspections of UK based pharmaceutical manufacturing facilities compared to only 79 overseas facilities. Given the large number of imported products, even allowing for products manufactured within the European Union (we were full members during this period), that is a substantial differential of regulatory oversight of domestic versus international manufacturers. As previously summarised in this thesis the MHRA use three levels of classification for quality deficiencies and these are critical, major and others. On analysing the data, it is apparent that similar trends to those observed by the FDA exist within the MHRA reported data. Events such as quality system failures, documentation failures and poor-quality control are demonstrable areas of concern, quality systems being the primary cause. The maintenance of a robust quality management system is the backbone of the pharmaceutical industry. During this fiscal reporting period over half of the critical deficiencies identified were classified as failures of the quality management system. The establishment of a quality management system is not a new expectation on industry and is very clearly defined within ICH Q10. The harmonised guide ICH Q10 was first published in May 2007 and effective just over a year later from June 2008. This guidance has been widely regarded as being a sensible and practicable guide as to how to develop and maintain a robust quality system. At this point we should consider this

quotation from the introduction (section 1.1) of ICH Q10.

“ICH Q10 describes one comprehensive model for an effective pharmaceutical quality system that is based on International Standards Organisation (ISO) quality concepts, includes applicable Good Manufacturing Practice (GMP) regulations and complements ICH Q8 “Pharmaceutical Development” and ICH Q9 “Quality Risk Management”. ICH Q10 is a model for a pharmaceutical quality system that can be implemented throughout the different stages of a product lifecycle. Much of the content of ICH Q10 applicable to manufacturing sites is currently specified by regional GMP requirements. ICH Q10 is not intended to create any new expectations beyond current regulatory requirements. Consequently, the content of ICH Q10 that is additional to current regional GMP requirements is optional.

ICH Q10 demonstrates industry and regulatory authorities’ support of an effective pharmaceutical quality system to enhance the quality and availability of medicines around the world in the interest of public health. Implementation of ICH Q10 throughout the product lifecycle should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities. “(ICH guideline Q10 on pharmaceutical quality system, European medicines Agency, June 2008).

Whilst recognising this is a guidance document, it is also sensible and logical overview approach to quality standards and provides the reader with a framework within which to achieve acceptable quality of pharmaceutical products. The data demonstrates that adherence to the principles, if not the letter, of the guidance document is not being achieved on a wide scale in 2015, seven years after this guide came into effect. The MHRA identified individual contributing deficiencies noted all fit within the QMS structure, such as:

- Poor training and lack of subject matter experts
- Change control
- Deviations and corrective and preventative actions were poorly controlled or implemented

- In appropriate facilities to manufacture the products under inspection

These deficiencies were identified domestically and internationally, however, the rate of domestic inspections is far higher than those for international manufacturers therefore the likelihood is a higher rate is present from international sites than that represented by the data alone.

Whereas the FDA cite their deficiencies against the code of federal regulations (CFRs) European inspections including the MHRA cite against Eudralex, references to specific chapters are often used in deficiencies which gives the reviewer an opportunity to determine greater granularity of the individual deficiencies. This also applies to good distribution practice (GDP) and good clinical practice (GCP) as well as good manufacturing practice (GMP), the emphasis being the product quality reflects the sum of all the processes and not one process in isolation.

MHRA identified trends and overall quality systems from the data reviewed in this research across all the reporting periods leads to a conclusion that manufacturers, both domestic and internationally, were not improving on quality standards. Indeed, considering 2018 the MHRA conducted 286 inspections, an overall higher number than those conducted in 2015, however, of that 286, 228 were in the UK and 59 in international locations, an even lower percentage of the overall inspection resource being applied to overseas inspections compared to 3 years previously. It is also important to consider that these 286 inspections resulted in a staggering 6209 quality deficiencies being identified. This is not indicative of a process being under control, with well-defined and controlled product quality characteristics. Furthermore, in 2019 deficiencies related to quality management systems still ranks as the highest identified efficiency across all the inspections conducted in 2019 both domestically and internationally. The trends of deficiencies in company documentation, production facilities and quality control continue year on year with no substantial improvement and no obvious common attributable cause as to why the agencies still detect these deviations and efficiencies despite the plethora of guidance available.

Like all regulatory agencies, in 2020 MHRA experienced substantial resource issues due to COVID-19. However, they did demonstrate an ability to conduct industry aligned “rolling reviews” as predominantly seen in the rapid approval of COVID-19 vaccines within the UK. This thesis has discussed previously the common process for product reviews and registration where the originator files an application for product registration which contains all the relevant pharmacy and clinical data as a single data package. In the case of the rolling review the agency aligned resources with industry to review and approve data as it became available. Data such as manufacturing control strategies, emerging clinical data and stability data were all reviewed individually as each protocol of work was completed. This facilitated a rapid approval for products considered for an essential response to an ongoing public health emergency. It did result in the impact that other applications were delayed and the resource available for other regulatory agency activities was significantly impacted. This shows that, whilst a rolling review can be extremely effective from a time scale perspective, there is a resulting impact on available resources which would impact other key activities and therefore, with current funding and resources it is an unsustainable model as a long-term solution.

### *5.3 Australia / TGA*

In contrast to the data gathered in North America and the United Kingdom, the latter being generally representative of issues faced by major European agencies, the data generated by the Therapeutic Goods Administration in Australia shows similar interesting trends. Like other agencies the number of inspections of pharmaceutical manufacturers decreased in the last reported year. It is interesting to contrast this with the other agencies from the perspective of number of inspections as a function of population, or in this case the number of potential patients. Table 26 shows a comparison of the number of inspections conducted in the last reporting year for FDA, MHRA and TGA and the respective populations of each country.

**Table 26: Comparative table to show the number of inspections conducted by  
FDA, MHRA and TGA**

<b>Country (Agency)</b>	<b>Number of inspections</b>	<b>Population (as of 2020 census)</b>
United States of America (FDA)	1346	331 million
United Kingdom (MHRA)	286	67.9 million
Australia (TGA)	163	25.5 million

Table 27 illustrates the number of inspections expressed as a percentage of each country population compared to America, the country that conducts the most inspection by number.

**Table 27: Comparative table to show the number of inspections contrasted with  
country populations**

<b>Country (Agency)</b>	<b>Ratio of populations compared with USA</b>	<b>Number of inspections per million of population</b>
USA (FDA)	100%	4.1
UK (MHRA)	20%	4.2
Australia (TGA)	12%	6.4

As can be seen for the table above the ration of inspections conducted by TGA per population size is greater than that for MHRA and FDA, both of which are very comparable. These inspections include domestic and overseas inspections. This almost 50% relative increase between TGA and the other two agencies adds greater weight to the TGA findings as being more representative of the actual state of pharmaceutical manufacturing quality. Between 2018 - 2020 there was a significant drop in TGA inspections. On comparison to previous reporting years for FDA and MHRA the relative ratio between the agencies remains, with Australia conducting a higher proportion of inspections. It is also important to note that there was, as assessed by the TGA, a significant drop in acceptable inspections compared to previous periods, trends also seen with other agencies across this period, TGA found a variation of -18% on overall acceptable inspections and an increase of +14% for inspections that were still under

investigation at the time or reporting.

Data that is interesting from the TGA published reports is the demonstration that the majority of acceptable inspections come from the United States of America, India, France and China however they also cite the majority of unacceptable inspections also arise from the United States and India, this reflects their major importation markets for internationally manufactured pharmaceutical products. What is not distinguishable is whether there is a division between the importation of active pharmaceutical ingredients as a differential to the importation of pharmaceutical drug products. Greater granularity is gained by reviewing the breakdown of inspections which demonstrates that over 60% of inspections were for pharmaceutical drug products and only 13.5% of inspections being for active pharmaceutical drug substance.

Similarly, to the MHRA and FDA the TGA identified poor investigations, poor deviations root cause analysis as well as basic planning and implementation of GMP as major sources of deficiencies. Given the slightly varying reporting structures between FDA, MHRA and TGA and ignoring the differing classifications of critical, major, minor or Eudralex and CFR regulations the common themes are consistent as below:

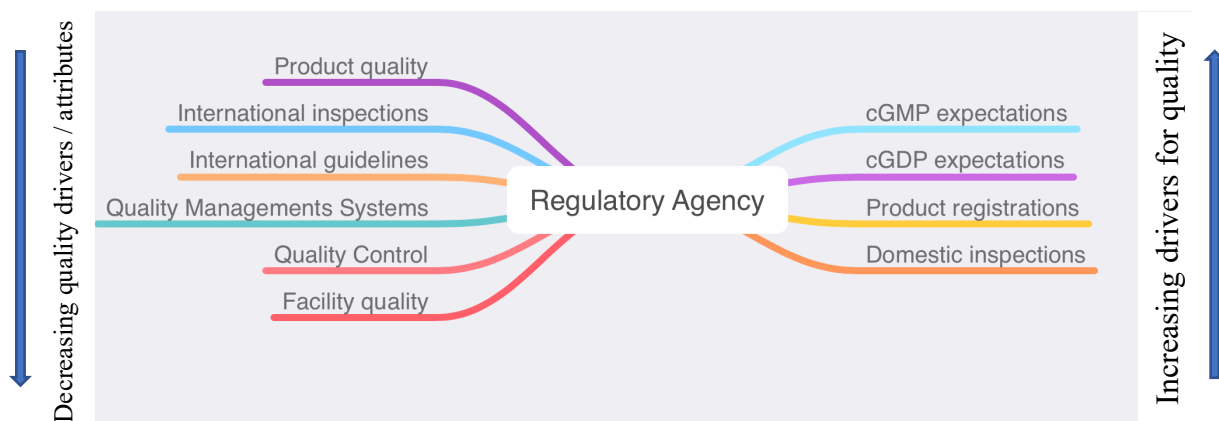
- Deficient quality management system
- Poor good manufacturing practice
- Poor good distribution practice
- Inadequate facilities
- Poor application of resources
- Unsatisfactory process or equipment validation
- Procedural controls

The TGA also reported a small increase in the number of recalls, 3%. On considering drug products alone the number of recalls was typically high at over 40%, again primarily due to issues with nitrosamine contamination as also reported by other regulatory agencies. Therefore, whilst this data appears to be trending upwards it is actually a result of greater process and product knowledge and understanding which is driving that recall, in effect a validation of the recall process.

In summary of the reported regulatory agency data reviewed for this thesis a number of inductive conclusions can be made:

- Quality of pharmaceutical drug products is decreasing based upon inspection observations made by regulatory agencies
  - Deficiencies primarily cantered on facilities, procedures, validation and quality control
- The number of inspections varies between countries however the recent drop in both domestic and international inspections is atypical and primarily due to the COVID-19 pandemic
  - prior to the pandemic inspections were relatively static in number or with marginal nonstatistical increases primarily driven by specific factors such as the Latin America supply of alcoholic scrub and disinfection agents to United States of America.
- Overseas inspections are not as frequent as domestic inspections and are not representative of the volume of products being imported into each market reviewed when compared to domestic inspections
- The rate of new product registration applications continues at a steady rate requiring inspection of either new companies or new facilities which will draw resources from routine inspections

These summary changes are shown in Figure 58 below to illustrate the potential for increase in product quality and the factors that have driven a decrease in product quality.



**Figure 58: Summary representing agency drivers to maintain or improve product quality and agency detected drivers that have forced a decrease in product quality**

### **Inherent review variability**

When considering the research objective of is there is inherent variability in the current process from many sources, it is clearly demonstrated by the aforementioned data. This data from three major regulatory agencies in sections 5.1 -5.3 shows that there is a wide range of variability that is reflected in variable quality product when measured by a number of characteristics.

### *5.4 Product quality attributes and quality systems*

When considering product quality attributes and regulatory expectations adherence to guidelines and other published materials are either poorly understood or implemented. These deficiencies can be linked directly into ICH quality guidelines as shown in table 28.

**Table 28: Illustration of product quality attributes referenced to ICH guidelines**

ICH Guideline/section	Product quality attribute
ICH Q1A stability testing of API and DP	Is the product suitable for use? Meets predefined criteria. Suitable for inclusion or next stage processing if API or intermediate
ICH Q1B Photostability	Predefined light exposure studies to assess long term storage or short-term exposure (in use)
ICH Q1E Evaluation of stability data	Assessment and standardisation of trending data
ICH Q2 Validation methods	Suitably qualified and robust methods being used
ICH Q8 Pharmaceutical development	To ensure good practice and consistency

At this point it is worth considering a different perspective on quality determinations, that of operational excellence. The premise of operational excellence (OpEx) is a philosophy rather than a specific process, concentrating on the premise that systems and processes require continuous improvement and finds that continuous improvement will, by definition, lead to improved quality or at least make quality a more consistent feature. This definition is very broad and quite ambiguous. The premise of operational excellence has been adopted by the pharmaceutical industry with limited visible success and also by the FDA as part of a joint venture with academia. The FDA partnered with Saint Galen university (Friedli, et al., 2019) for an investigation into operational excellence and the quality metrics that the FDA capture and used to guide their resource allocation when overseeing the pharmaceutical industry.

