

Subject 94772

“Is the current regulatory purpose in the UK fit-for-purpose as it currently stands with regard to domestic versus international manufacture of products?”

Probably not, no, no, I think there's definitely some significant weaknesses umm and you know you've kind of just got to look at some of the recalls umm certainly some of the clients we are dealing with that have you know / I've been working with another client this week who is facing a suspension from the <redacted> / we've got other clients who have had suspension. We can often get involved when people have had inspections and the umm they've gone quite badly and by definition, once you get to that stage, the agency are kind of thinking there's a pretty good chance of some sort of patient harm event or likelihood and therefore I think if the system were really preventing that threat, then you would see less of those events, umm, and so I think the model / it's not bad but it could certainly be better.

Would you say that's the same across all the countries in Europe, for example?

No, no, 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 <redacted> and umm you know I have been saying for a number of years now I think it's time for the sort of <redacted> 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, so one example was I went to a site in <redacted>, to look at umm / we were looking at the capsule process there, non-sterile capsule process, where we happened to look at an aseptic clean room they had, and you know I indicated that I was amazed that it was an aseptic clean room. I didn't think it was and you know I indicated that would have probably been shut down in the <redacted> decades ago and they very happily showed me a GMP Certificate for it and indicated their inspector had / was very happy with it and it was kind of a horizontal laminar air flow room, inlet in the ceiling, the operators could stand between the air inlet in the wall and the filling machine, so directly upstream of aseptic fill. Operators could stand there. And you know it was extremely poor, of a very poor standard, and at the time I'd been involved in the <redacted>, we were pushing sites to the point where they sort of surrendered their ability to make sterile products because they hadn't got full ramp systems in place and yet here was a site with completely open machinery and operators stood between the filter and the product and fully accepted and no seemingly compliance challenges, so I think there's too much variability for one and I think there are some segments of the industry as well that perhaps have particular compliance challenges umm possibly things like <redacted> and we do see a number of our clients have had some difficulties with the <redacted> area and perhaps the approach and attitude and maybe the consideration that it's just a bit of packaging and you know I've got a client now where umm the <redacted> are looking at offering them a / or giving them a suspension because of significant shortcomings in management oversight, QP responsibility, and so on, and that again I think there are some vulnerable sections of the industry perhaps where the level of regulatory oversight perhaps isn't quite delivering the right balance between umm pro-active engagement before significant action is required.

Pro-active engagement from the agency or from industry?

I suppose I was thinking from the agency really, umm, you know, we see a lot of people where the agency kind of goes in after quite a period of time and hits them hard and clearly that's not great for the patient, it almost always leads to some sort of supply interruption, umm, and it does indicate that the product's been made prior to that inspection, there's some doubt over it, umm, in terms of its quality, umm, and so I think it might be you know / if you look at / so the classic model, the inspectors turn up maybe every two or three years for a few

days and it's a short burst of pain and often uncovers things that kind of throws in to question that previous manufacture. You would think, in this day and age, you could perhaps move to more of a process analytical type approach. I think the inspection model is a little bit like when you do testing isn't it, you take a small sample at the end and make huge assumptions on it, whereas maybe in the world of process analytical technology, the inspection model could move to some more kind of real time data analysis that actually you know the agency has got a much better overview of site activities, key events, umm, more pro-active monitoring in a way and looking for signals in the data to prompt things perhaps rather than just a what is fundamentally a relatively low skill risk assessment process and a calendar-based event, umm, it does feel a little bit kind of Victorian almost in its model.

Are you describing a policing model of regulation rather than an interaction, a joint striving for quality between industry and regulators?

Yes, I think it's more of a kind of a policing approach than is perhaps best or perhaps you know the best option for industry and the patient I think probably, umm, I think / and obviously there's a lot of variation within there, so I've got clients who have a very open relationship with <redacted>. I had some poor compliance sites when I was an inspector that we'd ring up virtually every week, you know, it kind of wouldn't be Friday afternoon if this site hadn't rung up with / you know / the latest disaster.

But even though they weren't so good and the problems were quite big, I felt very comfortable that they would tell me so you can kind of give them that lee-way is perhaps the wrong phrase, but you gained assurance, because I trusted them to tell me, even though it wouldn't be great news and then there's these other sites where you know umm / I was on a call with a client last week and there's a big dispute between the owner of the company and the head of quality as to what level of disclosure was required in an interim compliance update to the <redacted> and there was very much that policy of tell them the absolute bare minimum.

And again you / if you look at what we preach about the self-inspection model or internal audits, that they should be absolutely at full disclosure and I do audits now where I come on site and say look I'm being employed by you and you know I can spend a few days looking and see what I can find, but actually we could start with you telling me the / you know your biggest worries and we can evaluate that and assess that, umm, you know, some companies take me up on it, some want the sort of the more virtual inspection type process, but if inspectors could get more to that full disclosure open trust, then maybe the model could change and maybe it could become more truly umm collaborative. I think there are some segments of the industry that do think it's more collaborative. So historically umm when I used to do / inspect <redacted> units they / it was quite interesting, because I came from big pharma, they / you know the <redacted> and they kind of / they hadn't really done a lot of prep and they kind of just thought it was somebody else from the <redacted> popping along for a visit and you know they kind of thought oh can you pop this in the report because we'd like a new lab cabinet, training / you know whatever it might be, they kind of viewed it as more of umm / almost like an internal audit and almost like a mechanism to get what they wanted and I think some of them got caught out a bit with that model because agency wasn't really doing that at that stage, at that time, and obviously the NHS have lost <redacted> I think that was a model but it was not really at the time reciprocated perhaps by the <redacted>. I think / and again I suppose another area where the MHRA has perhaps taken a lighter touch approach, maybe in the area of <redacted> / some of the <redacted> units and when I joined the <redacted> there was kind of a cohort of folks who had been around for a good few years who liaised quite closely with some of the <redacted> bodies, so the nationwide bodies and forums, and there had been almost a lighter touch approach kind of

agreed in some areas umm around things like specials manufacture and that type of thing and whilst there was some good justification for it, <redacted> processing and so on, there was a way of working within that umm and maybe later, as more commercial bodies have come along in to the specials world, the agencies had to increase kind of the approach and the rigour because actually what might have been okay for a small <redacted> unit to stop the / you know the pharmacist doing it under a Section 10 or something, perhaps umm didn't really apply when you've got these large commercial organisations coming in to that space. So I think there definitely could be a bit more collaboration and more openness and I think that would benefit everybody really.

Do you see a difference between the big pharma and little pharma approach with regards to agency interactions?

I think generally the bigger more established pharma is often a bit less afraid of the regulator than almost the medium kind of size players.

Umm and I think certainly where we've got family-owned uhh or / you know / or companies owned by one or two individuals, you know, so I used to work for <redacted> and then <redacted> ultimately, well clearly that was owned by shareholders and the ethos was probably different and you'd get in perhaps some of these Indians or you know companies that are now actually sizeable operations with perhaps thousands of employees but are fundamentally owned by one or two very dominant characters and where in a big company you've perhaps got more checks and balances, corporate systems, corporate governance and so on, in these smaller companies where one or two key people actually own it, or have huge sort of patriarchal roles, then I think that can lead to quite interesting decision making at times and I think we still see some of those organisations where it's, you know, things are done by almost like fear and respect for somebody's position, not necessarily respect them as an individual, or the way they conduct themselves or do the business and I think that can have some detrimental effect at times in terms of the relationship with the agency and / or agencies / and almost along the lines of misleading them and that's not to say that you know there aren't companies across the full spectrum that do strange and un / you know unwelcome things I guess the regulators but you definitely do see differences between sort of perhaps the governance or the approach that you might have in a large corporate global organisation as opposed to perhaps some of these smaller companies and there are good and bad in both, certainly, but umm / yes, there are definitely differences.

From the agencies you have worked with and dealt with, do you say agencies are you know autocracies or meritocracies?

Hmm the agencies themselves. I think my experience is really limited to <redacted> and only within the <redacted>, the GMP Inspectorate, and I do think that was / there was obviously a dimension of politics, as there is with any organisation, but I genuinely think the <redacted> had a fairly open process for recruitment, promotion and so I think that, you know, there are a lot of people who moved in to roles that was entirely warranted on their umm performance, so I think yes, I think the <redacted> is a pretty good model of that. I can't really speak to other organisations umm but yes the / the limited sample that I dealt with in the <redacted>, kind of the thirty so GMP Inspectors, it seemed to be fairly well run on a meritocracy basis, <redacted> and transparent.

I've done a co-audit with ex-FDA Inspectors, but I never did any with FDA.

Do you feel that we have sufficient control over imported pharmaceuticals?

I think / I think it is weaker and I think the overseas sites certainly are under less threat of an unannounced inspection, umm, that would almost / that would probably never really occur at

all umm with <redacted>, whereas unannounced sites in the / unannounced inspections in the <redacted> were more / certainly you know much more common, so I think there is a difference there. I think 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 to and you know even speaking about the <redacted> or <redacted> or <redacted>, I think it is harder for the regulators in some parts of the world to gain that same level of oversight, umm, the amount of time the <redacted> or a European Regulator would spend on site in China, would be the same as the site in their own country. Well clearly when you factor in the challenges around translation, language barrier, that probably doesn't make a lot of sense, because it is a lot slower to audit through a translator. You / you know if I'm on a site in <redacted> then I won't be able to read the majority of the documents. I won't even be able to make head nor tail of them to be honest. If I was to look at site in the <redacted> I'm constantly able to absorb more information. I'm able to listen to the side chats. So I think there are challenges with imported medicine umm in that regard in that it's / there's no real option for the unannounced inspections and it's just much harder and much less effective to audit outside of your native language and umm and so I think there is less / often less rigorous audits because of that, or less effective audits, maybe, umm, so yes, I think it is somewhat weaker, yes.

If you were given the option, you had to take a drug product would you choose domestic or internationally manufactured product?

I'd probably go with the domestic one. I would. You know I would generally select for a product made within the <redacted> umm simply because I am biased I suppose [laughs] I have / you know / yes, I would go for that. I / for whatever reason, believe it / product made in the <redacted> is probably some of the finest pharma in the world. I'm not really sure what that's based on, other than probably a bit of bias, a bit of understanding that the <redacted> regulation I think it does / you know / although not perfect by any means, probably does a pretty good job compared to many other regulators and I suppose, to some degree, my personal knowledge where I might well have visited some of these sites or you know it's probably a combination of those things that would typically make me steer toward <redacted> first umm and then maybe <redacted> and then perhaps outside of <redacted>.