In the light of the existing FDA metrics already discussed in this chapter let us now consider the validity of those metrics in the light of the St Galen university research. The pertinent points of the St Galen investigation into FDA metrics are summarised below:

- The linking of quality as a minimum standard is greater than just acceptance of regulation and abidance with those regulations. The St Galen data attempted to link quality culture to patient driven acceptance criteria and attempted to link

quality metrics to an embedded quality culture. To measure and assess and embedded quality culture is very difficult and is subject to interpretation and variability. Even with the use of an arbitrary pharmaceutical quality system point scoring system the ability to assess an embedded quality culture is extremely limited. However, the research team developed the following models:

- Effectiveness of quality culture by efficiencies demonstrated and any correlation between culture and effectiveness
- Some metrics concentrated on supply scenarios such as stock keeping units
- Resource allocation was identified as a key metric
- QC laboratory metrics were reviewed, and an assessment of quality maturity was created, for example how embedded were the QC processes?
- The impact of operational stability was assessed as being key to quality
- Quality culture as a concept has been more widely adopted but how was this implemented and exhibited?

One primary conclusion from the St Galen study is summarised as that, within pharmaceutical manufacturing, product quality should drive operational excellence applications. In addition, that the FDA metrics program specifically related to quality was valid.

The FDA/St Galen reviewed metrics data captured from over two hundred global pharmaceutical manufacturing sites that manufactured either commercial products or investigational medicinal products and that were additionally monitored by the FDA. In doing this they monitored FDA defined key performance indicators on the presumption that these were objective and quantified measures of operational performance. Of these, 13 key performance indicators were selected in areas that covered facility maintenance, facility quality and acceptable product delivery and resources. They also included a category defined as ‘enablers’, for example an arbitrary measure of the degree to which the organization under review adhered to regulatory expectations and best practice. The latter is a very weak category from an analytics perspective as there is no true definition when considering variable practices and processes. Additional data was collected against what was termed ‘practice maturity principles’, again a very weak category covering such diverse topics as social status, employee statistic and a vague definition of technical tools. In conclusion the St Galen study concluded that quality metrics and quality culture

programs are a good business practice and an important element of modern pharmaceutical manufacturing. This is not a surprising construct, indeed from an industry experience perspective it is a logical supposition rather than driven by data. Which devalues the analysis conducted in this study. The indication that the FDA selected metrics were indeed applicable even without the supposition adds validity to the data trended by the agency.

#### **5.4.1 Parity of international approvals**

From the above data it can be summarised that when considering the research objective of determining how to ensure that international approvals for imported medicines reach the standards as those for local market approval that there is clearly a deficit in this regard. The assessment of metrics and the resulting output of those metrics demonstrate that currently there is no parity across international markets. This has become an area of concern to the pharmaceutical agency regulators.

From the FDA data and the correlated MHRA and TGA data reviewed a number of conclusions can be drawn.

1. Batch release rates, domestic or international are not a good indication of the ability of the site to manufacture acceptable quality drug products. The use of out of specification and out of trend data analysis would be beneficial, and as these are linked to product quality and performance, these would provide a useful surrogate measure of quality.
2. Process capability measures specific to product, product types or technology types would be beneficial to understand specific technical inputs to product quality. Where risks exist, this could be greater utilised in resource allocation and planning for all drug products when viewed as a single holistic supply chain.
3. It is obvious that an effective pharmaceutical quality system is an essential component in the production of quality drug products regardless of where the product is manufactured. This is based upon the sheer scale of deficiencies identified by all agencies reviewed.

4. Increased use of statistical quality control applications such as Statistical Process Control (SPEC) and Process Capability Index (CpK) and other aspects of a lean sigma approach. These could be applied to both industry supplied data by agencies and also primarily at source by industry manufacturers.

The researcher's pilot study demonstrated the suitability of a mixed methods approach to the research question and yielded valuable data. Whilst accepting that the data pool is relatively small it was still possible to recruit a range of participants that had many years' experience in the pharmaceutical and regulatory industries. The main study yielded data that further supported the conclusions resulting from the pilot program. It was essential to the claim of internal validity that the subject matter experts that participated held substantial industry experience. The participants having a minimum of twenty years' experience with many having greater than thirty years aids that assessment. The initial data captured and analysed shows that there is an issue of quality and parity of medicinal products across the pharmaceutical industry and that this has been exacerbated by globalisation and importation and is worthy of further study.

The pharmaceutical industry produces many drugs that provide huge health benefits to mankind, the role of the regulatory agency is by their very nature a political construct and it is viewed as being essential to not only police the pharmaceutical industry but also to engage and support it via sufficiently robust procedures to protect patients from any unsafe or non-efficacious medications.

It is essential to remember that the pharmaceutical industry is a business and therefore, as with any business model generates profits. Whilst there is often great public scrutiny in the press regarding pharmaceutical profits, any regulatory agency must see past the business drivers and incentives that can conflict the industry to look purely at medications in current manufacture or under review dispassionately. All pharmaceutical products must undergo a risk benefit analysis, initially it should be conducted by the company developing the medication but ultimately a similar analysis must be conducted by the Regulatory agency. This is not a conflict between agency and industry, this should be a supplementary process by which the two groups can agree and ultimately provide safe medications. There have been documented occasions of industry applying pressure or vague threats to regulators and political oversight of the regulators that impacts on local

and country economics this was discussed previously by Abraham (2002). In his paper in 2002 Professor Abraham highlighted concerns regarding pharmaceutical industry influence over regulatory agencies via direct agency or political approaches. Abraham highlighted intra EU competition is a threat to public health and the potential impact of the EU centralised parallel procedure. He proposed a number of measures to minimise the influence of industry on oversight frameworks, these proposals still remain in the most part unfulfilled 20 years later.

As previously discussed by Drew (1997) the economic and regulatory difficulties that faced pharmaceutical industry in the latter part of the 20th century were in many ways existential. Many of these challenges still exist today and no more so than the economic framework within which the industry resides and the political framework that created and maintains the regulatory agencies tasked with overseeing the industry. As evidenced by Yu and Kupchak (2017) the approaches to pharmaceutical quality are now centred around statistical and lean processes with a purported benefit to patients. The degree to which these processes are embedded within the industry is often vague or is limited to mission statements and charters. Concern on progressive product quality has been raised by numerous agencies and addressed by Yu and Woodcock (2019) and FDA (2019) leading to the strategic development within FDA of Centre for Drug Evaluation and Research (CDER) Office of Pharmaceutical Quality (OPQ) with the specific aims of simplifying regulatory processes and removing non-value added aspects, whilst advancing regulatory standards, utilising appropriate expertise and with a key aspect being regulatory oversight, not only of data but also facilities and supporting structures/organisations. To meet these objectives will be the requirement of the implementation of innovative and systematic approaches to product quality specific knowledge management and intelligence. This new FDA office was created in 2019 and with the subsequent COVID-19 pandemic the full potential impact of the creation of the CDER-OPQ has yet to be fully realised.

#### **5.4.2 Relevance of international approvals**

On reflection of the data collated from the agencies in this research and in consideration of the SME experiences it can be concluded that the relevance of international markets is

of limited value. There are exceptions, such as those recognised under mutual recognition agreements. This is likely a very small percentage of the pharmaceutical trade.

Before discussing the main body of questionnaire and interview data it is worth reviewing the conceptual mind map shown as Figure 8 in Chapter 1.

This conceptualisation identified a number of areas that were believed to impact regulatory oversight and therefore have an impact upon pharmaceutical product quality. They formed the basis for the thoughts moving forward to design the questionnaires and then therefore have an impact on the interviews. On reviewing the regulatory data in the light of this framework certain aspects were born true. Other aspects appeared which hadn't been touched on previously in this plan mind map. During the coding process for the interviews, it was noted that a number of preassigned codes were not utilised primarily because respondents did not generally feel these areas were of concern

On initial analysis of the questionnaire and interview data it is clear to see trends within the full participant group, regarding where they believe issues have arisen and their current concerns at least within this pilot study, further questioning of a larger population was conducted on the main research population sample. However, it was noted that these trends also agreed with the micro trends seen in the much smaller previously conducted pilot study work. The top five concerns when dealing with production of a safe and efficacious pharmaceutical drug product and product parity can be summarised as:

1. Barriers to change and improvement
2. Deficient or inappropriate regulatory framework
3. Incentives for change do exist, these are not always positive
4. Politics plays a significant part in influencing industry and regulators
5. Drivers for change do exist, however these are often poorly defined and nebulous

That there are significant barriers to change is driven by knowledge, understanding, intellectual property protection, politics or at its most basic, a cultural impact. Culture in this context describes the business culture or company culture. A 'company culture' may be a buzz word or maybe a phrase that does not have an exact definition. For the purposes of this study it is a process that develops organically from management across the organisation it is the sum of all the systems, employees, and management to work

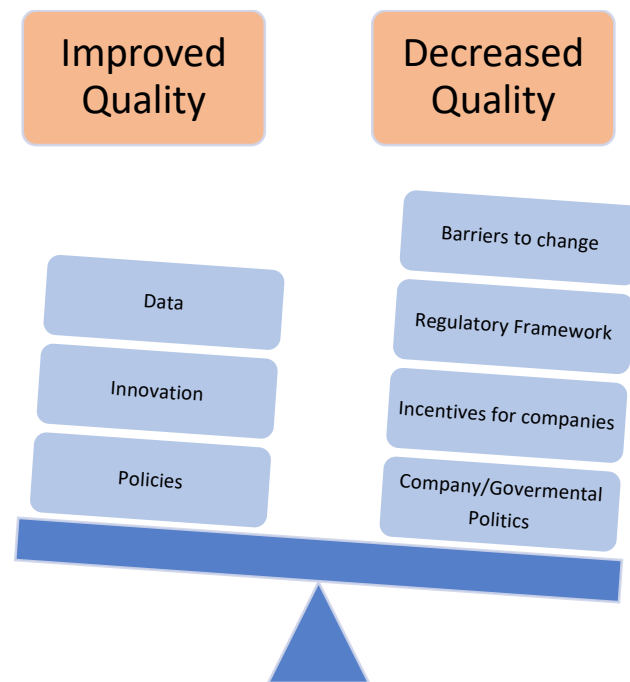
within the environment that encourages transparency, best practice, in summary a collective force and shared values.

From this research it is clear from all respondents that the company culture can pose a barrier to improvement. There is also the concept of country culture having an impact on how industry or regulators function. In this context country culture as defined is a diverse group of intangible drivers that influence individuals and the state. It can have significant impacts on how not only how companies function but also how regulators function, for example a deferential state regardless of best practice or suitable experience may exist. Another opinion that was common to most participants was that they felt that the regulatory frameworks that exist within their respective countries were inadequate and either did not represent required best practice to produce safe and efficacious products or did not to ensure parity between international and domestically manufactured products. It is clear from the regulatory data discussed in this thesis that this fear of non-parity and a different regulatory scrutiny of international manufacturers is borne out by the differential between domestic and international inspections (the COVID-19 pandemic induced differential in 2020-2021 data is obviously excluded from that statement as 2020 represented an atypical year due to the pandemic). It was common to the participant pool that incentives for change did exist. However, as became clear during the interviews, the incentives on offer were often quite diverse and, in some cases, unquantifiable. For example, an incentive could be tax offsets from additional production or research development activities. Alternatively, an incentive could be the ability to find a rapid product line extension or a reformulation to strengthen a patent position. Many of these incentives have to be viewed on a company or corporate scale to appreciate the drivers and it is difficult to attribute those to one particular product. However, it is clear that incentives can offer undue influence on decision making processes and therefore can have an impact on product quality from a manufacturing perspective. Incentives for change are not directly applicable to regulatory agencies however that does blur within the remit of political oversights and political funding, and this will be discussed elsewhere in this chapter.

Participants agreed that politics, in its many guises, does impact product quality. There are two main trains of thought on a political component:

- these are internal company/employee politics
- governmental politics.

It is also noted that other aspects were highlighted as contributing factors, and these are represented in Figure 59 below:



**Figure 59: Visualisation of the impacts upon product quality as determined by survey respondents**

The survey highlighted key findings in the drivers and barriers for change, these are shown in Table 29.