So what about product manufacturing in the <redacted>.? Would you take that readily?

I would take it pretty readily, umm, I'm not a fan of <redacted> sterile products I have to say, umm, but in my experience, there were a lot of differences, some of the worst science I've ever been to in terms of sterile have been in the <redacted>., and I'm not saying they are necessarily science that is harming lots of patients, but in terms of compliance with <redacted> expectations, understanding of <redacted> expectations, and indeed, even willingness on the time to engage with <redacted> regulation, umm, you know, for example, autoclaves, uhh, <redacted> sites often didn't really understand porous load autoclaves. They'd often were only really interested in steam quality testing <redacted>, umm, their idea of a Grade A room uhh wouldn't be accepted in <redacted> and I think to be honest in some of the sites I've been to in the <redacted> there was a bit of an arrogance in a way that kind of thought we're covered by <redacted>, so what are you <redacted> going to be uhh you know / you know / we're covered by <redacted>, you <redacted> clearly aren't going to find anything that <redacted> haven't, and I think there is that subtle difference and I was not a great fan of the <redacted> for that basis and if you look back at some of the work the <redacted> has done over the last decade or so, they've really taken to task a number of <redacted> sterile sites quite aggressively and challengingly for those very reasons umm / as I say it comes down to a matter of compliance and you know I'm not suggesting these

<redacted> sites are routinely killing lots of patients through sterility assurance issues, but they didn't comply with <redacted> expectations around sterility assurance and umm yes yes I've seen some pretty bad stuff in the <redacted> with steriles, yes.

So do you think you know is there a principal component there with regards to regulation? Does the local "not invented here" position apply?

Yes, I think there is a very much a feeling in a lot of <redacted> sites that the <redacted> was the world's best regulator and we were just coming along almost as a bit of a token gesture and they'd often not probably done the prep umm that was required to / you know to get the site compliant with <redacted> I think there is a / yes, I do believe umm again probably reflecting some of my bias, uhh, if you look at perhaps the way some of the <redacted> treat some overseas facilities, maybe they are / maybe even within <redacted>, there's perhaps a little bit more of a / maybe there's a bit of a bias towards <redacted> manufacture, maybe, umm, and I have no data to back that up, it's just kind of a hunch, umm

Are you surprised on that basis that the last recorded 12 months Jan to Dec last year there was huge increase in recalls?

Wow, umm, I didn't know that, yes. I am / I am surprised. I'm probably surprised there's such a / a / a quick correlation between the absence of overseas and that and that action I guess really and I suppose what I'm thinking is is that increase in the recall figures because there are genuine problems with the products coming in, or is there some other factor at play, that you know is it purely because of the absence of the overseas inspections or are there some other mechanisms perhaps because you know people in the pharma companies haven't been able to do their audits, so their supply chain the same, or is there some other you know / is there something else at play, but yes, that's a surprising number.

It was said that politics would always trump pragmatism, do you agree with that when it comes to pharmaceutical regulation?

Umm / I think it does, I think it does to some degree, definitely, umm, and I think you've perhaps only got to look at <redacted> really umm as an example of that and I think it would be very hard for / you know I think it's extremely hard for <redacted> to argue that we don't in the <redacted> meet and 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. I'm not saying it's perfect by any means umm but because of politics we are now in the situation where there's all these challenges and you know stuff's going to be <redacted> there's all these problems of moving things, so I think in that case that is an example with <redacted> where the politics have trumped the pragmatism and the realities that actually you know the <redacted> I would argue is perfectly safe to be taken in <redacted> without any further controls, but the politics have kind of lead us to where they are, and yes.

Is there a moralistic component to pharmaceutical regulation?

Do you think it's purely politics and risk-based that are the main drivers?

I think / I think, yes, those two components are definitely important. I do wonder if there's an element of uhh protectionism as well, umm / you know so / there's been a case reported in the news recently where <redacted> wanted <redacted> to repeat some clinical trial data in <redacted> and you do wonder well given that's you know a pandemic vaccine, given the amount of units that have been dispensed around the world etc., is that really required for <redacted> patient safety or is there some other driver behind that and so if you look at a

decision like that, to me, that was kind of / you would have thought that there could have been some pragmatism applied there to kind of say we need to get this in, umm, so I do think there definitely is a political dimension that perhaps the protectionism umm / probably again if you look at kind of the politics that have played out across <redacted>, again, with the <redacted>, <redacted>, can we use it, no it's only for the over 65's, despite you know you're saying for everybody, and I kind of do wonder what is behind that, is that regulator genuinely concerned or is there a dimension of some political or protectionism or you know what is behind that and I guess we'll never really know, but it does make you feel / I'm always a bit concerned or worried when the <redacted> makes a pronouncement of safety or otherwise and then the individual regulators choose to do something different and I'm always a bit puzzled by that, umm, as to what's driving that kind of local <redacted>

Regards regs then of the various agencies we've got ICH, we've got PIC/S and professional bodies. Do you think there will be any benefit to having a global system, I'm thinking more along the lines of you know we write a submission, you say for tablets that you manufactured, yes, the submission will say Mannitol, you know, Mannitol, BP, JP, USP, NF, and we have to list them all out and they are all effectively the same. There may be one or two very very small changes but nothing that is functionally going to impact the product's efficacy or safety. How can we overcome that nationalistic approach?

I think it's a problem. I think to some degree I've been talking about, for example, Annex 1, and PICS and as I'm sure you're aware, you know obviously PICS came out of the European Free Trade Association many decades ago and therefore just adopted kind of E.U. GMP at the time and has stuck with that, but as its expanded up to kind of 55 or 54 nations around the world, umm, in theory they are kind of aligning behind the / E.U. GMP, E.U. directs GMP pretty much, umm, and it was interesting that FDA joined a few years ago and so / and so through that PICS Forum, for example, FDA have been involved in sort of / very closely involved in the authoring of the new draft Annex 1, so I've been kind of joking on the steriles core saying well does this mean that FDA are going to be following Annex 1, the members of PICS, and PICS is supposed to follow E.U. GMP, and they have been involved in the authoring of Annex 1, does this mean they are going to apply it, and I say that very much tongue-in-cheek, but it does make you wonder if that could come about and I think your point, it's absolute nonsense really isn't it, all this / all these differences between different pharma companies, different geographical regions, and I'm a big supporter of you know ICH, umm, I'm a big supporter of things like the PICS. If you go back to / I joined / moved to part of <redacted> API facilities at the time and at the time there was that document that was quite new and exciting called ICHQ7A and over the period of kind of two and a half decades or so, that's moved from being kind of an optional thing to basically mainstream standardised GMP for API. Its taken a long time but I think that is now pretty much almost a global / well it is pretty much the global standard on API manufacture and so you think if we can do it there why can't we do it with the pharma <redacted> why can't we do it with you know agreeing standards umm and getting rid of things like the CFR's and getting rid of maybe EudraLex and having more of a global standard, you know, as global supply chains have developed it makes less and less sense to have these relatively petty geographic or nationalistic differences and umm I think it probably does more harm than good, but I think there's a lot of pride isn't there, you know, there's probably a lot of pride behind the BP and umm and I think that will take some breaking down umm but I think it should be broken down really.

Who would lead that change? Who do you think should lead that change?

I think it would have to be umm organisations with broad support, like PICS, but I'm not sure they really have that / you know I've no idea what the actual charter of PICS states, but I'm sure it doesn't state we're here to establish one global quality system for the world pharma industry. I'm sure that isn't kind of in their remit. They've probably got something much more gentle umm / I think it does need some of the big regulators though to kind of get together and start making noises of dissatisfaction umm but because the regulators are primarily umm servants of political masters, you know, is that ever going to happen and you know <redacted> immediately need to stop all this difference and immediately just fall completely in line with the <redacted>, and you know politically that's probably not a message that's very easy for a lot of politicians globally to deliver, despite the benefits I'm sure it would deliver for patients, despite the benefits it would bring for industry, umm, cost savings all round and you know if we / and you know I thought that <redacted> having a core inspectorate of inspectors that are employed directly by the <redacted>, because at the minute obviously the <redacted> in effect is a virtual organisation, sub-contracts all its work to / all its inspections, as I'm sure you know, are sub-contracted <redacted> s and therefore you know it's like sub-contracting calibration, to one calibration company, and then a different calibration company. You automatically get quite a lot of differences and there's no / you know there are some token tools to drive consistency, but it's not the same as if they were all employed. Ultimately you could see that kind of expanding and you know what if PICS employed a team of inspectors and that team covered the 50 or 60 nations that were a part of that and clearly there would be a lot of legislative blockers and problems about having some inspector from you know, I don't know, some part of the world, going to a different country and kind of pronouncing that medicine's safe, you know, say an inspector from the U.S. were to travel to France, inspect a French site and determine if that site was safe or not and the French Government directly responded to that finding, I think that would be very difficult politically when things went a bit array, but it makes a lot of sense, 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 <redacted> 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, so I think that you know the future has to be that, but I can't easily see a forum that's going to deliver that or even you know.

Are you effectively saying that politics has a greater weighting than patient safety?

Uhh, yes, I think / yes, I think it does, think it does, yes. Yes.

I think you have to change the finance model uhh for regulators. I think umm / you know / the political will to fund regulators is relatively limited and given the global finance crisis, given umm you know Covid, and you know the public finances, there's going / there's only going to be an increasing squeeze on kind of the number of regulators and salaries that you can pay these regulators and the regulators are increasingly getting out-competed by the industry for resource and therefore I know <redacted> typically always running with levels of significant vacancies and that is causing a drag, a constant drag, on what they are able to do, so I think that needs to be addressed. I think a little bit like I've touched on previously I think there has to be a / you know when umm / in the olden days when QA lived in the QA building and periodically would wander down to production and give them a good telling off, it's a little bit like that with regulators isn't it, in that, you know, the regulators, every couple of years, wander down and give a site a good caning or whatever, umm, again / and the concept that industry moved to was kind of QA online and QA embedded on the production facilities and part of that team and again it would be nice if we could come up with a model, with this magic wand, to do that with the regulators, without them losing their kind of independent oversight and not becoming kind of snow-blind and not kind of going native, but

umm you know / rather than very intense bursts of audit and inspection, maybe there could be a greater frequency of visit for maybe a shorter duration combined with a better automated data gathering you know / the tax man is talking isn't he, there's all this talk about us moving to kind of real time taxation and there was an article in <redacted> I think at the weekend where they are saying that any income you get from your bank account will be linked to <redacted> so they will instantly see what the numbers are coming in to your bank account and instantly calculate what that means for your tax, so again, if you kind of / if we can do that with tax why could we not do that with pharma regulation and so the regulators have some sort of links, or portals, that automatically dock in to companies QMS systems and feed triggers in automatically and that then prompts more real time analysis and trending by the regulator and perhaps lead us to a more timely intervention than just turning up every couple of years and going, oh my goodness, what happened six months ago, you know, we'd better have a recall, kind of scenario, so it's more of a pro-active approach really and less of the you know less of the uhh significant response to poor / to big compliances usually that are discovered frankly too late in the day often to really have any impact, but recall, that's kind of the only option we've got.

Can I take you back to an earlier comment you made then. You said there about inspectors going native. Please elaborate?

Yes.

Some companies use inspectors as a consultancy firm, effectively, and you know, <redacted> and you know the phone calls etc. Does that in itself you know preclude an inspector, or the agencies, from having that third party or <redacted> view of what's actually going on? I think it can do certainly and I think the <redacted> were very keen to rotate inspectors at a reasonable frequency and umm you know ideally I think they do no more than kind of three inspections over perhaps a period of five or six years, you know, you'd kind of rotate in and rotate out, umm, and I think definitely there is problems, if you go along with them, that / I did a site in the <redacted> it was dreadful, and they had the same / I mean they were dreadful from even a <redacted> kind of compliance point of view, but umm it was their first <redacted> inspection and they'd had the same <redacted> inspector for 27 years and she was kind of a friend of the family, went to BBQ's and you know they'd kind of lost that / lost that umm independence I guess, and if you / even as a consultant, if you go anywhere too often, you become snow-blind don't you, you don't see the / you do need that fresh pair of eyes, so I think there's definitely some level of rotation needed umm still but it would be nice to have maybe shorter umm more frequent visits in a way, that keep a bit more of an eye on things, a bit like the management review process, you know, Chapter 1, 1.5, 1.6, etc. management need to have a process to review the compliance and the performance of the PQS and really the agency should be reviewing that perhaps more in real time for me and responding to that data umm / rather than wait and just turn up every now and then and discover everything has been going wrong for 12 months or 18 months, so it's / it's that / it's more / I guess I'm probably talking about a kind of drip drip of data analysis really that leads to a timely intervention.

Are you referring to a rolling review process?

Absolutely, yes, yes.

Rather than a product dossier basis?

Yes. Yes, definitely, and I think there's a lot of benefit for that, umm, and particularly with some of the tools that are available now and you know people have got much more used to remote working and you know we've talked about some of the challenges of remote working, but you know what if there was a / each inspector had / I'm just making this up now without

really thinking about it, but if each inspector had maybe a one to two hour call with a number of sites each month, or each / every couple of months, or even once a quarter maybe, as kind of a just, right, okay, you know, these are some basic metrics you need to present every quarter based on the segment of the industry you're in and lets review them and where were you last time and it's / it's almost like a sub-set of what senior management get. You know it's like almost another level above that isn't it that could be formally reviewed umm by the regulator as kind of a rolling review audit as you say, yes, and umm."

Subject 89525

“Is the current regulatory purpose in the UK fit-for-purpose as it currently stands with regard to domestic versus international manufacture of products?”

[laughs] Umm /

[laughs] Well certainly within the <redacted> I think they are now / and we're seeing they have / we've seen this just in recent times, they're certainly becoming more pragmatic with the regulations, but I / to answer that question generally, I would say probably not because they are just over-complicated and difficult and especially in this time now <redacted> and we've had our / we've got <redacted>, which obviously we're still following. We are now getting more Regulations, obviously updates to <redacted>. PICs seems to be going off you know in one other area. So it's complicated and I'm not a regulatory expert. I follow <redacted> and you know rely almost you need to rely on somebody to help pick out and understand all the regulations, so you can then / I'm an ops person, a manufacturing person, so I can make sure what do we need to follow, so umm, so I think they are complicated I think and <redacted> are very much trying to be pragmatic. Certainly we've found that when we've been trying to get obviously new drugs through in doing those parallel reviews for clinical trials and doing that risk-based assessment and certainly from their inspection process, the way they look to apply those regulations, I think they are being pragmatic, but yes, you know, they are complicated and certainly not aligned to all authorities either, you know, very much <redacted> approach is that risk-based approach and then when you have an inspection from <redacted> Authorities, for example, or <redacted> it's kind of black or white, it's quite different, so it's very / for somebody in operations trying to run a manufacturing site, I think it's very difficult.

So how would you gauge equivalency between the various agencies? You just mentioned there the difference between <redacted>. How would you describe the equivalency of those agencies?

Umm / how would I describe the equivalency in how do they /
On the basis that their role is effectively the same.

Yes.

Do you feel the way those agencies approach that role has been equivalent?

Well if their role, which, I believe it is, at the end of the day, is to protect patients from harm, you know, ultimately that's what the Regulations are there in place to do, then yes. I think it's just then the approach of sometimes the application of those GMP requirements. I mean maybe it's because I've come from sites and worked with sites that luckily have not had critical, so it's been a lot of those observations, minor observations, which you kind of sometimes, say come on, we're meeting the standard of the GMP, say if I take the example of <redacted>, they just don't seem to have this risk-based approach, however, yes, if that site were to have a critical, would all agencies probably highlight that as a critical, probably yes, so I mean yes there has to be some equivalence and there's got to be because we manufacture drugs worldwide, but I think it's just, in answer to the first question, it was just / the regulations are difficult are complex, they are open to inter / well the directive is open to interpretation in to national law, and then you've got other countries that then have their interpretation slightly differently, but I don't know whether I've answered that question for you but /

You said that you agreed that their aim is the same to ensure patient safety and safe medication. From that perspective, would you always be comfortable with that material because it had been inspected or under the auspices of that local regulatory agency?

Yes and that's where it comes back to doesn't it, depends on which country that's coming from, yes, I mean and this is where / yes / if they've been inspected and / well / it's coming back to the duty of the <redacted> isn't it, at the end of the day, because you've still got to ensure yourself that they are manufacturing in accordance to <redacted> GMP, so / and that's where you then you have to ensure that additional audits are done, whether that's done by yourself, or somebody else, that you know you know will do that properly, so no, I mean if / yes, if my Procurement Department suddenly said I've got this API that I'm going to purchase from <redacted>, 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.

You mentioned the role of QP and European GMPs from the perspective of patient safety, the role of the QP, notwithstanding, from a patient safety perspective, other factors may contribute, which may not be captured in European GMPs, on that basis would you feel comfortable taking material from another site?

Yes.

Because a site had been inspected would you have confidence in the fact that that local agency had inspected, are you saying that it's the agencies that are equivalent?

Yes.

Yes. We've got to have faith haven't we in the agency, like, okay, if I take my manufacturing hat off, just as a patient taking drugs, that will have come from wherever, you have to rely on the regulatory controls that are in place, so if I'm going to be prescribed a drug to take, a generic product wherever it has come from, I'm relying on the controls of the regulate / where that product has been made and that I'm relying on the fact that that facility has been inspected and they are manufacturing appropriately. So I suppose the answer to that question, yes, I have / I'm not / I'm putting my trust in those regulatory authorities to make sure that they have done their job correctly.

Are you trusting the system regardless of where that system is based?

As a patient I you know / yes, I do, like with the vaccine at the moment, I have no question of well who made that, where did it come from, it's / I know that this has been approved and there are regulations around supply chain integrity and management and I have to put the trust in the fact that those things are in place.

So that's as a patient perspective?

Yes.

With your professional experience does that change your perspective? So for example, if a drug product would you take a domestically manufactured or internationally manufactured or not care which?. You choice, what would you take?

Yes. And again it's just perception isn't it. It's / I mean it's kind of your knowing some of the regulatory issues that have happened in the past, and a lot of it is history as well isn't it.

Yes.

So I mean, yes, if you asked me that question, if I had a choice to say, okay, give me the one that's come from domestic manufacture, so <redacted>, or actually just the finishing has been done there, because that's the question isn't it?

Considering you don't always have that transparency of the supply chain, does that influence you?

Yes. No, I think this is the problem isn't it, 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 <redacted> on those aspects, which then, yes, somebody with some of that insight, you think, hmm, okay, well if I had the choice, would I rather actually take something that had been API and

manufactured in a domestic country, probably yes, because I believe whether that's rightly or wrongly, because actually I've never been to an <redacted> facility but you know I perceive that the <redacted> and control and regulatory framework is of a higher standard, but that's I suppose from just / from / my perception and the information and the assessment that I've done myself, so yes, I mean I've never / as I say, gone to an Indian site, or been / seen the <redacted> regulatory authority in action.

Do you feel, with your experience, that companies have quality as a first intents, I mean quality with regards to key characteristics, efficacy, safely and so on?

Yes.

Do you feel that they will go for the lowest common denominator and the agencies are enforcing that quality upon them as a process?

Well so umm / I suppose, from my experience, the companies I've worked for and you know I chose to work for because of their ethics, so Merck, worked for a Japanese company, <redacted> you know / very much their whole ethics and culture of the organisation was to produce a quality product and quality was very much / we're talking that we're assuring quality in our product rather than / you know even having QA and QC even within a facility, enforced operations to do these things a certain way, so it was very much that was the organisation's culture of making sure that they were making a quality product and then the regulators were there just to obviously do that, audit that snapshot in time to make sure that we were, so I definitely I've been lucky, but then I chose to work in those organisations where that was very much the case. But I have, as part of doing, when I was in those roles doing audits at other facilities, actually my last role before I joined <redacted>, I was working for a CMO, in corporate operations, and certainly I found there, within a CMO, the pressures, the financial pressures were a lot greater, so from the point of view of capital investment in some of these facilities, I would say there the balance was getting a little bit more what can we / I think there was still very much quality in mind and we need to make sure that the driver is that we are making good compliant products, but then the question was a little bit more of, you know, we've got to sparing with our investment and therefore what can we keep going and what is okay and what absolutely needs to be done, so I saw that a bit. Now since I've been <redacted> in a consulting role and now that I'm doing more training, I haven't been out in to / also the pandemic, I haven't been out to facilities for a while, but I had in my early days at <redacted> spent some time at some generic manufacturers, <redacted> - owned, in <redacted>, and certainly the feeling that I got there, with my limited work with them, was it was just we want to scratch the surface to tick the boxes for the regulators, but you know underpinning that we're pulling in operators that have been stacking shelves in <redacted> and we're paying them minimum wage and we're expecting them to do this job that we're not giving them any resources or training for, so that I've definitely / so in answer to the question it's a broad spectrum because there are companies that are research-based driven companies, that have invested a lot of money in this and have a reputation to uphold and are doing the right thing and there are other companies that are selling paracetamol for a penny a tablet and are trying to make money and probably are focusing on the money and / (<redacted> circles of we need to balance obviously compliance, the profit of the organisation and the patient, the customer, this was more around well if you're going to focus more on your profits, then your compliance and then ultimately potentially the safety of your customers is going to suffer, so I have seen that as well and I think it's very much dependent on the company.