**Table 29: Summary survey responses in rank order for barriers and drivers for change in pharmaceutical quality for the full population surveyed**

Parameter	Cause for concern (ranked from responses)	Impact
Barriers for change	Cultural	Cultural impact is the primary barrier experienced by the SME population surveyed. As summarised by a USA SME. <i>“There is a difference in terms of the culture between many different parts of the world and I'm not sure the regulators fully account for that culture and I think as a regulator from one part of the world visiting another part of the world, that culture can take some time to get used”</i>
	Knowledge sharing / best practice	Poor practice has a significant impact as there is little or no cross-company or cross agency sharing of information. As highlighted by a UK SME. <i>“You see very little in the way of umm science-based pro-active risk management. It is used largely to justify inappropriate behavior, inappropriate results and from a regulatory point of view you only have to look at financial services and what risk-based oversight did to that, to know that this is a terrible mistake”</i>
	Education and expertise	Linked to the above criteria of best practice, general education is a concern. Illustrated by an EU regulator. <i>“Sharing of information between industry and regulators could be of great benefits and give insights into what either party are trying to do sometimes it's just educational but either because there's no world to do it or because there's no need to do it doesn't get it done”</i> <i>“We are supposed to be scientists driven by data driven by knowledge and understanding and that really does get lost sometimes”</i>
		<i>“I would like it to be based upon data &lt;redacted&gt; science based upon process understanding and clear quality and efficacy goal. I joined the industry not just to make tablets I joined the industry to make medicines to help people.”</i>

Parameter	Cause for concern (ranked from responses)	Impact
		<p>Australian perspective as:</p> <p><i>“always a drive to reduce cost of goods, but in my experience, certainly in development, if a product gets in to a clinical trial, well, if a molecule is shown to have efficacy and has the promise of being develop-able (that's not a word but I've made it up) if there's a chance of getting that to market, for the most part, in my experience, money is always found to do work”</i></p>
Regulatory framework	Regulatory complexity and non-transparency	<p>A former UK regulator summarised the issues surrounding regulatory frameworks as:</p> <p><i>“The regulations are difficult are complex, they are open to inter / well the directive is open to interpretation into national law, and then you've got other countries that then have their interpretation slightly differently”</i></p>
	How to improve parity of products?	<p>Many participants expressed suggestions of methods of improving quality parity from all sub-populations illustrated by:</p> <p>EU SME</p> <p><i>“A single quality standard! One standard for countries for all agencies can only be beneficial.”</i></p> <p>Japan SME</p> <p><i>“I certainly think a more harmonised approach globally would be helpful, certainly within the major territories”</i></p> <p>US Regulator</p> <p><i>“Harmonisation of regulatory guidelines, not cutting corners, cherry-picking the best parts, and then utilising them appropriately will help the industry to bring good quality efficacious medicines to people that need them.”</i></p>

### 5.4.3 Application of expertise

From the majority of SMEs surveyed and interviewed, with a combined experience of greater than 1,500 years of professional practise, the application of expertise is at best patchy and sometimes almost invisible. There are areas where both industry and agency do conduct best practise but this is not consistent internationally. The overarching concern was parity of application and how that can be improved.

From the interviews conducted there was commonality between sub-populations (between EU QP / International Industry SMEs and Regulators) on concerns raised on parity of pharmaceutical products from domestic and international manufacturers. For example:

United Kingdom SME example

*“In my experience would suggest it's very variable and I think there's / for me there's far too much variability in the rigour of application standards across Europe”*

United States of America example

*“I think it is weaker and I think the overseas sites certainly are under less threat of an unannounced inspection”*

Japan SME example

*“We spend far more time and resource reviewing internally manufactured materials in our countries of origin than we ever do for overseas material and let's not forget that even when we're inspecting local products often there is some component of that, could be the active drug it could be a key excipient, which came from overseas”*

Considering the perspective of EU Qualified Persons adds validity to the perceptions of the wider group with a unanimous feeling of lack of control and parity for imported products into the EU and UK (note for the purposes of this research, as this covers the period of the United Kingdom leaving the European Union, the role of the QP remains the same except that post UK departure the two QP groups are separate) lack scrutiny and therefore parity cannot be assured, as illustrated by the extracts below.

United Kingdom QP

*“In my biased opinion again we're probably one of the leading countries in terms of the rigour of the regulation and the standards with which our industry applies itself”*

*“Certainly, outside of Europe it needs enforcement, because people will do what is needed to be done for economic or financial reasons and then will try and clear up some of the issues later, ahead of an inspection, so those inspection dates are massive events to get prepared for, particularly for facilities, in the second and third world. I'd love to think that the UK and EMA are not quite as bad”*

European Union QP

*“Based on my experience we are very similar here to the European approach “*

*“There is a lot of history and just what we see <data> that's come out of <EU> agencies and problems in say challenges in countries like India and China”*

This collective concern can be coupled with reports from the United States Senate Committee on Homeland Security and Governmental Affairs (2019) who concluded in their assessment report that the United States of America were vulnerable to supply chain variation due to quality and cost. Indeed, they noted key areas that have been further supported by the data in this thesis. For the United States of America:

- FDA lacks adequate oversight of imported drug products with only 1% (at the time of the report) being tested and assessed by the FDA prior to USA market entry
- At the time of the report 80% of active pharmaceutical ingredients were sourced from non-USA sources, primarily India and China
- Protective business practices are contributing to a lack of new products
- Generic drugs contributed 90% of all USA prescriptions in 2018
- Between 2001 and 2011 drug recalls increased by 500%

We should however be cognisant of the possibility of bias from each participant in the study, obviously the aim of this research was to gain perceptions based on experiences

however a number of responses alluded to a biased or potential for biased reply, such as:

*“In my biased opinion again we're probably one of the leading countries in terms of the rigour of the regulation and the standards with which our industry applies itself” (USA SME)*

*“Well, certainly outside of Europe it needs enforcement, because people will do what is needed to be done for economic or financial reasons and then will try and clear up some of the issues later” (EU Regulator)*

*“I think there is a very much a feeling in a lot of U.S. sites that the FDA was the world's best regulator” (USA Regulator)*

This research has demonstrated that many aspects drive the perception of parity of products and registration, aspects such as resources, expertise and access all play a significant part however all are equally contributing rather than one major influencer.

From this research it is apparent that parity is of general concern, regardless of where you sit on the pharmaceutical spectrum, industry or regulatory or country. It is noted that a minor group of respondents felt that there was parity between individual markets however when challenged as to what market products they would take personally there was an apparent order of preference indicating other drivers that would contribute to acceptable quality from their perspective. This correlates with the early findings presented by No and Sharma (2017), which concluded that quality management is an essential function of the pharmaceutical industry and that, at least within the industry, skills are evident and can be applied if given the opportunity.

There was a consistent response from all groups surveyed and interviewed on the need for greater harmonisation and promotion of best practice. It is worth noting the content of EudraLex Volume IV at this point.

The principle of EudraLex volume Iv guide to good manufacturing practice states:

*“The holder of a Manufacturing Authorisation must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the*

*Marketing Authorisation or Clinical Trial Authorisation, as appropriate and do not place patients at risk due to inadequate safety, quality or efficacy”*

This scope and principle are wide in nature with no clear definition. However, of what constitutes acceptable quality, regarding safety and efficacy it is clear that these are product specific criteria that need careful consideration and exploration to determine appropriate acceptable measures and the onus for that is clearly on industry. From this research it is clear that industry professionals do not always have a clear vision of how this is applied. Without a clear framework the ability to interpret can lead to variation. A former regulator in this research claimed:

*“there’s huge variability, some countries how much better than others. Some countries just take the lead from the major players in Europe. Although it is supposed to be an integrated market it behaves as a number of separate entities sometimes with conflicting goals”*

In addition to the following:

*“there’s no transparency there’s nothing clear about how they review and assess documents you are not allowed to challenge the reviewer to ask why they came to that conclusion in many agencies and in the ones where you are allowed to do it completely so scared to be answering one problem creating another it’s very hard to understand what the main drivers are.”*

In addition to this inherent ambiguity specifically, section 1.1 states:

*“Quality Management is a wide-ranging concept, which covers all matters, which individually or collectively influence the quality of a product. It is the sum total of the organised arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use. Quality Management therefore incorporates Good Manufacturing Practice.”*

It can therefore be challenged that quality management, including quality risk management can include the regulatory agencies and the key roles that they fulfil in the

global pharmaceutical supply chain. Whilst efforts are made to increase harmonisation, the perception is one of lack of harmonisation. This is illustrated by the cross regulatory inspectors group PIC/S, this research yielded the following comment from an EU SME:

*“PICS is at least the inspectors trying to harmonise themselves, but it doesn't of course involve the industry”*

It is important to note though that PIC/S is not legislation enshrined, nor is it binding on either the regulatory agencies of the pharmaceutical industry. The need for enforcement or at least verification of adherence to expectations and best practice was raised in the interviews.

*“If you're going to have global standards, you need global enforcement. If you don't have a consistency of enforcement you end up with a situation where we've got in Europe where you've got you know 27 different interpretations of what Annex 1 means and so on, umm, and different levels of rigour”*

As discussed earlier in this thesis it is valuable to consider the perspectives of industry and regulators in the form of a DMAIC analysis. To this aim the researcher has divided this into two populations, regardless of country, of regulators and subject matter experts (excluding regulators). A representation of a DMAIC output and how this can be applied to product quality and parity is shown in Figure 60.



**Figure 60: Visualisation of application of DMAIC controls to drug product quality**

Having described the process for DMAIC assessment Figure 61 now describes the application utilising the SME insights gained in this study.



**Figure 61: DMAIC analysis from SME perspective for acceptable minimum product quality**

Given the SME perspective above the regulator's focus is slightly different, this is represented by Figure 62 below.

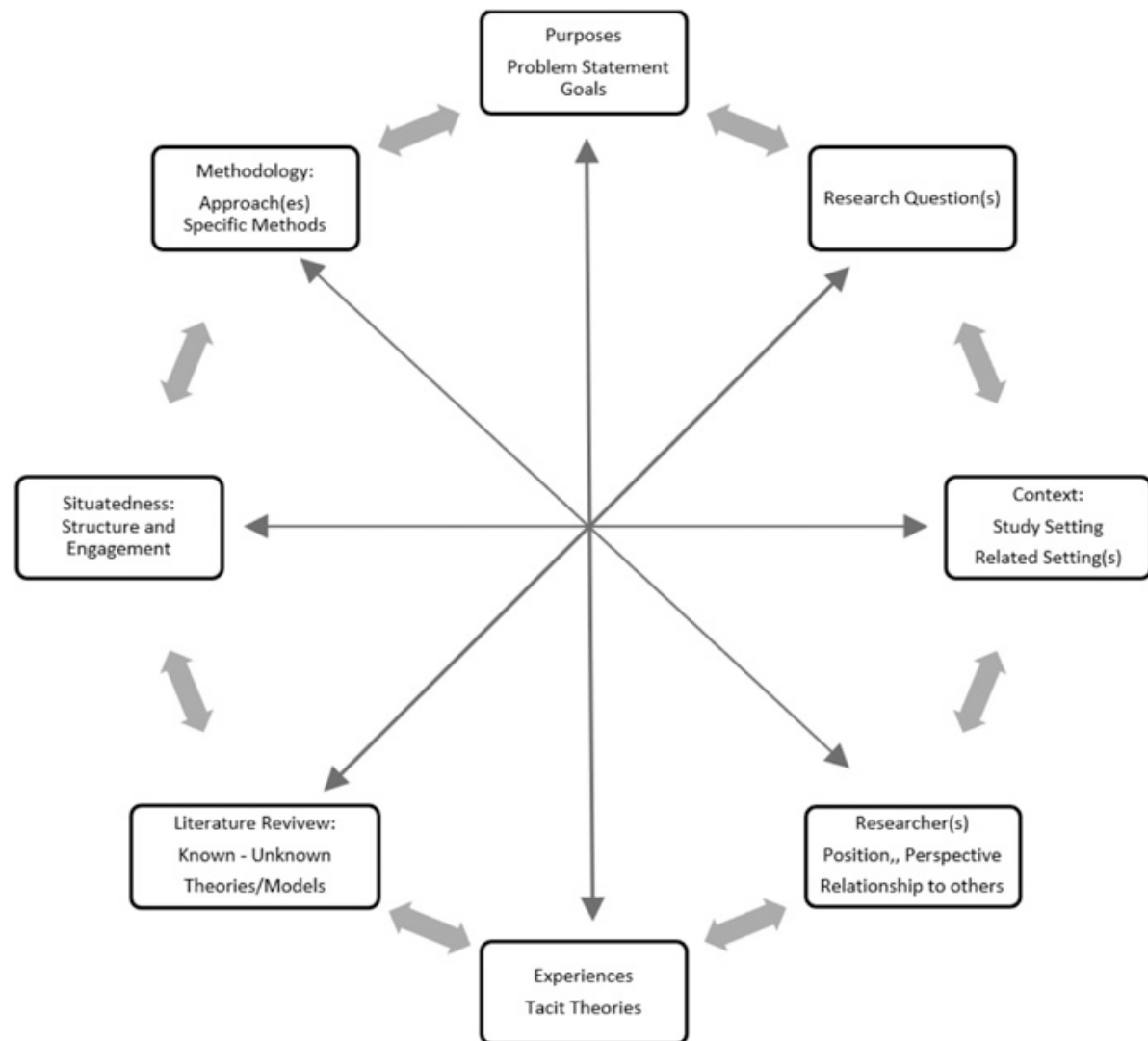


**Figure 62: DMAIC analysis from regulator's perspective for acceptable minimum product quality**

When considering the data in this thesis one must consider the aspect of validity, not only of the data but also the process by which data is generated and the reasoning taken during assessment. The sampling utilised in this research project is consistent with that proposed by Onwuegbuzie and Collins (2007) in that it is both representative and legitimate for the purposes of this topic. In addition, it fulfils the requirements of Maxwell (1992) regarding interpretative validity when considering the interview aspects of the mixed methods approach. Two aspects require discussion, internal validity, and external validity.

Internal validity with regards to this study is the approximate correctness about inferences regarding cause-effect relationships between regulation and site of manufacture. With the data reviewed and the inferences from interview analysis it is important to consider the weaknesses in the process. As previously discussed, the data set whilst substantial is incomplete on a global perspective. Therefore, internal validity is limited in claim due to this even considering the volume of the three main markets considered in this research combined is approximately 45% of global pharmaceutical market consumptions by value, USA being the single largest market by revenue.

As proposed by Johnson, Adkins and Chauvin (2020), for healthcare research, it is essential that the researcher be reflexive and aware of one's own potential for bias. Johnson, Adkins and Chauvin proposed a modified model for developing a conceptual framework, as shown in Figure 63.



**Figure 63: Johnson, Adkins and Chauvin adaptation of Ravitch and Karl's conceptual framework process**

(Reproduced from Johnson, J.L., Adkins, D., Chauvin, S., 2020. A review of the quality indicators of rigor in qualitative research. American Journal of Pharmaceutical Education. doi:10.5688/ajpe7120)

It is clear from this framework that a professional doctorate such as this research clearly falls within this descriptor, with the researcher as an emic researcher fully embedded

within the project due to their professional experience. In this research this potential for bias was mitigated as much as possible by the research of multiple empirical sources of data, such as the personal reflective experience of the researcher, perceptions of a cadre of industry and regulatory agency professionals and historical metrics published by key regulatory bodies, the latter as discussed in this thesis, that represent almost half of the global prescription (ethical and generic) drug products.

It is clear from this research that the reflexive approaches discussed in previous chapters that led to the identification of the research question, primarily based upon the research near four decades of professional practice has been supported by the populations of global industry SMEs, Regulators, and historic regulatory metrics. Reflecting upon the mind map presented in Figure 8, it is apparent that this research has demonstrated the level of concern that exists within the researcher's professional industry that regulatory oversight is clearly required. This research has demonstrated that it is more than just oversight that is needed, areas such as:

1. Harmonisation
2. Best practice
3. Education
4. Engagement

These are also key factors in the continued improvement required for pharmaceutical quality when viewed as a global single supply chain.

As described by Slack and Drauglis (2001) The information needed to determine the internal and external validity of any research project is relatively well understood. For this study internal validity is the extent that the data establishes the cause-and-effect relationship between the site of manufacture and the resultant quality of the pharmaceutical drug product, specifically in addition in this case is the role that regulation and regulators play in that causal relationship. In this thesis the researcher has produced a logical framework within which to conduct this study as demonstrated in previous chapters and the utilisation of cognitive maps throughout highlight this process. There are threats remaining to the claim of validity, whilst mitigated as much as practicable these remain as:

- External variance due to agency reporting structures differing between individual competent authorities
- Unconscious bias, as an emic researcher there is always the risk of unconscious bias, whilst to a degree mitigated by the inclusion of subject experts this cannot be fully excluded
- The generalisation of the findings by trending, this remains and will be discussed in the connect of abductive reasoning later in this thesis

Specifically for external validity we should consider Reiss (2019) who claimed that external validity is problematic primarily due to data extrapolation conducted under poor evidential reasoning however still recognising the need for external validity whilst also expressing its obvious limitations. In addition, Bo and Galiani (2021) highlight the importance of external validity and the researcher has sought to encompass both aspects in this thesis.

In addition, Huebschmann, Leavit and Glasgow (2019) when investigating clinical research also stressed the importance of external validity, hence the claim in this thesis of the applicability and global validity of existing quality measures contrasted with regulatory perspectives. More importantly, to understand the contextual premise of the data collected, for example the drivers for each regulatory agency, the experience of subject matter experts and the potential for varying perspective based on role such as an EU Qualified Person versus a non-Qualified Person was considered.

During this research project the pharmaceutical industry and regulatory agencies have had to contend and respond to the COVID-19 pandemic, as mentioned in various sections of this thesis this has impacted many areas addressed manufacture and regulation. In November 2020 the European Commission published a discussion document entitled *a pharmaceutical strategy for Europe*. Within this document it presented full main objectives for the industry and regulators. These aims were to provide access to affordable medicines, innovation, sustainability and to improve responsiveness, obviously the latter as a direct response to COVID-19. One key aspect of these changes is to strengthen the role of the European Medicines Agency and as part of this the suggestion to incentivise the industry in areas of innovation and unmet medical need however what

is lacking is a commitment to quality or a minimum quality standard that needs to underpin these aspects. The European Union published a road map in 2021 on how it planned at that stage to revise pharmaceutical legislation, that proposal is still under revision. Initial suggestions include an increase in regulatory flexibility anchored within a firm basis of technological developments. On the basis of this research those approaches are most interesting and supportive of new drug registrations but do not address the issue of quality parity or concern on product importation.

In parallel to the European Union roadmap for pharmaceutical products, the United Kingdom MHRA issued a business plan in mid 2020 that differs slightly from the EU road map in that it states that the primary aims of the MHRA are to ensure the patients have access to safe efficacious medicines with no mention of country of origin being a differential between domestic or international manufacturing. The second objective is to support the development of new pharmaceutical drug products that meet acceptable safety and quality standards. For the purposes of a safe and efficacious medicine, monitoring of medicines and medicine usage is absolutely key, one artefact of the United Kingdom leaving the European Union is that the UK would not have access to the EudraVigilance system. To counter that lack of pivotal data the UK will stand alone, and we use an artificial intelligence-based system to assess real world data that is generated within the United Kingdom National Health Service. This will in part mitigate for loss of access to the wide European pharmacovigilance data package whilst maximising UK centric data available in the much smaller patient pool.

In addition to the European Union and United Kingdom approaches it is worth mentioning that the World Health Organisation (WHO) also have a series of guidelines and import procedures for pharmaceutical products. The WHO procedures, updated in 2018, this as close to a global guideline as is currently available. This document does not directly address product quality of parity, merely documentation and process so it is therefore of limited value in this research.

The European approach still stands as that described in EudraLex Annex 21 and some key aspects are worthy of discussion.

*“2.2 All stages of manufacture of imported medicinal products which are carried out in third countries should be conducted in accordance with EU GMP or equivalent standards and in conformance with the Marketing Authorisation (MA), the clinical trial authorization (CTA) and the relevant quality agreement, as applicable.” (EudraLex Annex 21)*

This guideline directly references European expectations for Good Manufacturing Practice. It should in that case be clear as to what is expected however how is that to be assured given the evident extremely low percentage of overseas sites that are inspected for general compliance (not including non-conformance or for-cause audits). This in effect pushed the inspection aspects and verification of regulatory compliance downstream to the EU Qualified Persons. Whilst this is an EU document the same approach is in effect in the United Kingdom. This is a major concern for Qualified Persons as illustrated by the response below from this research:

*“If you're going to have global standards, you need global enforcement. If you don't have a consistency of enforcement, you end up with a situation where we've got in Europe where you've got you know 27 different interpretations of what Annex 1 means and so on and different levels of rigour” (EudraLex Annex 21)*

This lack of consistency, if evident in regulation or enforcement must also therefore appear in subsequent products. This also applied to the level of available and applied expertise within agencies cited by a participant in this research as, when discussing the role of regulatory agencies from a USA SME:

*“I don't think they want to admit they don't know everything. And that is a worry”*

*“2.4 The Qualified Person certifying the batch has to ensure that all the medicinal products for human or veterinary use that are imported into the Union from a third country were manufactured in accordance with EU GMP or equivalent standard and tested in the Union, unless there are appropriate arrangement in place between the Union and the third country (e.g., Mutual Recognition Agreement).” (EudraLex Annex 21)*

This downstream monitoring by the QP, whilst a legal responsibility for the QP, places significant pressure on named individuals. The role of the QP, in Europe and the UK, is

summarised as:

*“The QP is responsible for ensuring that each individual batch has been manufactured and checked in compliance with the laws in force in the member state where certification takes place, in accordance with the requirements of the marketing authorization with good manufacturing practice.”* (European Directive 2001/83/EC)

These duties are summarised as:

- Manufacturing has been carried out in accordance with GMP regulations. The QP might need to check additional documents and take part in quality reviews.
- Manufacturing and testing processes have been validated. The QP should have access to all documentation, including deviations, investigations, change control, CAPA, etc.
- Deviations or changes in production or quality control have been authorized by the responsible persons.
- All necessary checks and tests have been performed and all production and quality control documents are complete and authorized.
- All audits are carried out as required.

The latter bullet is of key importance, is this a downstream regulation or a delegation of responsibility from national competent authorities to an individual QP? Whilst a QP is a registered individual on a manufacturing licence in the UK and EU they are not expert in all associated technologies, they do have an appreciation of them. Regulatory enforcement should sit outside of the QP framework.

*“2.5 Testing in an EU/EEA state covers all the tests needed to demonstrate that the medicinal product meets the specifications that are set out in the marketing authorization.”* (EudraLex Annex 21)

The aim for testing a representative sample within the importing European Country is not unique to Europe and also applies to the United Kingdom and the United States of America. However, as with any testing, this is subject to variation, highly dependent upon

the suitability of the analytical methods, including sensitivity, and the sampling process undertaken. The sample size itself is controversial because it then relies upon statistical extrapolation and having a statistically valid sample size for the manufacturing process. This requires a robust and reproducible drug product output from the manufacturing process, something that cannot always be assumed. Therefore, this sample analysis within the importing country is of little value to actually determine quality. In addition, consider the researcher's previous claim of quality being the sum of all the manufacturing process aspects and the need for good development pharmaceuticals to underpin them.

This should also be considered in light of this research as cited by a respondent as:

*"You see very little in the way of science-based pro-active risk management. It is used largely to justify inappropriate behaviour, inappropriate results"*

Within the current regulatory framework within some countries there is a poor appreciation of science-based risk assessment or quality risk management.

*"3.0 The site(s) conducting importation activities should have an appropriately detailed documented Pharmaceutical Quality System in accordance with Chapter 1 of the EU GMP Guide and reflecting the scope of the activities carried out"* (EudraLex Annex 21)

Whilst the above appears to be a clear quality ensuring requirement in reality this is insignificant to the quality management system of the manufacturing source. This nebulous statement could imply that the importer company QMS is not subservient to the manufacturer whereas they should be of an equivalent minimum quality standard.

*"5.1 The MIA holder responsible for QP certification of the batch should have access to full batch documentation at all times."*

This requirement raises the question of QP access to all documentation and how is that ensured? There are no implementation guides or frameworks in which to demonstrate compliance and not selective reporting.

*"5.3 Batch documentation, including batch certificates, supplied by the third country manufacturing site should be in a language understood by the importer. It may be necessary to provide documents in more than one language to facilitate understanding."*

This statement alone does not ensure quality or parity; indeed, it is suitably vague as to permit a QP to import with minimal oversight which feeds back to the primary challenge to those process, that of where the regulatory oversight sits, regulator or importer. This was also raised by respondents as an area of concern as illustrated by:

*“You see very little in the way of umm science-based pro-active risk management. It is used largely to justify inappropriate behaviour, inappropriate results and from a regulatory point of view you only have to look at financial services and what risk-based oversight did to that, to know that this is a terrible mistake”*

*“They were concerned about giving us that information or whether they didn’t think it was significant, that was the key”*

### **Critical Quality Attributes**

*“A Critical Attribute is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials) and drug product.*

*CQAs of solid oral dosage forms are typically those aspects affecting product purity, strength, drug release and stability. CQAs for other delivery systems can additionally include more product specific aspects, such as aerodynamic properties for inhaled products, sterility for parenterals, and adhesion properties for transdermal patches. For drug substances, raw materials, and intermediates, the CQAs can additionally include those properties (e.g., particle size distribution, bulk density) that affect drug product CQAs.*

*Potential drug product CQAs derived from the quality target product profile and/or prior knowledge are used to guide the product and process development. The list of potential CQAs can be modified when the formulation and manufacturing process are selected and as product knowledge and process understanding increase. Quality risk management can be used to prioritize the list of potential CQAs for subsequent evaluation. Relevant CQAs can be identified by an iterative process of quality risk management and experimentation*

*that assesses the extent to which their variation can have an impact on the quality of the drug product”*

This is the how and why. How do we know what the quality attributes are, how are they defined? Why do we control them?