You mentioned the company culture there. Do you feel there's a big component of that? Of whether an organisation is compliant?

Yes

Absolutely, yes. And it comes from the leadership, yes.

Do you think that is a cultural basis within the company or a culture within the region, so for example, in Japan, there's a very different culture with regards to quality, as you rightly said already? India there's a very deferential culture with reporting lines and structures. Where do you see that cultural balance? Do you think it's more the company has the impact, or the general population culture has more of an impact?

Yes, I mean it / it all depends on the ownership of that company I suppose as well, so if I take <redacted> for example, it's an <redacted> -owned company, but obviously have facilities globally, in different regions of the country, that have different country cultures, like you were mentioning the differences between Japan and India, and so forth, but ultimately it comes from the top doesn't it, setting that quality policy and manual and then obviously those within a global organisation, you have to maintain those standards and they have their audits of that, umm, but you know / so / I think / yes / going back to your question, the culture of region can have an impact because I know what you're saying, in India, it's very much hierarchical and if my boss tells me to do this, I'll do this, umm / but / and again I don't have a lot of experience with Indian companies, but ultimately they / if / if it comes from the culture of the organisation from the leadership they have to know what's right or wrong, or they should know what's right or wrong, and therefore know that telling somebody to be fraudulent is wrong, but yes / Do you see that more in Indian companies, over Western companies? Probably, but again I don't have a lot of experience working with Indian companies, but I've worked with a Japanese company, in <redacted>, but it was Japanese-owned and, yes, there was very much the seniority, the culture of not speaking up necessarily, didn't want to obviously your boss to lose face, but it was incredibly strong quality culture for them, the Japanese, it's / it affects their whole brand if they get a customer complaint, so it was / again that was different, it was very much a quality culture engrained in the organisation, but I suppose the management style was different.

We talked about regulation, we talked different agencies, and you mentioned potential for policing. Last year there was a large increase in recalls and defects and complaints for USA imported pharmaceuticals. Are you surprised by that?

Right, okay, so let me just / so they were / obviously the FDA were stopping their inspections, but then they were on importation because of quality issues or whatever, the recall, that the country was then finding by those imported products they were then had recalls. Yes?

<redacted> No it doesn't surprise, so it doesn't surprise me, because I think this has been / it's an underlying concern once you know regulated authorities can get out, because obviously they've been doing remote inspections, but there's only so much you can do, once they get back out there, is there going to be a huge a massive increase in critical and majors because that's it, some of these companies that have been doing the bare minimum, up until / whilst they were being inspected, because obviously companies have been still, under<redacted> and things like that, so yes, then these companies / the pressure the sort of the / the pressure has been taken off them because they haven't had these inspections so they've let things go because there isn't that regulatory authority pushing down on them, so it doesn't surprise me that there's been some of those quality issues. The number is / that's huge. And it will be interesting, as I say, to see what countries that was from, but yes, no, it doesn't surprise me.

In your experience do you feel the same level of rigour is given to domestic and overseas inspections from the enforcement perspective?

Umm / difficult to say because again it's probably me just making a sweeping statement. Because you know you would sometimes just see yourself working for a global company that some sites, and again it might be biased, but you seem some sites within your network that were inspected that you think, hang on a minute, they've got some issues, but came away lightly with an inspection, whereas then the local site that I was at, kind of there was / you'd find maybe the inspector was nit-picking on things that really weren't an issue, so is there / yes, so do you believe that, for example, the <redacted> are tougher locally than they would be overseas, or the other way around. I mean / I don't know, I haven't really got any evidence to state an opinion on that probably.

From your experience dealing with inspectors and from any agency, do you feel in your opinion, your experience, that most agencies are either autocracies or meritocracies?

I mean at the end of the day inspectors are human aren't they and I'm sure if we asked the <redacted> they are trained such that there is no / that they obviously are always bringing it back to / if their sighting and observation, they are bringing it back to what does it say in the regulation, but there's / yes, you've definitely seen different inspectors with different approaches and their areas of / their favourite areas where they want to highlight and yes and I've seen it as well where you've had / been inspected myself, when I was in operations with a lead inspector, but then a / a trainee inspector that was then kind of wanted to show that they / were adding value but then would bring up minor things really. So yes, so you asked me whether that happens, I suppose, yes, it does.

It's also the position of meritocracy or autocracy is do they always have the right people with the right skills and expertise reviewing those areas?

Can you elaborate?

I mean I haven't got experience of dossier review of seeing that, but I can totally hear that approach, because that's it, agencies are / well they are struggling to recruit, they are limited aren't they I think probably in some cases with their resource. We just look at the massive growing technology in selling gene therapy, I mean, within <redacted> we're struggling to get subject matter experts to help us with client enquiries and then you've got to have people within these agencies that can do then / have the knowledge and experience and understanding to do the appropriate reviews and do the inspections. Now, yes, okay, the manufacturing, aseptic technique is aseptic technique, but there's still / there are still different things to think about in selling gene therapy. So I can completely see that that might happen and maybe some agencies aren't as rigorous as others in ensuring that they've got the appropriate subject matter expertise in place because they've got to do these reviews, but I haven't got any examples specifically where I've seen that, but it must be difficult and then there is that concern of whether it's being done thoroughly or appropriately. I mean I know just talking to, I was just talking <redacted> the other day, because she's coming to do a guest speaker slot on <redacted> and obviously she's kind of their ATMP expert now I think and has been trained up in that area, obviously hasn't got sterile background, but hasn't come from that area, so it's definitely trying to train up other inspectors, so it must be difficult for them making sure they've got the right subject matter expertise, but as an industry, we're relying on them aren't we, that they are putting the most of the appropriate people to carry out that work. You would hope

Do you feel there's enough agency industry interaction?

Enough agency?

Industry interaction, the use of scientific advice meetings, briefing documents, is that interaction there and being used appropriately? Any difference between big pharma or smaller companies?

Umm / I mean I don't know how much is going on to be honest. But I think certainly within the <redacted> they are trying to do that. I can't speak for other agencies. But I think this is where MHRA need to look upon industry almost to teach them don't they to help them with some of these new technologies, so that they can understand and then make sure that they're taking the right approach. The question of well what is enough interaction because it might be different, depends on peoples perception of what enough industry interaction means, but yes, I suppose / there's certainly there's a lot of / you see a lot of communication coming out of the <redacted> with their blogs and information that they are putting out there. There are lots, from what I gather, lots of scientific meetings and they do have the innovation office asking people to approach them for independent advice and support and help, so definitely it feels that the <redacted> are reaching out and are trying to bridge those gaps, but how successful that is, I don't know.

What about the impact or potential impact of national interest, politics, do you think politics has a role in the pharmaceuticals?

I think there must be massive pressure mustn't there, I mean, just thinking about the umm / umm / the whole Brexit situation and where we currently are and keep kind of umm delaying decisions, delaying decisions, or saying this is what's going to happen, because yes, politics has to be, there is that politics does get involved to a degree to put then pressure on the <redacted> to make some decisions accordingly, so it's that / so / in answer to your question, yes, I think politics does have a role to play there, but I / my thought is that it wouldn't impact patient safety.

What about the “not-invented-here mentality”, so for example, we do a submission for a tablet manufacturer and we'll quote Mannitol and we have to quote Mannitol BP USP NF JP and so on and the monograph for Mannitol is pretty much the same with some very minor tweaks around it, none of them will impact the safety or usability of the product or anything. But to get your submission in to Japan you've got to say JP, you've got to get USP to America and so on, even MHRA would expect to see (not essential), but they would expect to see EP or BP. Do you think that helps as well, these various monographs?

No, it doesn't do it. No. No, as somebody that you know manufacturing you just want to be able to make the product, but obviously you need to have that assurance that what you're purchasing is to an appropriate specification but if the differences between, yes, USP and EP are so minor, yes, it would be great wouldn't it if there could just be one monograph, so yes, I mean / that does add / it's just a nightmare from an operational perspective and just managing your supply chain, it's a nightmare then on controlling products, especially if you've got the purchase of some materials that only meet BP and EP and then you are having to make a product for another market that only / you can only use then this particular raw material. It's the same raw material but obviously a different specification. The control of that is very difficult and then obviously there's more opportunity for error and then it kind of adds.

Can you elaborate please?

Absolutely. And then it's kind of you know / and then it just fills your whole system with / because you want to make sure that you're focusing on those important things, those things that are going to affect the quality of your product and potentially then, worst case, it could affect patients. You want to be / and when you have all of this noise, because of all of these

other complexities, which are just noise, minor things, it makes that job very very difficult, so yes, I mean it would be great if they could / if it could all be harmonised, I mean this has been / will that ever happen?

Well that leads on to my next question about harmonisation. We have a global industry and global supply chains we've already said are very complex. We put out the API from China, compression from India, primary packaging could be in France and it's a very segmented industry. We have PICs, we have ICH, we have CFR 21 2 10-11, we have the professional body technical monographs and so on. People tend to pick and choose the ones they have to have and the ones they like to fit with.

Yes.

What's your impression of all of these various guidance's and roles, do you think they could be combined in to one? Do you think it will be beneficial if we have a single global standard?

I mean it would be / I mean that's kind of / I mean it would be great wouldn't it, but they would never agree / we would never have anything.

Can you elaborate? Why do you say we'd never have that? Why could we not do that?

Oh it would be great / well / because nobody's / the time it would take for all of these countries to agree on the content I suppose. I mean just look how long its taken to get where we are with the <redacted> of which, okay, again that's not / doesn't cover everything does it, but umm / so it's / because of the / just trying to get agreement between everybody that what should be / but then when you look at EudraLex and ICH, a lot of these things they are very much aligned, you know, so / is it people just trying to make jobs for themselves, work for themselves, it's just

Does this come back to my original question regarding the role of the agencies, the ultimate role of all the agencies, it is effectively the same?

Yes, and yes / I mean / yes, I'm definitely it would be fantastic if there was one standard I suppose, just then they / it's / there still has to be a governing body, as such, doesn't there over that and how would that / where would that fit and how would that be managed.

Who would you pick for that, that governing body?

God!

Would you fit it under ICH or PICs or where would you see that sitting?

That umm / that overarching governing body, if we were to have one global system?

Yes?

Well we have now / I mean because ICH is now pretty big isn't it with the number of members and observers and everything, is that / that's more so than PICs now isn't it?

So I suppose it would be ICH wouldn't it, but / uhh / but as you say just even to get a new ICH guideline out it just takes so long, let alone a whole set of GMPs.

And then with these advancing new technologies, the thing is things are now starting to move so fast aren't they, so it's umm / umm / yes / and then / you know and then you think of the corruption that there could be between so / I don't know, it's umm / yes / yes, its very difficult.

What would you do to change it that would help reinforce that role?

Umm / I mean I think / you know if there was more harmonisation between the inspections I think because umm / and I'm just probably coming back to just my experience in operations where I was working / I had an operational site that was supplying 60 different countries

worldwide and just the number of then inspections that you had, that all had then slightly different areas of focus and it's just, as you say, you know, if you could have just one or two / not to say totally happy to be inspected, because we need to make sure that we're being audited and we're following requirements, and we're being kept in line, but it's just you know the inefficiencies with just having these week after week after week and then you look at poor CMOs that have that as well as their customer inspections as well. And the other one is variations as well, complexity of just / if you're / especially in this world now where we want to innovate, we don't want to suffocate that innovation and you're wanting to make a change to your process for the better, but your process supplied sixty different markets, the change management just for the coordination and management of that, for some small little change, the cost and the whole / it's just huge.

To the detriment potentially of product quality because it's just too much of an effort to change, so actually I think that whole variation process.

What is your experience of agency engagement with quality initiatives in industry?

You know certainly umm / yes / definitely had that experience, because even / you know even from when I was last in industry and it was fairly new products that then were launched for / so it wasn't even if you were dealing with legacy products, so there were new products that were obviously launched commercially and then, as with everything, you want to do some minor changes, which certainly from an operational perspective, were deemed minor and it was just a / so difficult to change that, or you could change it, certainly, actually from a <redacted> perspective, that variation was fairly straight forward, but it was then the <redacted> market, it was all of those other markets you were supplying, that you needed so many months of stability data, so you were then / had the whole complexity of well I'm making a product, and I've done this change back and shipped to these markets, but I can't ship it to those markets, umm, because it hasn't gone through the variation process but actually / so yes, no definitely.

So I think that if those / yes / variations could be aligned, harmonised between authorities, but yes / it's fascinating this / your research that you're doing.”

Subject 97219

Do you think the current regulatory processes are fit for purpose to give us safe and efficacious pharmaceuticals for every product, generics and new chemical entities?

Well that's an interesting question I think maybe it's different here in Japan and that's our systems are very western in their focus but we do have very specific local application I think to Japan first nature really comes to the fore and takes the priority when it comes to products for our market. I can't really comment on exports but in my experience we do seem quite aligned with western major agencies.

So would you say that's the same across all the countries in Europe, is it comparable to Japan and Australasia?

Based on my experience we are very similar here to the European approach I can't comment on specific European countries however I think we are aligned.

Is there pro-active engagement from the agency or from industry?

Definitely not. industry appears to work in last nation there is digital practise sharing information and certainly not free and easy access to agencies. Although to contact our

Transcript data for submission CD with thesis

Ministry of Health is quite straight forward for us contacting other agencies often feels to be a step too far.

So do you think the access to international agencies would be beneficial?

yes I do.

Is it a policing model of regulation rather than an interaction and umm a / a joint striving for quality between industry and regulators?

Our agency certainly seems to encourage inspectors to shore adherence to expectations. That is not always clear from the regulations what is required or what the expectations are or why we have those expectations so I think it is probably as you say policed.

Do you have experience of FDA inspections?

yes and these are very different from the Japanese approach

Do you see a difference between big pharma and little pharma ? Do you see there's a difference there regarding the size of the business and the industry?

I do, most of my experience is based in a big Japanese company however from talking with colleagues and others I do feel that the smaller companies are more responsive they can move faster and be more engaged with requirements.

Do you believe agencies are autocracies or meritocracies? Local or international.

I think to be honest it's a bit of a mixture realistically we know that there will be a mixture of both types in every agency probably just based upon how we've experienced our own professional lives I don't have a clear believed one way or the other

Have you ever done an audit, a co-audit with an FDA Inspector?

Not with the FDA but I have done the inspection with representative from European agencies and also the TGA in Australia

I now want to talk about, imported pharmaceuticals, so something that's manufactured outside of the current domestic structures.

Do you feel that your country has sufficient control over imported pharmaceuticals?

I don't really know I think we've seen issues of product failures and recalls but then we see that for locally manufactured products as well I don't really have a feeling strongly one way or the other. We do have some countries that we don't like to work with and some countries that will be our preferred suppliers or partners maybe that has something to do with it but I don't know whether that's just perception or based upon fact.

So that aside, if you were given the option, you had to take some, say Pantoprazole, you are given the option of Pantoprazole manufactured in Japan or Pantoprazole manufactured by a company in Russia, which one would you take?

If I had a choice I would take the Japanese product

Why?

Because I perceived that to be of the better quality I don't have any data to justify that it's just a feeling

So what about product manufacturing in the U.S.? Would you take that readily?

yes I would. I generally feel that product manufactured in United States of America will be of high quality because of that regulation

Do you believe all agencies are equal with regards to enforcement?

No I don't

Can you explain why?

No it's more of a feeling rather than based on experience

Are you surprised that the last recorded 12 months Jan to Dec last year there was an 80% increase in recalls of overseas medicines imported into the U.S. and that corresponds with the lack of overseas inspections?

No I'm not surprised at all

Are you surprised it's that high?

it does seem quite high though

Do you agree with the statement "politics would always trump pragmatism", do you agree with that when it comes to pharmaceutical regulation?

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

Is there a moralistic component to pharmaceutical regulation?

I don't know because we make products for sale, to make a profit so even if those products are used as medicine it's easy to confuse politics profit and ethics together

Do you think it's purely politics and risk-based that are the main drivers?

Sorry I don't know

Regards regs of the various agencies we've got ICH, we've got PIC/S we've got PDA. Do you think there will be any benefit to having a global system, how can we overcome that nationalistic approach?

A single global approach has obvious benefits but being realistic what is the likelihood of that being achieved? Likely very small I don't think we would never get agreements not in the near future I still too many vested interests at play.

Who would lead that change? Who do you think should lead that change?

Laugh. I'd like to but I really don't think I'm in position to do that and I'm not sure who could. I think it would be a very hard job

You're effectively saying that politics has a greater weighting than patient safety?

I think it's a balance I think sometimes politics has too much of a role and sometimes we also play it too safe if we are always we're too safe we would have missed some very good magical and drug developments in the past

<redacted>

A single point of registration with a single process. It would be easier for companies. It would be easier for reviewers. it would simplify supplies. I don't think it could ever happen but there would be obvious benefits if it did.

Do you feel there is enough interaction and collaboration between companies and agencies either domestic or international?

No I don't I think they're kept very separate; I think there are areas where sharing information could be hugely beneficial but for various reasons it just does not happen and I don't know how we can encourage that to happen.

Subject 79869

Do you feel the current regulatory set up we have within the UK, within Europe, and wider is fit-for-purpose?

I think it is fit-for-purpose in the sense that it is driven by trying to ensure quality medicines and the fact that medicines should be regulated. There should be rules about that. So the fundamental issue is that I think we do have fitness-for-purpose. It's more in the detail about how it all fits together where I think things perhaps could be a bit clearer.

So when you say the detail, do you mean the application, or the actual approach to it? Is it more of a holistic view of quality or do they get too bogged down in the minute detail which doesn't necessarily add a great deal of benefit to the end-user, the patients?

Yes. I think there's two aspects. I think number one is the sort of compliance versus science debate and number two is that you mentioned focus on the patient, absolutely, although we say we're focused on the patient and, of course, we are, I think in our industry we don't actually get close enough to the patient in terms of the real requirements and I think this latest virus thing has brought that to light. I think personalised medicines bring that to light when you're really having to think what the actual patient requirements are and the other thing that also I find interesting is umm one of my son's is a surgeon and the conversations I have with him, I have a very good relationship with him, it's not like we talk about this all the time, but when I talk about the subject of what the medics do versus what the pharmaceutical industry does, there's a real gap with the communication there, so I think there's that last bit of the bridge, from what we do in the industry to the actual patient requirements is significant.

So when you say communication between which parties are you referring to?

So I think I'm talking about the way the actual medicines are made and whether they / the link through the / I tend to think of / I mentioned science to risk based, so all this stuff on CQAs control site, which I'm a very strong supporter of, because I think it brings it to light, umm, this sort of site to risk based. When you start to bring / we tend to talk about the science to risk being within the manufacturing plant or the way an operator works or the way we've got our documents running, but are we really thinking about that risk and extending it right through in to the way the patient risk is, tricky area this, I know, because we're not medics and I wouldn't want to suggest that we should do that, when we have to work very closely with the medics, but I think that understanding of risk and that boundary is quite important.

Do you think then the regulators need to have a greater consideration for the medical application rather than just viewing as a comparison to the guidance document that you've submitted?

I think it's more about ensuring that the pharmaceutical documents etc. and what we do is lined up as closely as we can do to what the patient umm requirements are and if I can tell you a brief story, if I may?

This is an example whereby I was working in <redacted> organisation, where people from industry and regulators met, completely informally, but these were people you know / and at that time there was a regulator came in to the room, who I knew reasonably well, so all this was informal, and there had suddenly been a genotoxic impurity come on to the **supply** chain, right, and he was obviously really annoyed that the industry could have actually allowed this to happen and when that actually / when it was all investigated and all that sort of thing, what really came to light, in my opinion, was the fact that when we talk about risk, the usual thing of severity, likelihood and detectability, we had a potentially high risk of

severity, in terms of the patient, likelihood of it happening was extremely low and because likelihood of it happening was extremely low then we then finished up saying, the detectability requirement got missed and the fact that that detectability meant the severity comes in to play, if you excuse that complicated discussion. I think it's really important we have / that the safety element of medicines and the efficacy element of medicines really played in in to our thinking and we tend to get buried in to a lot of you know documents and detail and compliance-related things which can sometimes mean we miss the important points like that.