### **Control Strategy**

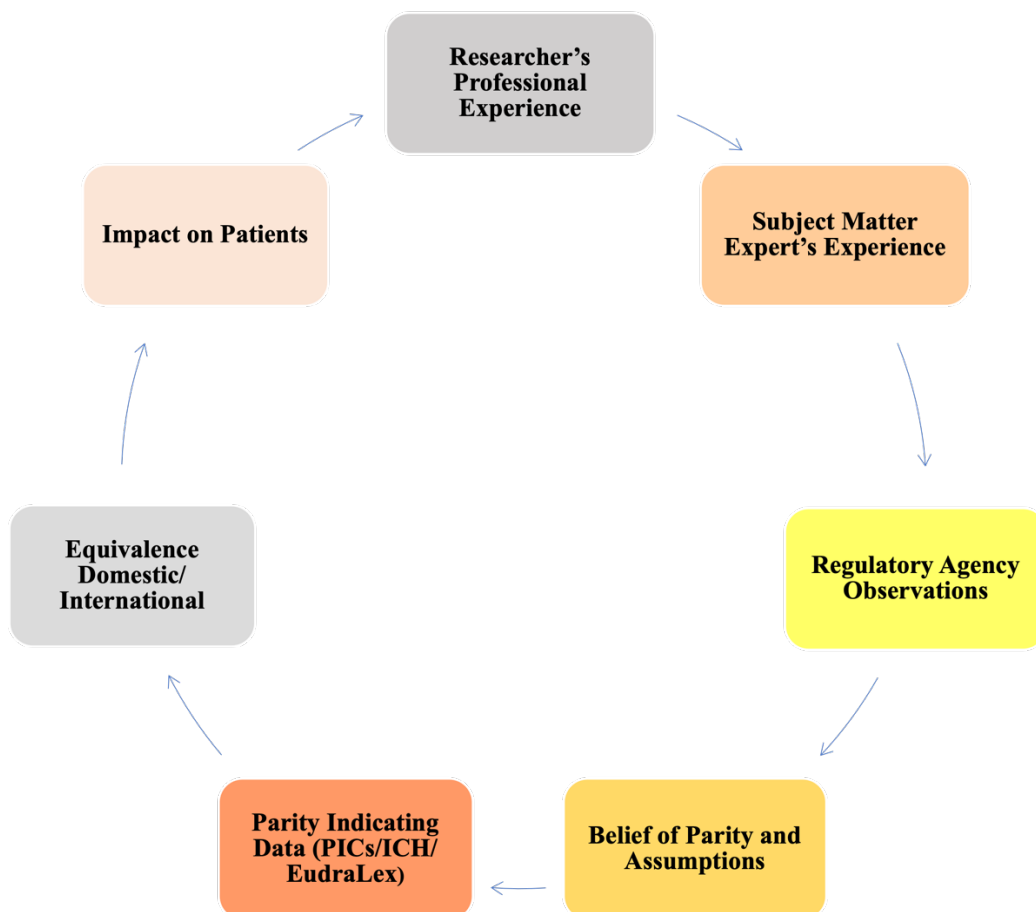
*“The section of the application that includes the justification of the drug product specification is a good place to summarise the overall drug product control strategy. However, detailed information about input material controls and process controls should still be provided in the appropriate dossier format sections (e.g., drug substance section, control of excipients, description of manufacturing process and process controls, controls of critical steps and intermediates”*

This is the data that defines how to achieve a robust and reproducible dosage form.

For a research project such as this the researcher has three primary methods of assembling the data into an applicable model or at least into a framework that will aid further discussion and development. Given the nature of the pharmaceutical industry, its scope and volume, only a small fraction of data can be reviewed and there is a risk of western hemisphere bias therefore the approach of abductive reasoning is appropriate in this case based on the following premise:

- Abductive reasoning: based on incomplete observations, in this case a partial set of data as it is impractical to assess all regulatory agencies and industry professionals for all countries concerned.
- Deductive reasoning: leading to a specific conclusion that would, most likely, always be true. In the existing data such variation exists that would prohibit the formation and argument of specific conclusions.
- Inductive reasoning: based upon specific observations leading to a conclusion that may be true.

Given the aforementioned data limitations the researcher concluded that abductive reasoning is the logical approach and has been adopted throughout this thesis. As stated in the prologue the researcher's own professional experience initiated this research into the parity of international drug products, by analysing the perspectives and experiences of subject matter experts from various geographic areas and coupled with regulatory data reports from key markets the researcher has reviewed the question and concluded that there is an issue of non-parity between domestic and internationally manufactured pharmaceutical drug products. Patient safety is paramount to both regulatory agencies and pharmaceutical industry however it is clear from this research that the drivers should show that patient safety are different. The researcher has developed the iterative figure shown in Figure 64 to illustrate the research cycle with regard their professional experience.



**Figure 64: Illustration of the researcher building upon their professional practice**

Based on the data generated in this research it is essential to rethink and define pharmaceutical quality as more than just validated process, testing, and regulatory agency policing, rather a model of total product quality could be adopted. To discuss total product quality, it is first essential to discuss total quality management. Total quality management is a process of detecting and reducing and ultimately eliminating defects in manufacturing, supply chains allowing fully provision of the desired product quality attributes. Essential attributes of this are training, accountability, expertise, transparency, and these equally apply to manufacturing organisations and regulatory agencies regardless of location. A total quality management approach requires that all parties involved be held accountable for the overall quality of the final product, in the case of pharmaceuticals that includes the following:

- All suppliers of starting materials and components
- Manufacturers and associated laboratories
- Packagers and repackages
- Warehousing
- Distribution
- Exporters
- Importers
- Regulatory agencies

Total quality management was developed by William Demming as part of the 6 Sigma / Lean Sigma approaches to product quality improvement processes. Whilst total quality management has some of the same characteristics in 6 Sigma it is not the same as 6 Sigma process improvement. It is an essential component for total quality management that all procedures policies and standards are fully aligned with process improvement and fully aligned with quality standards. In the case of pharmaceutical product manufacturing, it is evident that the different global standards currently in effect contribute to poor product quality in certain cases and, therefore, an obvious recommendation from this research would be the adoption of a single quality standard. ICH have attempted to address this with their quality standards. However, the integration of ICH quality standards it is still only one part of the overall quality picture when viewed with country specific requirements. The challenge facing industry and regulators alike is to find a

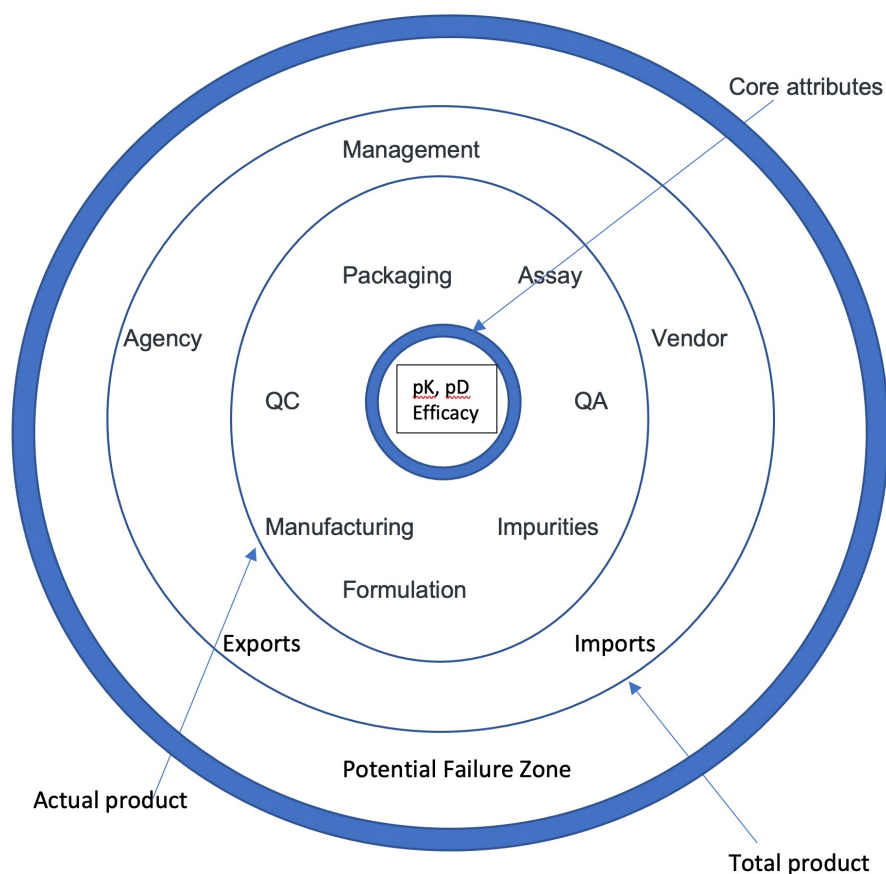
format with which to harmonise regulatory expectations to such an extent that quality becomes a collection of global standards. It is recommended that any quality standard combines the following characteristics:

- Development of a robust methodology for detecting and reducing and mitigating errors and failures
- focus on streamlining supply chain management and training for all concerned
- constant review of internal practices whether industrial or regulatory
- promotion of transparent processes and transparent accountability for the overall product quality

A quotation from B.W. Tuchman (1980) sums this approach, which applies equally to pharmaceutical as well as other non-related industries:

” ... a condition of excellence implying fine quality as distinct from poor quality .... Quality is achieving or reaching for the highest standard as against being satisfied with the sloppy or fraudulent.”

On the basis of this approach to total product quality, with regards to pharmaceutical products, the researcher has proposed the following conceptualisation as shown in Figure 65.



**Figure 65: Researcher developed model of total pharmaceutical product quality**

Total pharmaceutical product quality approaches could have a significant effect on product quality and therefore an impact upon patient safety. It could also have beneficial effects on companies, employees, and regulation agencies with a commensurate increase in product quality assurance, decrease losses and access resources applied by industry and also decreasing the amount of time and resource required by agencies to police regulations. This could in effect create a single micro culture that encompasses both the pharmaceutical industry and the regulatory bodies while still maintaining the regulatory bodies independence and ability to regulate. In summary, it could lead to long term benefits for industry, regulators, and patients. A total pharmaceutical product quality approach would also help in the identification of skills and expertise deficiencies moving companies, this could also be applied to facilities.

This approach can also support improvements in training and mentoring frameworks for both industry and regulators. As a science-based industry pharmaceuticals relies upon

innovation and scientific rigour to develop new products. This can only be done in conjunction with regulatory agencies as they would also need to understand and appreciate new emerging technologies under applications. This would always be a challenge for the pharmaceutical industry, given its dependence on intellectual property and patents, however considering patient benefits sharing of knowledge and best practice must be improved. Related to varying management approaches the formation and identification of cross functional teams, working in a matrix to share knowledge and gain greater understanding leading to an increase in communication and a coordinated response from previously disparate groups, will benefit knowledge management and also a similar approach could be taken for regulatory agencies.

#### **5.4.4 Communication**

In any organisation communication is key, in a regulated industry even more so. The research objective of determination if communication barriers exist has been fulfilled and as can be seen from the SME testimony's it is an issue. When considering communication this research has highlighted a number of areas where communication is less than ideal, in addition to areas that could be classified as sharing best practise, this included quality management.

From a company perspective a total quality management approach has obvious potential tangible benefits such as:

- Decreased number of product failures, a right first-time approach, a compliant first-time approach.
- Patient and Regulatory agency satisfaction will be increased
- Less wastage, for example resources personnel and materials
- Greater engagement from employees and regulators that can develop Common Core values for product quality

This summary contains a number of different conjectures. The underpinning stance of post positivism is based on the belief that human knowledge (professional experience) is conjecture, and that underlying knowledge can be questioned unchallenged appropriately.

this previously being discussed by Groff (2004), this research has attempted to find the underlying truths underpinning the researcher's professional practice. From this research it appears there has been a substantial decrease in regulation inspections from 2015 to 2021, notwithstanding impact of the COVID 19 pandemic, in addition to this general decrease an even larger relative decrease in the frequency of overseas inspections certainly by European, North American, and Australian regulatory agencies and it cannot be discounted that this lack of policing of regulatory expectations has led to an increase in product defects.

In consideration of regulatory roles, it is worth reviewing the role and aim of the regulatory agencies reviewed in this research. The TGA state:

*“The TGA is responsible for protecting the health and safety of the community by regulating therapeutic goods for safety, efficacy, performance, and quality. Consistent with the Therapeutic Goods Act 1989 we:*

- *Apply scientific and clinical expertise to assess whether the benefits of a therapeutic good outweigh any risks to health and safety*
- *Assess the suitability of therapeutic goods for supply, import and export from Australia*
- *Regulate manufacturers of therapeutic goods to ensure they meet acceptable standards of manufacturing quality*
- *Assess the quality and compliance of therapeutic goods on the market, including through laboratory testing where appropriate*
- *Implement a range of regulatory actions (in response to non-compliance or emerging safety concerns) that are proportionate to the potential risk arising from the non-compliance or safety risk.*

*We achieve this by applying risk-based processes for both pre-market assessment and post-market monitoring, as well as promoting regulatory compliance through clear and transparent decision making, providing education and guidance, and using innovative technologies and ideas to streamline business functions.”*

Similar statements exist for the MHRA and FDA:

## FDA

*“The Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation’s food supply, cosmetics, and products that emit radiation.”*

## MHRA

*“The agency is responsible for:*

- ensuring that medicines, medical devices, and blood components for transfusion meet applicable standards of safety, quality and efficacy*
- ensuring that the supply chain for medicines, medical devices and blood components is safe and secure*
- promoting international standardisation and harmonisation to assure the effectiveness and safety of biological medicines*
- helping to educate the public and healthcare professionals about the risks and benefits of medicines, medical devices, and blood components, leading to safer and more effective use*
- supporting innovation and research and development that’s beneficial to public health*
- influencing UK, EU, and international regulatory frameworks so that they’re risk-proportionate and effective at protecting public health”*

Of particular interest is the final bullet in the MHRA statement regarding international frameworks, this research has shown that these international frameworks are of considerable concern and do not, currently, function as fit for purpose. Although a counter claim can be made that domestically manufactured products from all three regulatory agency territories also fail specification and do sometimes fail on stability and some are manufactured in substandard facilities.