So do you feel in that case then that the right people are reviewing these dossiers?

I / look I'm not a dossier expert on this. Dossiers are big documents to review. A lot of detail in them. There's a lot of science in them, a lot of practical application. There's also approval. So people who have got to review those documents have got a tough job. But I will say one thing. I know that there's a certain type of character needed in terms of these documents, so if you get a / and we've seen it you know in normal industry, if 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.

Do you feel that the same level of scrutiny is applied to imported products as opposed to domestic manufacturers?

[laughs] That's a tough question to answer generally. Umm /

In your experience.

I'm not sure I'd like to label it as imported or not imported.

Let's go on the basis then that domestic manufacturers are inspected a lot more frequently than international manufacturers, that's across the board, the same for the FDA, MHRA, EMA, so on.<redacted>So unless we have a situation where regulation and regulatory control is by a policing rather than / because some companies first intents, lets be quite honest about that

Do you feel that there is a parity there just on how the inspectorates actually view that domestic versus international supply chain?

Right, I know what you're getting at and there is something in what you say, okay, about somewhere / and I think the best way of me describing it is, since leaving working for a big pharma company, a good big pharma company, you know, 10 years or 11 years ago, I've now been in the fortunate position of seeing all sorts you know in the industry and I've seen some pretty terrible things in the UK, okay, as well as abroad, and I've seen some really good things in the UK as well as abroad, and sometimes from the same companies actually, so it finishes us quite often where a local management, maybe the people that are actually having that really big influence on product quality, and that local management might be in the UK or it might be internationally and I think that's where the / where it really comes in to play and as long as these companies that start out with you know really great intentions, be they based in UK or U.S. or whatever it is, as long as they're actually able to ensure that that high quality really gets embedded right down in to the design and manufacture of products, wherever they are located, then I think it works. But 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 and I've also worked in different / excuse me, some really soft stuff here / I've worked in different cultures where

there's been a real hands-on quality focused culture compared with people you know wanting to just do what the rules say.

On that basis then, you've seen good in good and bad in bad, are you surprised then if I told you that last year, the last set of reported data in the U.S., when they suspended all overseas inspections, they kept some domestic going, but suspended overseas, there's been an 800% increase in manufacturing defects and quality defects resulting in recalls or lost stock?

I'll have to understand what that 800% means.

It's \$6 billion worth of pharmaceutical product lost.

Right. So I suppose the answer is / the answer is, yes, I am surprised, umm, because I think that umm / you know people do do / try and do / most people try and do the right things in my experience. They are not you know / I'm sure there's companies out there that one or two years back they were supposed to be doing things deliberately or something, but I'm not dealing with that, I'm talking about trying to / people trying to do the right thing, on the whole seem to try to do the right thing and the ones that are getting it wrong are being a bit naïve, or they're under pressure for some boss to cut corners. It's that sort of thing. <redacted> I'm not therefore / wonder whether that 800% is coming from the fact that the boss is beating them up even more, whether something like that is happening because of that, rather than us actually saying, well, we're losing the supervision, so the quality is going out the window.

Talking about the agencies and how they approach activities, all activity in you experience, do you think the agencies are autocracies or meritocracies in the way they structure their activities?

Right. I think historically they / they have been autocracies. Right. And I don't know whether I should said or not, but certainly that's been my sort of perception of many years ago, from the FDA, where I think they even talked about the fact their starting position was to / on an inspection was kind of you know the company was doing it wrong almost. The company had to demonstrate that they were not doing it wrong. I think that view has changed considerably umm and I think the regulators are very much geared up to product quality and that sort of thing. I think the other thing that has changed considerably, and I think it was the umm / it'll come to mind in a minute what it was / yes, it was when that event happened in China, Heparin in China, uhh, I heard an FDA person talk about after that event, that really got them to focus internationally, whereas before they were sort of you know keeping it to U.S. borders and recognised it was international work gone on, that really caused them to say, hey, we've got to think more internationally is what I heard, and 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.

What about the interaction between agencies and industry? How do you feel that functions?

Right. Umm / my / I mean I suppose when I take things like ISPE I've seen that working well, ISPE, I think, you know, the / I've heard the regulators, not in a formal sense, but I've heard the view is organisations like ISPE and PDA, because they're non-profit, the regulators want to / will tend to liaise with them rather than profit-based organisations and my perception is there's a real wish for the regulators to want to get / say alongside / but want to understand what industry is doing and learn from it and that sort of thing. So I see that happening more and more umm and / but at the same time, I think industry recognises the

regulator the boss, and they know they're the boss, so in the end, if they disagree with something they expect industry to do as they say, even if we disagree with them.

But do you feel, particularly from the industry side, there's that sufficient interaction with the agencies? I'm thinking more here about new technologies or new drug products, new chemical entities?

Yes.

Do you feel there's a partnership almost waiting to happen there, or it's very much a them and us situation?

I think it has traditionally been them and us. I think it has moved a long way. New technology is coming in, especially where you've got things which is improving quality. I think the latest situation of this virus thing will really bring it closer together. I think we are going to see much closer interaction with regard to that.

So you are referring there to the / that the rolling review the UK agency did in the UK of the vaccine?

Yes. Yes, and the fact that where there's a need for medicines to be approved very quickly, I think that will start to happen more. It can be demonstrated that industry can develop drugs incredibly quickly working closely with, one assumes that's what's happened with these medicines, working very closely with the regulators, where they can see what's actually happening and then as soon as these medicines are available to go to patients, the regulator is there to try to make absolutely sure they approve them as well.

So are you referring there to a tiered approach system to submissions then, because not all submissions are equal, like everything is for a medical need, not everything is for a life-threatening disease?

Yes. Yes. I would be okay with that, with some kind of tiering because I think, yes, it's a difficult subject this isn't it in terms of whether one patient is more / has a greater requirement than another, but in real life, that's actually what happens. It does happen. And because we all struggle about that, when that debate is made very directly, you know, is one individual more important than another individual, kind of thing, these are terribly difficult debates, they really are, but fundamentally I think there is still some kind of need to recognise that the world's not perfect and some kind of prioritisation has to go on.

So you're coming in to that area of sort of socio economic and political drivers then for medicines policy?

Yes.

<redacted>. I understand about the way the / if you like the bigger bureaucratic organisations, I don't know, let's just say that they're different to deal with in a small faster moving one, I see that, and I see the small faster moving ones which maybe more science focused as being able to have that engagement with the regulators much more easily and perhaps them being more comfortable with that. Perhaps that reflects on the fact when I look back at my big pharma experience, you know, it was always terribly structured as to who was / you know who could talk to regulators and I know when I used to go on those informal meetings, that was always a why are you doing that, you know, make sure you don't sort of finish up where you're sort of talking about the company products and all this sort of thing, umm, whereas with smaller companies I think they are able to do it, and I'm a fan of the latter, having that interaction, because regulators are no different to you and I, they are still trying to do the right thing. I'm not sure whether I've quite answered your question there?

The mentality that you know we can always do it better. We can rethink it, rather than try and take what we've got and you know develop it further or improve upon it.

Yes, yes, I mean, I / that's / <redacted> certainly that's my experience. I've seen that as well and I've also heard other / when I say heard stories, true stories, real stories, of companies getting fed up with the fact that when they take a QBD approach they they have the regulators all over them to look at it and somehow it was much harder for them to actually make the case and whereas actually the case was a better case because of the fact one was getting closer to the science.

Would you agree that decisions are not always driven by the science rather driven by a piece of paper that says this is how we have to do it?

Yes, I think. I would / I think one opinion I would have, maybe this is too strong an opinion, I'm not sure, but if things like there was an actual regulatory requirement for a company to produce CQA, CPPs, critical material and a control strategy and that had to go in to some kind of you know permission document, now companies will say well that's what they have to do now, but I would want to make it really clear you know / give us a 10 page or three page summary of what your control strategy is, full stop, and I think that clarity would then act as bridge between the regulatory requirements and the site to risk based requirements.

So on that basis then, if you were going to a chemist to pick up a prescription, and you were offered domestic or internationally manufactured product which would you pick?

Oh I can't. I can't answer that. You are getting in to this emotional stuff now aren't you, whereas these are individual perception of quality.

Do you feel, from what you've seen in the industry, that markets are you know / because they have a much / a product licence are they going to be equivalent by default?

I think I'll just go back to what I said earlier. I have certainly / so if we replaced / I don't particularly want to label these two separate countries, but I have seen examples of the very thing you're talking about, of one organisation taking a very lacks attitude to saying we can sort of squeeze this through or get it done on the cheap kind of attitude and another organisation, could even be within the same company, which says we're going to do this right, even if it is a bit disruptive. In terms of the patients taking it, I think you know / in / I've seen some individual people say they won't take drugs from a certain country or something like that. But I'll go back to another / again a simple but personal **example of my** dear mother-in-law, who is no longer alive, and she was obviously being treated with medicines towards the ends of her life and she used to put on the table / when we used to see her, a couple of coloured tablets, and one time it would be a white tablet and a pink tablet, and the next time we went down it would be a yellow tablet and a brown tablet or something. She had no idea what's going on. But that was the control of that medicine was being done very very carefully to suit her requirements. What was critical in her case is the colours were right because then she knew what was going on! Alright. So we sometimes, in our industry, us experts, yes, we're all experts in a different way, sometimes get a bit carried away that the actual patients umm want something much simpler.

In terms of you know persuading them if you like that this drug is safe.

Do we need a rethink of how we control pharmaceutical products from a regulatory perspective?

My answer, yes, make it simpler.

So would a global standard help?

I'll give you an example. Even something as simple as Mannitol, you know, Mannitol goes in to probably 75% of tablet formulations that we sell at market. You write a submission for tablet formulation, Mannitol, and you get a list BP, USP, NF, JP, EP and they are all of a muchness, very slight little tweaks here and there, but the U.S. unaccepted EP because it wasn't developed in America.

Yes.

The Europeans they won't accept the NF because it wasn't developed in Europe and Japan won't take it because it's not Japanese.