As previously referenced in this thesis, in June 2020 in a testimony before The United States Senate, the FDA director of healthcare stated that in 2019 the FDA investigation workforce identify persistent challenges was trying to conduct foreign inspections. This

was recited by the FDA as raising serious concerns of the equivalence or foreign to domestic inspection specifically. In addition, it was noted that FDA inspections in the United States are routinely conducted unannounced whereas it was common knowledge that overseas inspections are pre-announced sometimes up to 12 weeks in advance, this may have in many cases giving manufacturers the opportunity to fix or hide problems ahead of the inspectors' arrival. It was also noted that the FDA do not always have translators available on its audits when required, this is also an issue with European and United Kingdom inspections. This research and the summary in this thesis build upon the work of Danzon and Chao (2000) who found that price regulation contributed to development of new drugs, investment in facilities and overall acceptable quality of products for identified markets. This study has shown that financial incentives do drive the pharmaceutical industry investment in facilities and productive element. It does not have an impact applying regulatory oversight or regulatory compliance. The route of the Regulatory agency is driven by political mandates and, whilst limited financial measures exist for example budgets or availability to travel, there is not the overarching financial driver that is felt in the pharmaceutical industry.

The European Medicines Agency uses terms such as proportionate approaches to verification standards. This has obviously been put under pressure by the COVID 19 pandemic that occurred in 2020-2021 as reliance on remote assessments has led to not only a decrease in the level and quality of oversight but also substantially increased the emphasis of the role of the qualified person within Europe or indeed in the UK who follow a similar approach. The regulatory agencies discussed within this thesis have made clear in publications that their lack of oversight does not waive the obligations of manufacturers to be compliant with regulatory expectations. However, there is no guidance on how to achieve this. The United States of America Food and Drug administration initiated in 2017 a high level quality metrics initiative to facilitate greater oversight of manufacturers and quality drivers and efficiencies, one aim being to manage potential drug shortages. However, the other aim is to ensure drug quality, given the data in this thesis it is clear that regulatory oversight via inspections is still required and policing of regulations, as when they decrease leads to a decrease in product quality. Even with this desire to increase quality from the FDA this was still met with negativity by the pharmaceutical industry. In the past two years the majority of the product recalls for the markets researched have been due to products failing to meet their release

specification or due to failures on stability assessment. For these defective products it has been demonstrated that the majority of these were from overseas manufacturing facilities which have for the aforementioned reasons discussed in this thesis been inspected less frequently by regulatory agencies than their domestic counterparts. Therefore, it could be concluded that, although some products are recalled by appropriate recall procedures, some products may also still have entered into the patient market which are substandard or even potentially harmful.

The global pharmaceutical industry had, as of 2002, a global budget of US\$6 billion, the market for prescription pharmaceuticals in the United States of America was approximately US\$130 billion, with the UK a much smaller market at UK£7 billion (approximately US\$9 billion) and the European Union at €69 billion (approximately US\$79) (Abraham, 2002). This market has grown in the subsequent years. In 2020 the European market alone had grown by 480% to €335 billion (including the UK at that point) (EFPIA 2020). Product recalls and deficiencies resulting in loss of product, globally, from the data in this thesis can run as high as 20% in certain drug categories. A more meaningful approximation would be 5% across all products, with a 2020 global market of US\$1.27 trillion (Statistica 2020), including generic medications. That amounts to a potential global revenue loss to industry of US\$ 63.5 million. A significant sum that does not include internal company resource costs that were not realised in sales and associated regulatory agency costs in resources to monitor these failed products. From this perspective alone it is logical to conclude that an increased level of quality would benefit both industry and regulators alike, in addition to patients who are the ultimate consumer.

The generation of a single global policy standard integrated regulatory agencies and a clear transparent supply chain could lead to improvements in patient health the provision of cost effective, safe, and efficacious drug products. These aspects of harmonisation and clarity on regulatory expectations and specific key responsibilities of regulators and industry (such as the role of the EU or UK Qualified Person) warrant additional research in the spirit of continued process improvement, in this case the improvement in development and manufacture of pharmaceutical products with regulatory agencies as a key team member of the quality process on a global scale. This research has targeted large volume key markets with a focus on acceptable medications for primarily European

or USA populations, the drivers, and impacts for other diverse markets such as the Indian or Chinese internal markets would add a further dimension to this research and given an even greater global context for what makes a safe and efficacious medicinal product.

### *5.5 Limitations and further work*

It is acknowledged that there are limitations to the scope of this current research, such as the agency data limited to three major markets. These markets albeit significant in size still only represent a relatively small proportion of the global pharmaceutical market. Likewise, the mesarch could be expanded into emerging areas such as oligonucleotides and advanced therapy medicinal products. The addition of these areas would increase the applicability of this research and increased relevance to a global market and multinational companies.

In addition to research into other markets, a project focussing on the impact of outsourcing of drug product manufacturer into third party facilities would provide valuable insights into the potential for impact of this activity with respect to quality.

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## APPENDIX I: EXAMPLE INTERVIEW TRANSCRIPT

**Subject 97219**

**“Is the current regulatory purpose in the UK fit-for-purpose as it currently stands with regard to domestic versus international manufacture of products?**

The regulatory approval process?

**Yes, the approval process.**

No, no, I don't, I don't think it's fit-for-purpose. I think the / one of the interesting things that's come out of the vaccine development and licence submission and then to manufacture, is this perception that the MHRA used one of these clauses within the European Regulations to do real-time piecemeal licence review and they didn't have to wait until the final licence was given to them. So I think that says / I read somewhere that somewhere between six and 12 weeks is the approval process, which for something like a vaccine, is absolutely life-changing isn't it, for the amount of people that could be vaccinated in that period. So I think what's interesting there is that the <redacted> didn't invent this process and it wasn't a process specific to the UK, it was actually, I believe from what <redacted> told me, it was already allowed within EMA, but it wasn't enacted by anyone else apart from the <redacted>.

**Can you elaborate?**

So I think from that perspective we do need to have a proper look at the way licences get approved, so that you know, therapeutics going to address unmet medical needs are approved, the licences are reviewed and approved far quicker than what they have done before.

**So from what you've said then you believe that the process the UK adopted have the capacity to be fit-for-purpose, but they are not necessarily used the way they could be used?**

Yes. Yes. Yes, that really surprised me when I saw that, because you know why wouldn't the MA do exactly the same thing?

**A related question though, what do you think the drivers are for that difference in approach then?**

Umm / well from what I've read so far, and there's an awful lot of bluster going on, <redacted> under a lot of pressure at the moment over this, a lot of pressure particularly from the German authority, is that it would appear that that particular clause was wrapped up in this desire to have collective bargaining, a collective review process and a collective acquisition process for the vaccines for all 27 member states.

So it was already there that any of the individual member states could have used that clause, umm, but they didn't do it because they didn't want to break the uhh / kind of collective E.U. you know broad E.U. relationship and I believe Brussels you know were not comfortable with anyone going against that collective review process. So you know to wait until the very last / you know the very last piece of data before you review a whole licence seems completely crazy to me because, you know, fundamentally, I mean, you know this more than anyone, you may well find that the first piece of information that's submitted doesn't pass muster anyway and the earlier you know that the better.

Rather than leave it all until the last minute and reviewing the whole lot when it's all in place seems to me a very old-fashioned and kind of serial process rather than a parallel process.

So I think that's kind of / that needs another look at I think and I'm sure <redacted> will be having some sort of debrief and <redacted> analysis of all of this to see you know what went wrong because there must be scores of other licence <redacted> that are being made that should be expedited, you know, not just for unmet medical needs, but also for products that are in short supply, an alternative umm supply chain to be proposed and licences need to be submitted.

**So if you view it as a set of scales with patient safety (particularly with the Covid example) patient safety on one side and politics on the other, which side do you reckon has tipped in the last 12 months?**

Uhh / well / yes, hard to say really, because on the one hand of course there is a huge political will to get these therapies approved, but I really think that because of litigation and everything being in the public eye and 24-7 news, <redacted> I don't think any of the agencies across the world would short cut the patient safety requirements in any way, shape, or form, really. So in terms of the science I think science is being respected but political will is huge as well.

**Can you expand?**

Clearly. I know some people like to think of it as a binary choice or you know a sliding scale, but I think both of them have kind of come together here. You do hear some things in the news about how you know some member states <redacted>

And you know some people were saying well clinical trials have been rushed through. Well actually the number of people who were put on the clinical trials <redacted> basic minimum required, so umm / there's a third part of this kind of argument and that's the media isn't it and public perception.

Which is maybe somewhat different to what we normally see because you know normally we are just driven by the science, most of the time politics don't really come in to the review and approval of a therapeutic agent, umm, this time round its got both, and on top of that its got the media and the you know insatiable sort of appetite for 24-7 news, so everybody's you know / even people who have no affiliation with pharmaceuticals at all, suddenly seem to think they're experts in it all.

So yes I think there's like a three way pull here isn't there, there's the media, there's politics and there's the science.

**Do you think they're equally weighted at the moment?**

Uhh I would yes, I would. I think there's a constant battle between all three of them. Yes, I would.

So I think the review process definitely needs another look at, no doubt about that. In terms of inspections its been amazing really that the agencies have not adopted some form of remote inspection sooner, you know, we've had the best part of nearly 15 - 16 months now haven't we with almost no enforcement action whatsoever and we all know, over the last 15 months or so, there's been a lot of staff turnover, there's been a lot of stress, there's been a lot of additional risks I'm sure that are occurring in pharmaceutical firms as they are increasing their demand on capacity. They are introducing new products. You know they are turning over basically facilities to make vaccines etc. etc. and I don't get the sense that the agency, at least <redacted>, have been terribly involved in it, as much as they normally would. I'm thinking of <redacted> here because a friend of mine in the

Quality Director there and you know they've turned over at least half their steriles output to vaccine manufacture and its been done with very little scrutiny by the agency, very little.

**Do you think, do we rely on quality being enforced, do we rely on policing by agencies to ensure quality, or in the West, do we have more of a quality by design from day one?**

Well, uhh, certainly outside of Europe it needs enforcement, because people will do what is needed to be done for economic or financial reasons and then will try and clear up some of the issues later, ahead of an inspection, so those inspection dates are massive events to get prepared for, particularly for facilities, in the second and third world. I'd love to think that the <redacted> are not quite / Europe are not quite as bad as that but the proof of the pudding here. is maybe in a year or two's time when the agencies are back out on the road, maybe with some new inspectors, maybe with a more deep and broad audit schedule, it will be amazing to see how many enforcement actions <redacted> and warning letters and <redacted> meetings are going to be needed because, while the cat's away the mice play. Now the general feeling is that there will be a lot more enforcement action needed, as a kind of catch-up.

You know even in my experience, as a QP, would I take more risk on a facility that was inspected just by, for example, the Ukrainian authority, compared to the UK authority, absolutely definitely. Would I be forced into it or expected to do it, absolutely definitely, so they / the agencies do have a real role, a really important role, in enforcement.

**The Covid has given a great opportunity to look at different processes, so if I tell you the last set of data from the <redacted> last year showed in the previous 12 months, up until the end of last year, there was a 300% increase in defects and recalls for imported medicines as opposed to an 18% increase in domestic recalls. Are you surprised by that?**

Uhh / I'm not surprised that there's such a difference between domestic and imported products, but that level of increase is huge isn't it?

<redacted>

Well that's telling you something straight away isn't it? It's telling you that people are releasing a product that has a higher risk than what they would normally do.

And maybe they are doing it because they've got the smoke screen of Covid and the agencies in stasis.

**So from your perspective and obviously you've had a number of imports from various countries and dealings with agencies and as the QP, if you were taking a product and you had a choice of a product for example, generic product made by <redacted>**

**the <redacted> equivalent was made in Europe?**

Oh 100% Europe, every time. Because I used to work / I used to have several <redacted> and there was a little cohort of maybe five or six people all doing this quite regularly and we all made a pact / we all actually convinced and influenced that company to sort out the insurance for this that if any of us ever got ill, in any way, shape or form just get us on a flight, get us home. At first, when we first went out there, we were given packs of like infusion bags and syringes and it was just pathetic really, it was just ticking the box, and so we said look we'd much prefer to have the insurance, even if we're on death's door, just get us on a plane and get us to <redacted> as soon as possible. And I think that's certainly the case for / well it was certainly the case back then, especially if

you're going to need IV. In terms of anything else, you know, tablets, capsules, Ibuprofen, Paracetamol, I think we've all become accustomed now to the fact that the <redacted> can only afford generics made in India, China, and the Far East really.

**So the complexity of the product would influence your decision as well on that?**  
100%.

**Thinking about the agencies then, the agencies you've dealt with, if you had to view them holistically, globally, the ones you've dealt with, would you view them as autocracies or meritocracies?**

I would say, at least in my experience, I can only speak on my experience really. I would say the <redacted> that I've come across have been definitely a meritocracy. And I've got a lot of respect for their experience and their views on what they're being presented. I've also had reviewers and inspectors from <redacted>, really it was just tick boxing exercise and they actually didn't really fully understand the questions they were asking, so they may have a checklist, or an aide memoire of what to request and review and ask for, but when you presented them the information, they barely knew what to do with it at times. They couldn't really evaluate it very well. So it's spotty. Another example of this for us, contradicting myself a little bit, is I think we had two experiences in last couple of years where two facilities in <redacted>, making sterile products, clearly weren't meeting Annex I. It had been approved without any comment, not even a Category III or a comment observation from the <redacted> agency. There was no comment at all from them and I was asked then to sign off a certificate to say it was in compliance with a GMP. I couldn't sign it because it in no way, shape or form met Annex I, but their agency had signed it off, so umm / there's obviously a fair amount of disparity in the approach and experience, maybe even the influence within the European member states as well, you know, roughly dividing north to south.

**What do you think would be the biggest benefit for global quality, We've talked about ICH. There's various topics of mutual recognition between various agencies that have been having / even between the UK and the U.S. mutual recognition has been going around for decades now. What do you think would be the biggest benefit to get a global system, to push a global system of qualification and recognition?**

Well I would have said this a year ago but I'm probably going to say even stronger now and that's PICS, without / with what you're reading in the papers at the moment about Brexit and MHRA, there is a sense that we may not always follow exactly what's in the EudraLex but we will follow what's in PICS. Now everybody hopes that PICS isn't going to diverge too much from EudraLex and vice versa, but actually why not just have a single world standard and <redacted> the way forward isn't it.

**So who would?**

For example, EudraLex, the way they're splitting up EudraLex to allow for specific regulations for ATMPs, and certain types of biologics, just seems crazy. It's just fragmenting the key messages and as soon as you get some ambiguity there's going to be Finance Directors and dare I say QPs and Quality Directors that are going to work on those loopholes.

You know lead / some form of umm / uhh / apology for not meeting one requirement when another requirement doesn't require it.

Do you know what I mean?

There is an important role for the industry, however if there's no profit in a product, they

very rarely develop it, unless there's exceptional status for it, or some over driver.

**So what would be the biggest driver to get the industry, the global industry, to adopt a single standard do you feel?**

Umm / well on the one hand I think industry seems to work best when you've got a clear true north, you've got a kind of non-negotiable unambiguous set of regulations that everybody works to, so that then you're umm competitive advantage is based upon efficiency and process excellence rather than a degree of risk-taking against different regulations or regulations that are unambiguous or different across the world, you know, how we can look ourselves in the mirror and say, well, I'm going to make this particular product and it has some risk attached to it, whatever that may be, so therefore I'm not going to release it to the U.S. or Europe, but I can release it to Nigeria and South Korea, because it meets that specification or meets that requirement, you know, it seems that there really ought to be one global standard. What's the driver / what's the economic driver for that? Ooh I'm not sure because there's going to be a fair few companies who are going to have to raise the standards to delete that global requirement, which is going to add cost to them, so they are not going to buy in to it, umm, whereas the firms, parts of the industry, perhaps that are very used to working to European, UK, U.S. standards, will be very happy to do that because they are not being undercut by others. So I don't know whether there's modular and economic driver across the world to unify standards to be honest.

**You've got economics, a political will, do you then see a tiered healthcare system stratified to effectively related to the wealth of the respective countries and territories?**

I do, yes, yes. Yes, I do, I mean, after all, you know, when you look at umm what we as a country pay in tax to fund the NHS, the investments made over the last 40 years in to the NHS, you know, how on earth can we ever expect Angola and Mozambique to have anything like that, they just / they're never going to have that.

So therefore they are going to have to find ways of sourcing products at a considerably cheaper price aren't they?

Services at a considerably cheaper price.

You know, unfortunately, it's a bit like a meritocracy isn't it, the countries of the world that benefited from the industrial revolution and empire and all the rest of it, are going to be the ones that are literally decades ahead in development and umm implementation of all the various technologies.

I mean I heard on that FT Global Board Room that you know way back in the industrial revolution what really umm made the UK, Germany and even parts of Holland, the global force that they were was coal. If you had coal you had steel and you had iron and you could build things and you know you could build faster ships and bigger ships to trade and all the rest of it. Then it became obviously after World War II, it was all about nuclear power, and nuclear weapons, but in the FT Global Board Room they think that the third generation of what we're going through is all about 5G.

So if you're well connected you're going to get products and goods and services that other people can't get and I just can't imagine vast parts of the world having the degree of connectivity that they have in Japan or you know South Korea or even Europe I guess.

**Do you think there's a certain contribution of nationalism to this argument as well because, you know, we write a submission in America, for example, now you list Mannitol, BP, USP, NF, JP, and for the most part a lot of those specs are aligned**

**and it's where there are differences they are exceptionally minor differences, but you still have to sign the local pharmacopoeia. Do you think that helps or hinders or just a bureaucratic hoop we have to jump through?**

It probably hinders but it's definitely hampers doesn't it I think in about that umm <redacted> where we had to convince I think it was a firm around the Chinese expectations.

So yes there's certain hoops that you have to go through that are based upon national requirements and I don't see that changing very much.

**So talking about China as a specific market, do you have a lot of experience with China?**

Not really, no, not much.

**So as a QP then, in your / your QP role, with that hat on, if you're receiving an API from China knowing, as you do, that there are well documented issues of API issues in China and corruption that came about from that, do you feel confident that material from China would be equivalent to you know what's in your MAA?**

Umm / well just thinking from an experience of <redacted> to start with, the initial answer would always be no, not confident at all, but we always factored in a degree of additional oversight that we needed to budget for APIs coming from China, as opposed to almost anywhere else. So the level of umm qualification of that supplier and also the ongoing oversight, the audit frequency, umm, you know maybe even for one week we put in place a local person in plant and pay for that, to be sure that we were comfortable with that supply. The interesting thing with this though is that when you add all those additional costs up, then you add them to the cost of the Chinese supply and put it against maybe a local supply, the driver to go to China diminishes significantly. Where it's been interesting for us in the past though. is that it's a bit like right pocket, left pocket, you know, one half of the company is delighted because they are buying cheap material from China and they are being bonused on that purchase of procurement strategy, whereas the other part of the business is strongly with the quality regulatory and QA oversight aspects and having to put extra money into the business. So once you get a one company PL you'll be able to bounce off the two. Often times you find, well, either go into it with your eyes open, and put a sufficient budget for oversight qualification, or reduce your risks, pay a little bit more.

So you're already factoring in, consciously, the fact that there will be / there is that potential for issues there, even / not justified at that moment in time, you assume there will be?

100%, 100%, yes. I mean typically we would inspect API facilities in Europe, maybe once every three to five years, whereas Chinese are done every year, absolutely every year.

And if there was any issues that caused them to go late, or they didn't want us to come, or it was delayed, we would stop purchase straight away.

So we'd always needed a second supplier who we could slot in to place, or indeed, often times <redacted> To cover any drug shortages. Or API shortages.

Which is lost money as well isn't it?

**We talked about standardisation, we talked about global harmonisation and the role of ICH, PICS. As an industry leader, and a QP, you take personal responsibility for approving products for human consumption. You interact with international agencies. Do you feel there's a role here for people such as yourself to push this**

**change, this new modality, this new world? Do you have a role in that?**

Umm / this new modality meaning a different way of managing supply chains?

**Yes**

Submitting licences. Different way of manufacturing?

**Yes.**

To push that train forward, to make that quality step change, for all products, not just the ones we manufacture in the <redacted>, but the ones we import from other markets, do you feel you have a role in that?

Oh 100%, 100%, I do feel as if we should have a role in that. Where we get that opinion and that umm / perspective or desire projected to and how isn't so clear really.

You know would it be through professional bodies, I don't know, PDA, there's a variety of ways, but I'm not quite sure how effective really any of those are to make the sort of changes that we would like to see really.

**So what would work?**

Does anyone ever ask me.? Does anyone ever say, why don't we pick out the top 20% of QPs in terms of their experience on licences, get a conference together, and find out what's keeping them up at night.

And how they'd like to see the world differently in the future. No, I don't think I've seen anything like that.

**One last question. Have you found that big pharma engage agencies the same depth and frequency as small pharma or biotech or have you had a different experience of that?**

Umm / if you'd have asked me that question / let me see / if you'd have asked me that question when I first became a QP, which was around 1995, when I worked for <redacted>, I would say yes. If you were seeking that kind of conversation with the agency you almost had to get approval from CEO before speaking to them.

And what you said and how you said it and how you arranged a meeting would be scrutinised hugely before you even were able to suggest a meeting with them. But, since then, the amount of times I've been encouraged to, but also done, facility review meetings or submission review meetings, budgeting meetings, it's really taken off, so I think maybe in the last 20 odd, 15 years or so, it's got a lot better, even to the point I think maybe what made a big difference from the time at Piramal, was when the umm / annual compliance reporting system came out with the MHRA.

So you would summarise each year all of the risks that you've dealt with. You'd summarise any major changes on the site and there would be a section, within it, that would describe your development plans, so if we were to, for example, uhh, want to build a new facility for female hormone production, or contraceptives, or maybe a <redacted> product, we would make sure it was in that compliance review report that comes out annually, at least a year or two before we begin to build a facility, to initiate that conversation with the people involved.

I think that's a lot more common these days.

**So you're saying you've personally seen that change, that evolution in the way that the two groups interact?**

Yes, I think so, yes, yes. At least in the <redacted>, definitely, yes. I mean even to the point in which, during the inspection, we used to joke that we knew the inspection was coming to an end and they were comfortable with what they'd seen, when they then ask us at the last hour of so, two hours of the inspection, you know, what are your plans in the

next year, what are you spending your money on, you know, what products are you hoping to bring in? Is there anything you need to make us aware of, you know, and I think that was a good conversation to have because it was verbal, it was unscripted, it was unvarnished, they were talking to you know quality directors and production directors, technical directors, rather than having it written down, or approved by the CEO, it wasn't political, you know, politically approved in any way. I think that was a good thing to do. Yes, yes. So engagement is changing but it's also key to moving forward? 100%, 100%.”

## APPENDIX II: CONSENT FORM

The following consent form was approved by ARU ethics panel for use in the pilot study. No further ethics approval was required for the main study program and therefore this was incorporated into the online questionnaire requiring a positive result for the main study.



### PARTICIPANT CONSENT FORM



#### NAME OF PARTICIPANT:

Title of the project: Research into the parity between international pharmaceutical product development and registration processes with respect to product equivalence and safety

Main investigator and contact details:

Paul J Cummings

Email: [paul.cummings@pgr.anglia.ac.uk](mailto:paul.cummings@pgr.anglia.ac.uk)

Telephone: <redacted>

Members of the research team:

1. I agree to take part in the above research. I have read the Participant Information Sheet (7<sup>th</sup> June 2019 v1) for the study.  
I understand what my role will be in this research, and all my questions have been answered to my satisfaction.
2. I understand that I am free to withdraw from the research at any time, without giving a reason.

3. I am free to ask any questions at any time before and during the study.
4. I understand what information will be collected from me for the study
5. For the purposes of the Data Protection Act (2018), if this project requires me to produce personal data, I have read and understood how Anglia Ruskin University will process it.
- 7 I understand what will happen to the data collected from me for the research.
10. I understand that the interview will be recorded
11. I have been informed how my data will be processed, how long it will be kept and when it will be destroyed.
12. I have been provided with a copy of this form and the Participant Information Sheet (7<sup>th</sup> June 2019)

Name of participant (print).....

Signed.....

Date.....

PARTICIPANTS MUST BE GIVEN A COPY OF THIS FORM TO KEEP  
ADD DATE AND VERSION NUMBER OF CONSENT FORM.

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I WISH TO WITHDRAW FROM THIS STUDY.

*If you wish to withdraw from the research, please speak to the researcher or email them at paul.cummings@pgr.anglia.ac.uk stating the title of the research or send them this*

*withdrawal slip.*

*You do not have to give a reason for why you would like to withdraw.*

*Please let the researcher know whether or not you are happy for data that has been collected up to this point to still be used. You are completely free to ask for any data to also be removed should you wish it to be, as long as the data is not anonymised. When data is anonymised, it means personal data relating to it has been permanently removed, so the researcher will not know which belongs to you.*

Date 07 June 2019

V1

## APPENDIX III: QUESTIONNAIRE COPY

### **PARTICIPANT INFORMATION**

#### **Section A: The Research Project**

**Title of project: Research into the parity between international pharmaceutical product development and registration processes with respect to product equivalence and safety**

**1. Purpose of study**

The purpose of this research is to look into how we ensure that international approvals for imported medicines reach the same standards as those adopted for local market approval, such as those within the EU, USA, Japan and other markets. The evaluation of the processes of data generation, review, the application of expertise and where appropriate education in new technologies and the review process needs further ongoing evaluation to provide a meaningful platform for process change and potentially cultural shift. The ultimate aim of this research is to assist in the development and implementation of an open, transparent and effective development and review process.