[laughs]

If it is that nationalism that gets applied. Does it complicate?

Yes.

What about a global initiative, like ICH, to have a global standard for monographs, for example, very simple, monographs, do you feel that would help?

Well I was going to leave the word standard to one side right because [laughs] I know what you mean. I absolutely / in terms of the topic you are talking about, if we can have one pharmacopoeia that was global that would be great. Now I recognise there are certain specific requirements where it can't quite be like in Japan. Obviously there's certain specific requirements there where the whole nation is able to take drugs in a certain way for certain circumstances, you know what I mean, but on the whole, you can actually apply a global standard right across the piece so I'm a believer in things like the pharmacopoeias becoming standardised. I'm a believer in as many things becoming standardised as you possibly can because the population is the same all over the world, to all extents and purposes. The problem is the word standard, okay, because when we look at regulations, most of them are not actual formal regulations. If you take the U.S. the actual law is almost one step removed from the regulations and then when you get to ICH guidance's or something like that, it's not till they are built in to the you know EMA documents or whatever that they then become a bit more rigorous, but even then, question whether they are law or not. So you finish up with this real worry about what is actually a requirement versus what is given as sort of best advice and that is I think also really needs sorting out.

Do we tend to use the word guidelines rather too liberally in my experience?

We do, we do, and you know, yes, I'm on a What's App group of quite a lot of QPs, and you see all these questions going on, where people have been to a company, they see things going on, does anybody have any experience of this, and I look at this and think this is madness.

There are people with different QP experiences having to interpret what the view is in a particular circumstance. It should be much clearer. I know some things can be / do have to be interpreted. When you are talking about what some rule says, whether it / you know / it should be much clearer.

And that's why I think, again going back to Covid, being an interesting example because the vaccines that have been developed have a single specification.

A single internal monograph they have to meet and everyone's suddenly gone, yes, that's fine, we can take that, but if you take aspirin or something, there's probably a 100 different formulations out there, all slightly differently tweaked, you know, to do the same job and how does quality compare?

You know it's how we view that parity and what might / there are / and there probably always will be local variations but I'm thinking more from the quality perspective and we have, from quality, we have ICH guidance's. We have PICS. We have good documents from ISPE, good documents from PDA, there's good information out there, it's just maybe

not applied holistically and if I could give you one wish, if you could make / change one thing, with regard to pharmaceutical quality, what would you do?

I would make all these documents you're referring to much clearer and I would differentiate between principles and the application of those principles, okay, so the principle about having high quality medicines, the next level down is / sorry, things I've already mentioned, like control strategy and CQAs and stuff, and then the next level down is the detail requiring, I don't know, the way a piece of equipment works, or the way a material is tested and we need to get these really clear levels going down, from the principle of quality and medicines, and if only we could drive our documents written in that format, that would be much better.

Just one other point on the international thing, I think it's tricky because the comment I made earlier about the law versus other things, each country has its own set of laws, and then you finish up with what's a regulation associated with it and then the sort of all that then gets much more complicated, so we then start to talk about you know can you have international. I absolutely am not an expert of this, but if only we could crack that, then I think we could crack the medicines you know regulations and sort of documents becoming more globalised.

The pharmaceutical industry is an industry for profit, the healthcare industry, they are known as profit-making businesses. Do you feel there's sufficient transparency on lessons learnt and good practice, sharing best practice considering the financial constraints?

No, I don't, not at all. Not at all. I think part of it is human nature, I mean, I've / I remember, this is again just a simple example I'd choose. When I was / I was responsible for all sorts of things, all around the world, in my former job. I had engineers all over the place and I used to run a meeting umm whatever it was, once a month, or something or other, the normal sort of meeting and I used to get one of them to tell us about what they've been doing, so I just want you to give 20 minutes on what you have been doing, on your project, whatever it is, and all the others would listen, absolutely fascinating, so it enabled the others to learn from what they'd each / they were all highly competent people but you need to create these opportunities for that learning to actually get across and I don't think we're very good at that as an industry.

In other words, we do things and then we don't stop and say, right, what's the learning out of this before we move on.

<redacted>

Subject 64515

Do you think the current process we have within the UK and in Western Europe is fit for purpose to give us safe and efficacious pharmaceuticals for every product, ethical and generics?

Oh wow start with the easy question why don't you, I think it's a mixture and there are examples of both I think sometimes good products lost and forgotten in the system and I think sometimes bad products get approved I don't know whether that means the system we have is failing or whether its companies being too lazy to progress more difficult molecules or even if and I hate to say this even if there are occasions where companies hide poor data to get the products to market just to make profit. I don't have any examples of that it's just a feeling I have based upon my experiences

So would you say that's the same across all the countries, in Europe for example?

Yes I do. The majority of my experience is in Europe I've worked in England Ireland France Netherlands Austria and now I'm in Belgium and it always seems to be the same whether we

listened to the UK agency or we listen to the Irish agency or we listen to the European Medicines Agency everyone sometimes seems to have a different take on the same issue or the same question and it's not always based upon data or based upon experience sometimes it feels like a dogma. It's really quite frustrating at times

Is there pro-active engagement from the agency or from industry?

Ha-ha no agencies only come to see you when you want to prove you're not doing something wrong an industry wants to make money that's why we make products. I think there are many occasions when 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.

Is it a policing model of regulation rather than an interaction, a joint striving for quality between industry and regulators?

Very definitely policing in fact it's even worse when you consider the approach taken by the FDA or by China when they do inspections because their starting point is there to find what you're doing wrong not to see what you're doing right not to support you or to help you premises but they're there to catch you. Is not so bad in Europe and most of the European agencies oh more pragmatic. We can discuss with them we can talk to them you can I'll let you know negotiate I suppose to a point if you have the data to support something it's a different mindset it feels different. I know I said across Europe is different but thinking about it not all European agencies I've dealt with are the same some are better than others some are more open to discussions and a dialogue where some are quite narrow focused and that makes it more difficult. I suppose what I'm saying is that they're all different.

Do you see a difference between big pharma and little pharma approach? Do you see there's a difference there regarding the size of the business and the industry?

I've worked in both and there is very definitely a difference in big pharma there is just too much I probably shouldn't say this there's too much bureaucracy there's too much red tape there are too many people who are building empires or see their career path is not to develop medicines their career path is too accrue direct reports or to just get promotions and pay rises rather than actually develop the best possible products and I think but when I started work I started in a hospital and I felt very I suppose I suppose ethical moral about what I did because it was for the patient you saw the patient you saw the person taking the medication but in industry in big industry it's that's last it's all down to how much money does it make how cheap can we manufacture it I'll be going to upset this senior personal that senior person if we don't agree with what they're doing that is not to the benefit of the process as that's not the benefit of the patient that just adds a complexity that individuals that work in the industry have to deal with. I now work in small companies and these are a lot more based upon database to put information they want to talk to agencies they want to talk to experts it just seems more progressive.

In your experience are the agencies you know autocracies or meritocracies?

I think agencies, well, I just say a mixture although I think and hope there are probably more meritocracy based rather than autocracy. Industry though, laugh, that's definitely a mixture but with more autocracy based positions and I don't think that's good for it at all. We are supposed to be scientists driven by data driven by knowledge and understanding and that really does get lost sometimes.

Have you ever done an audit, a co-audit with an FDA Inspector or a non-domestic agency inspector?

I've never conducted an audit I have been part of audits from a number of different regulation agencies and this goes back to my one of my previous answers in that the agencies approach all slightly differently I like to think that I approach and audits being open and forthright and willing to discuss what I've done sometimes the atmosphere feels more oppressive and doesn't necessarily help me important information I wish to impart to the inspection

Do you feel, in the countries you've worked in, that there is sufficient control over imported pharmaceuticals?

Oh that's a tricky one I think again I'll refer back to the previous answer sometimes bad products get through and sometimes good products get blocked I think the systems we used to assess and the process is disposed to go through I don't always pick up failures and don't necessarily concentrate on the right parameters to assess I think I think sometimes cost becomes a driver sometimes expediency becomes a driver and that's very difficult to pull apart.

If you were given the option, you had to take a drug product, you are given the option of domestic or internationally manufactured, which one would you take?

Definitely the domestic products!

Why?

It's just a feeling of comfort I think I don't have any data to demonstrate that either product would be good or bad just it's a perception

So what about product manufacturing in the U.S.? Would you take that readily?

Yes I would, and I'm probably being very unfair in that assessment but I think I just feel that the countries that I have worked with the majority are very good so based upon my experience I'll dispense that product to be a suitable quality whereas products from some countries which have the smaller experience or smaller group of experts I just don't feel could be equivalent.

Do you think you know is there a principal political component there with regards to regulation? Is that "not invented here" apply?

You may be right I think sometimes it's more a case of you are more comfortable with what you're familiar with and if you've gone through the process to develop the structures to regulation often the product side if you've gone through the process to develop product you're more familiar with the quality aspect so you're more familiar with the quality control I suppose and gives you confidence. It may be wrong however boxing class just justice right. I also think 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.

Are you surprised on that basis that the last recorded 12 months Jan to Dec last year there was an large increase in recalls of overseas medicines imported into the U.S. and that corresponds with the lack of overseas inspections?

No I'm not surprised at all; in fact I would be amazed if there hadn't been an increase. So many companies run scared of being found defective by an agency that once they know an agency isn't going to turn up at any moment in time with no notice then I think they relax and when they relax things slip. Just my experience I'm afraid.

Are you surprised it's that high?

No not really although it does sound like a very high number it's hard to put that into perspective if it is an 800% increase and their normal rate is 1 per year then it's still not a

large number but I don't think it's actually one per year as a baseline is probably a lot more than that so in reality this is quite a scary statistic.

What do you think of the statement that “politics would always trump pragmatism”, do you agree with that when it comes to pharmaceutical regulation?

Hell yes! Politics always wins whether that's country politics or even internal company politics.

Is there a moralistic component to pharmaceutical regulation?

I think there should be a moral compass to product development I don't think when it comes to regulation there should be anything that's moral about it should be based upon the facts and data it should be on whether the product is actually going to deliver what it says it's going to deliver is the data satisfactory is the data correct will this help people I don't think that tomorrow I think it should just be a straightforward assessment.

Do you think it's purely politics and risk-based that are the main drivers?

For regulation?

Yes, that's really hard to answer because 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.

Regards regulations of the various agencies we've got ICH, we've got PIC/S we've got PDA. Do you think there will be any benefit to having a global system? How can we overcome that nationalistic approach?