**2. Who am I?**

I am Paul J Cummings a DProf researcher at Anglia Ruskin University

I am a pharmaceutical industry professional who has worked in the industry for 36 years. My doctoral supervisors at Anglia Ruskin University are Prof. Michael Cole and Dr Alan Coday.

**3. Why have I been asked to participate?**

You have been asked to participate in this research because of your experience and role within the pharmaceutical industry and/or the Regulatory Agency(s) that regulate it.

**4. How many people will be asked to participate?**

Up to 100 industry experts will be asked to participate in this research project.

**5. Do I have to take part?**

No you do not have to take part; participation is entirely voluntary. If you have any concerns or questions please contact the researcher before completing the consent form.

**6. Has the study got ethical approval?**

This research project has ethical approval to proceed from an ethics committee at Anglia Ruskin University.

**7. What will happen to the results of the study?**

The results of this research will be written up as part of a doctoral thesis and also potentially published in journals and presented at conferences. All data will be anonymised and no names of participants will be published in any form.

**8. Contact for further information**

Email: [Paul.cummings@pgr.anglia.ac.uk](mailto:Paul.cummings@pgr.anglia.ac.uk).

Telephone: +44 <redacted>

## Section B: Your Participation in the Research Project

### 1. What will I be asked to do?

You will be asked to complete this questionnaire and possibly a follow up structured interview with questions relating to the following topics:

- Your experience in the pharmaceutical industry (roles, scope, types of dosage forms)?
- If applicable your number of years with a regulatory agency?
- How many product types you have worked on?
- The number of international markets you have worked in.
- Whether on new chemical entities, line extensions or generics?

The questionnaire and interviews will be structured so that you will be asked to describe and categorize your experiences into ranked criteria such as number of years, number of products. No proprietary sensitive information will be requested. It is anticipated that the questionnaire will take up to thirty minutes to complete and the structured interview up to one hour, both will be scheduled at your convenience. The majority of people will only be contacted once, some participants will be contacted for both the questionnaire and follow up interview based upon the data gathered.

### 2. In relation to this specific research project, we need to make you aware of the following:

<input type="checkbox"/>	We do not need your personal data at any stage of this research project		
We are responsible for the personal data you give to us as a:			
X	<b>Data Controller</b> (We are in sole control over the research)	Who are we?:	Paul J Cummings
<input type="checkbox"/>	<b>Joint Controller</b> (Where ARU and another organisation are working together on research)	with:	Not applicable
<input type="checkbox"/>	<b>Data Processor</b> (Where the data will belong to another organisation and ARU is being engaged under contract/ agreement to conduct the research and provide an outcome but has	on behalf of:	Not applicable

	no rights over the personal data)		
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**3. I will be asking you for the following information:**

Personal Data			
	Name		Contact details
	Education		Experiences
	Location data		Opinions
	Professional Body Membership		Professional Registers (Such as EU Qualified Person)

The researcher is GDPR registered under the GDPR and Data Protection Act (2018).

**4. What will happen to your data?**

All your data will be anonymised. You will be assigned a unique identifier that will be stored on a secure server (Anonymisation refers to the process of removing personal identifiers that may lead to a person being identified from that information or combined with other information).

All research data will remain in the European Economic Area (EEA) and not be transferred outside of it.

All data will be stored on a secure protected server and not shared on any wider web-based platforms. Only data that is anonymised will be shared with the researcher's doctoral supervisor, no personally identifying data will be shared by the researcher.

Interviews may be recorded with the permission of the participant and in such cases they will be transcribed and the transcription will be anonymised as previously stated.

Questionnaires will be generated via JISC Online Surveys who have a GDPR compliant security policy, you can also find a link here to their privacy policy.

<https://www.onlinesurveys.ac.uk/help-support/online-surveys-security/>

The data will all be held within the EEA.

**5. Will I be reimbursed travel expenses?**

There is no requirement for travel or any other expenses to be incurred and therefore there is no reimbursement.

**6. Will I receive any payment to take part in the research?**

Participation is entirely on a voluntary basis and no payments will be made to participants.

7. **Are there any possible disadvantages or risks to taking part?**

There are no obvious disadvantages to taking part in this research as no sensitive data will be requested and all data will be anonymised by the researcher. However if you feel you are unable to commit to take part or to continue at any point please notify the researcher as soon as possible.

8. **What are the likely benefits of taking part?**

It is unlikely that there will be any direct benefits to participants however this study may yield some useful information that may facilitate a better understanding of the global development and registration process for pharmaceuticals.

9. **Can I withdraw at any time, and how do I do this?**

Participants can withdraw from the study at any time and without giving a reason. This can be done via email, telephone or simply returning the attached slip from the consent form retracting consent.

Your data up to that point may still be useful and in that case the researcher may seek permission from you to use this data. You still retain the right to withdraw your data completely from the study or to leave data collected to that point. Therefore, you have the option to withdraw from the study and have all data removed or to withdraw, but still be happy for the researcher to use any anonymised data collected up to that point. Once the thesis is drafted and any publications are complete you will be unable to withdraw your data.

You also have the right to refuse to answer any questionnaire or interview questions that do not wish to.

10. **What will happen to my data?**

**Our general privacy notice explaining our use of your personal data for research purposes is available here:**

<https://www.anglia.ac.uk/privacy-and-cookies/research-participants>

**Please visit this link for information about how long we keep your data, how we keep your data secure, how you can exercise your rights over your data, and make a complaint over our use of your data.**

11. **Can I withdraw my data from the study?**

I can only remove your data if you ask me before I anonymise it. After this, I won't know which is your data so will not be able to do this.

12. **Will I pass onto anyone else what you have told me?**

No information gathered will be passed onto anyone else.

13. **Contact details for complaints**

If participants have any complaints about the study the researcher can be contacted as below:

Email: [Paul.cummings@pgr.anglia.ac.uk](mailto:Paul.cummings@pgr.anglia.ac.uk).

Telephone: +44 <redacted>

However if the complaint is not resolved satisfactorily then Anglia Ruskin University can be contacted directly as below:

Email address: [complaints@anglia.ac.uk](mailto:complaints@anglia.ac.uk)

Postal address: Office of the Secretary and Clerk, Anglia Ruskin University, Bishop Hall Lane, Chelmsford, Essex, CM1 1SQ.

## **p. 2 Privacy**

All your data will be anonymised. Your answers will be assigned a unique identifier before analysis and reporting that will be stored on a secure server. (Anonymisation refers to the process of removing personal identifiers that may lead to a person being identified from that information or combined with other information). All research data will remain in the European Economic Area (EEA) and not be transferred outside of it. Only data that is anonymised will be shared with the researcher's doctoral supervisor(s), no personally identifying data will be shared by the researcher.

Please find a link here to the JISC privacy policy.

<https://www.onlinesurveys.ac.uk/help-support/online-surveys-security/>

## **p. 3 Consent**

1. Main investigator and contact details: Paul J Cummings Email:

[paul.cummings@pgr.anglia.ac.uk](mailto:paul.cummings@pgr.anglia.ac.uk) Telephone: +44 <redacted> Please read the following statements regarding consent for this study. I agree to take part in the above research. I have read the Participant Information Sheet (12th June 2020 v3) for the study. I understand what my role will be in this research and all my questions have been answered to my satisfaction. I understand that I am free to withdraw from the research at any time, without giving a reason. I am free to ask any questions at any time before and during the study. I understand what information will be collected from me for the study For the purposes of the Data Protection Act (2018), if this project requires me to produce personal data, I have read and understood how Anglia Ruskin University and the researcher will process it. I understand what will happen to the data collected from me for the research. I understand that the questionnaire and/or interview may be recorded. I have been informed how my data will be processed, how long it will be kept and when it will be destroyed. I have been provided with a copy of this form and the Participant Information Sheet (12th June 2020 v3) IF YOU WISH TO WITHDRAW FROM THIS STUDY If you wish to withdraw from the research, please speak to the researcher or email at [paul.cummings@pgr.anglia.ac.uk](mailto:paul.cummings@pgr.anglia.ac.uk) stating the title of the research.. You do not have to give a reason for why you would like to withdraw. Please let the researcher know whether or not you are happy for data that has been collected up to this point to still be used. You are completely free to ask for any data to also be removed should you wish it to be, as long as the data is not anonymised. When data is anonymised, it means personal data relating to it has been permanently removed

## **p. 4 Participant information**

2. Do you confirm you have read the participant information sheet (page one of this survey)?

Please follow the links below to open the information and consent forms in another window for you to save a copy for your records if required.

Information

Sheet: [https://static.onlinesurveys.ac.uk/media/account/115/survey/604276/question/participant\\_information\\_sheet.pdf](https://static.onlinesurveys.ac.uk/media/account/115/survey/604276/question/participant_information_sheet.pdf)

Consent

Form: [https://static.onlinesurveys.ac.uk/media/account/115/survey/604276/question/participant\\_consent\\_form\\_v2\\_pj.pdf](https://static.onlinesurveys.ac.uk/media/account/115/survey/604276/question/participant_consent_form_v2_pj.pdf)

## **p. 5 Your details**

**3a.** What is your surname?

**b.** Please enter a valid email address.

**c.** What country are you based in?

Please list the countries you work in.

**4.** What is your highest level qualification?

**5.** What best describes your primary academic area?

**6.** Do you have or are you eligible for EU Qualified Person status as per Directive 2001/83/EC?

**7.** How long have you been a QP / QP eligible or served as a QP?

**8.** How would you describe your breadth of experience?

## **p. 6 Career experiences**

**9.** How long have you worked in the pharmaceutical industry and/or for a Regulatory Agency?

**10.** Please select from the following areas you have gained experience in.

**11.** Please select from the following options the pre-clinical areas you have experience in.

**12.** What has been your primary work area? (Please select the area you have spent most time fulfilling in your career)

**13.** What clinical phases do you have experience in?

**14.** How many R&D products have you worked on that have been commercialised?

15. In what markets were these products registered?
16. Have you been involved in the importation of pharmaceutical products or the testing of imported pharmaceutical products?
17. Have you ever worked in a hospital or retail pharmacy or other related area in a patient facing role?
18. Has this impacted or influenced your approach to product development or manufacture?
19. Please describe the impact. If there is no impact please continue to the next question.

**p. 7 Personal perception**

20. Have you found that the concepts of cGMP were sufficiently understood and demonstrated in the markets you've worked within?
21. Did any particular market give you cause for concern, as a professional, with regards to delivering safe and efficacious products?
22. Can you list the markets/countries that caused concern in rank order? The first (1) listed being the market most concerned about.

**p. 8 Product recalls**

23. Have you ever been involved in a product recall?
24. What event initiated the recall?
25. Who initiated the recall?

**p. 9 Adverse events**

26. Have you ever investigated a serious adverse event caused by poor GMP and/or GDP?
27. In the case of a serious adverse event or death, what were the primary reasons identified from the investigation? (if known)
28. In your experience are the principles of ICH used to their full potential in associated markets/countries?
29. Why do you believe that?
30. Do you believe there would be a benefit to expand ICH to other countries?

31. Why is that?

**p. 10 Product / Process validation**

32. With regards to product validation, have you been involved in pre-commercial validation?

33. Do you feel that the same level of validation has been conducted with a comparable level of diligence for each market supply you have worked in?

34. In your opinion what is the primary reason for the difference?

**p. 11 Batch failures**

35. For routine commercial manufacture do you feel that companies evaluated batch failures in sufficient detail to prevent future failure?

36. In your experience what is the most common tool used to determine root cause analysis in batch failure investigations?

37. Please list the tools you have seen used in failure investigations, such as 5-whys, FMEA etc.

**p. 12 Other influences**

38. Do you feel sufficient effort is made in understanding pharmacogenomics and how they impact the development of new chemical entities?

39. Do you feel pharmacoeconomics has a detrimental effect on innovation?

40. Are there other drivers that impact innovation?

41. Please specify

42. Do you feel pharmacoeconomics has a detrimental effect on quality?

43. In your experience what other drivers do you believe impact quality?  
a Why do you believe that?

**p. 13 Innovation**

44. Do you feel there are additional constraints on the pharmaceutical industry that prevent innovation and the use of best practise?

45. If Yes, please specify and rank in order of priority, the first (1) being highest priority.



**p. 14 Drivers for innovation**

46. In your experience what is the most important driver for product innovation?

47. Do country-specific politics hinder or help product innovation?

48. Why do you believe that?

**p. 15 Corporate sharing**

49. Do you agree with the following statement? "The pharmaceutical industry is too insular and is not sharing or learning best practice across international markets. Companies internalise processes and systems rather than proactively sharing common best practice to achieve the best possible product in all markets for the benefit of patients."

**p. 16 Market access**

50. Are you comfortable with products from all markets being interchangeable from a quality perspective?

51. Do you believe national regulatory agencies are all of the same level with regards to diligence applied to product quality and efficacy assessments?

52. What do you believe could be done to achieve a truly global pharmaceutical market with parity across all markets for product development, manufacturing and overall quality?

**p. 17 Closeout**

There are no further questions, please proceed to the final page to close the survey.

**p. 18 Thank you**

This completes the survey; some participants may be contacted for further information by the researcher only as detailed in the participant information form provided.  
Thank you for your participation in this survey.