I think a single global system would be ideal I think looking at the difficulty in getting to where we are now with ICH just shows how big an issue this would be and I can't see it changing in my professional lifetime even though I think it would be great if it did I think it's something that is almost too big to comprehend at the moment and there are too many people stroke countries we have vested interests that would just make me such a complex issue to resolve. But I do think there would be a benefit to it

Who would lead that change? Who do you think should lead that change?

Oh not me as far too difficult, I also think realistically it will take far too long

Are you effectively saying that politics has a greater weighting than patient safety?

No I don't think so I think it's a mixture 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, again it's used as a football for different agendas.

If you could change the industry and the agencies and look at pharmaceutical products worldwide and equivalents and so on, what would you change, what would be your top priority to change to improve the overall quality of medicines, of imported medicines and domestic?

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.

Subject 63766

Can you describe how you started in the industry and how your career developed through the industry?

Thank you very much for giving me this opportunity and helping you with this research. Well many many years ago, 40 years ago, I arrived / I was born in Nairobi, Kenya and I arrived with a couple of A Levels to UK because I had a British passport and I couldn't work in Kenya, so I had to come to this country. I arrived and obviously at that time, <redacted>, there was high level of unemployment but I was willing to do anything when I arrived and I started off working with a local <redacted>. Eventually I got a job with <redacted> Pharmaceuticals so that was my first finished product job in <redacted> Pharmaceutical dealing with ophthalmic and dermatological products at the time and I was based in Romford and through that sponsorship I started doing my HNC, LRC, MSC and so on and so forth, so I started off with them. I was doing stability work around core development and learning the formulation as well and then I moved on to from <redacted> I moved on to Merck Sharp and Dohme and then from there to <redacted> in <redacted>. They were <redacted> at the time and then they changed from <redacted> and so on. And then from there I moved on to <redacted> and I worked there for 25 years and in <redacted> I was exposed to various different areas in terms of API development, and then finally I finished off the drug metabolism in <redacted>, so after nearly 35, 36 years of exposure in the pharmaceutical industry, I decided to call it a day and now I just do a bit of consultancy work here and there or pharmaceutical auditing or whatever comes my way to keep me occupied.

So if you had to summarise your primary role within pharma industry would you say it was research and development, product development, commercial product testing? Where would you feel that experience would sit on the majority?

25 years, more than 50% of the time was in R&D, and the rest of it was on high skilled / high volume manufacture of API, stability testing and yes / QC analysis.

And was all of this on products that were developed in-house or was any of it on products that came from third party manufacturers, CMO's, etc.?

Lately / since I finished off with <redacted> I was quite heavily involved with products coming from third party and API's coming from third party and finished product, yes.

So how have you found that umm comparison between third party manufacturers and in-house manufacturers?

In-house manufacture I think you have a lot more control of things, so your dialogue with R&D guys, you are in dialogue with your / in terms of communication is very smooth and you can resolve issues very very quickly, but even / I found that with my employment at <redacted>, when third party was involved it was good, but it used to be quite intense at times, just to make sure that we are all on same page was sometimes a bit of a difficulty. Sometimes language was a barrier as well and that I'm not / I didn't have much problem with Europe as such but outside Europe and America it became an issue for me and quite significant issues.

Thank you, so that communication with external / different countries, so for example, like America or whatever, have you / was that to agree a common foundation or what you expected from them, or was it just that they were not giving you a minimum quality deliverable, for example?

I think it's more to do with the issues. If you have an analytical issue or a manufacturing issue, then it could be misunderstanding of matter transfers and things like that, you know, that was a bigger problem. You know if they had a problem then sometimes you have to dig deep to find out what exactly happened.

So would you say they were not proactive in supplying information? You had to / if you do it as a push-pull relationship, it was more a case of you pulling information from them, rather than them providing it proactively?

Yes, yes. I think that's what it was. They were concerned about giving us that information or whether they didn't think it was significant, that was the key, yes.

Why would you / what would make you think that they didn't want to give you that information? You said concerned there about giving information, why do you think?

Maybe you know because we are the sponsors. 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.

It's that / or sometimes it's also, you know, like umm you know who are you dealing with within the organisation, sometimes people have the fear of you know in terms of not being so transparent.

Do you think it was they were concerned about the perception that people may have of them or do you feel it was more their ability to understand and deliver?

No, it's / sometimes it's understanding as well and perception as well, yes.

It's also understanding, when I say understanding, it's you see / they don't come to you and ask you the question. They will wait and wait and wait, rather than you know come / we are open you know because we are in business together, we want you to do work you can do, and then you can deliver what we want, that way we have that, but it never happened that.

How would you describe that in your experience, that relationship with overseas CMO's or overseas third parties?

I think it's / it's just / it's / I think it's that fear with them about loss of business is what sometimes worries me that they might not give us the information we need.

So what would you describe then as, in your experience, the drivers that these companies that you've dealt with had for product delivery? I mean I'll give you some examples, would you say it was quality, was it safety, was it cost, now was it business continuity, what would be the key driver there if you had to pick one?

You see I've had two different experiences all on this one, you know, I think I touched on that in the paper interview we had, and there are two aspects. The Western market is different to the Far East market and when you are involved with East the problem is is definitely the cost and quality as well, quality, you know, whereas with us here, in the Western end of the market, it's sometimes the understanding and fear to a degree, but on the other end, it's a totally at the other extreme, some companies. Does that answer your question?

So where you've had these experiences, good or bad experiences, how have you dealt with them, you know, when you've not had the level of communication, or commitment, or whatever, with an overseas contractor that's been different to your domestic experience, domestic market experience, how have you dealt with it, how did you feel about it?

Oh with a lot of difficulty, with a lot of difficulty, and I / one of the worst ever experience I've had is a product coming in to this country uhh which is completely different strength and <redacted> has been issued which says it's this strength, the product is labelled as for

example 50 mg per tablet, the product in the box is 25 mg tablet and the actual is 50 mg and it was unbelievable the errors they have made and the errors they were trying to hide was just phenomenal. It's just unbelievable and that was one. Whereas at the other end of the scale, if we look at other markets, for example the Europe and America and the Japan and all that, I think it's more sometimes communication thing as well, it could be a communication thing, that you know, we haven't been very clear or maybe I haven't told them, I might have told them everything but my expectations that they understand is there as well.

Can we move on to a related topic and that's the / you've lead in quite nicely to that there N. is the review process and the systems that we have to ensure quality for products that we sell and we produce for consumers. The current system we have of product oversight, product testing, review, release, umm, even for the approval of multi-authorisations, do you think that current process is sufficient?

I think we need to tighten that, we need to tighten and monitor more vigorously. We do monitor it, and I think sometimes through the auditing process we do monitor the suppliers, but it's that audit and the transparency and that's what worries me at the highest level you know to be very honest, with certain companies. Like I'm not going to hide anything, like I was doing / I was auditing one of the companies yesterday at this end of the market and they were very clear about things, they were very proactive, they were very good at giving me the information, you know, whatever I wanted and if there was something / if there was an issue they would accept it and say we will do X, Y and Z, and hopefully / and they do it I think. Whereas the other end then where yes, yes, yes, but nothing, nothing, nothing, you know, and that's the sort of thing that worries me, particularly with medical consignments.

<redacted>

Do you think it's more of a company issue rather than a country issue, so for example, if you had to name / and I'm not asking you to, but if you were to pick your / the companies you think were one of the worst to supply and work with, would they be in a single country, or do you think it's more of a company culture rather than a country culture?

I think it's a country culture, to a degree, for a certain companies, for example, I'm not saying India or China or anything, but what I'm saying is those countries, for example, India and China, particularly India, I've been to China as well as you know, but with India, for example, and then I'll come back to this side of the market as well / India, you see, it's / it's the company but at the same time the employees are worried about their job security, you see, there are not many whistle blowers you don't find them in India, easily, because you see they are constantly worried about their position, their job and their future, a very very different culture and that can't be healthy, you know, you need to have people who can voice their opinion in an organisation so that you can continuously improve the quality. Now not all the companies are like that, but there are traders who are like that and everybody's worried about what / if they have a capacity to produce a million doses, they are expected to produce two million doses, and if they say no, then the management pressure is there and then the whole cycle of cutting short cuts and hiding things kicks in and that's / it's culture and that aspect does worry me enormously about that. Here I think we do worry about cost and that's why we send our / we contract it out to these countries and take advantage of you know the risk benefit ratio, but here I think smaller companies sometimes, do engage in short cuts, but very rarely I've seen it and like I worked with <redacted>, it was a very small organisation at the time, and you know you could / those days you could clearly follow things and you know like, for example, if we autoclave a product for longer than 30 minutes, the QC manager and the people say can you put this on stability trial because I'm a bit concerned about this, you

know, and that used to happen and when I / on a smaller organisation I'd be saying as well you know.

Are you saying that for smaller companies the country culture they are based in is really driving or having huge influence on the company culture and the way they approach their product manufacture, is that an accurate assessment?

Yes, yes, very accurate, and , I / when I finished <redacted> I was helping one of the small laboratory in <redacted> here and the product used to come from India and it worried me immensely you know, it just / how can you have a 25 mg product in a 40 mg pack and you have certificate which is saying something completely different, that means you just haven't tested the product at the required level, you know.

The line clearance you could see the line clearance and the mix up as well and that / from that point, I said, I'm not doing this, you know, and I'm not getting more of this sort of nonsense and so when you start contracting out some of these developing countries you really do need to be in my opinion taller and bigger and you should apply all the brakes possible.

So what about multi nationals then which have overseas units, so for example, going back to <redacted> again, so <redacted> have a presence in China, for example.

Yes.

Do you feel and what's your perception of how <redacted> China would react? Do they react more responsive to the Chinese market and the Chinese culture, or do they have that corporate culture which is <redacted> led?

Yes, yes, I think

How would you see that?

Yes, I think what it is I've been to <redacted> India but again the thing is you know it's the same thing that people, it's the people you know, the management understand the systems and everything, but when you start coming down and everybody wants to have that umm chunk of the slice financially, you know, and therefore everything / you don't / sometimes you don't know what's running at the bottom end of the whole thing, that is / you know / <REDACTED> it's a multi-national organisation, or some / but when they go in to a different country then I think you do need to police it, definitely, you need to police it, simple. It's the people, it's the people.

So you are saying then that the country culture overrides the corporate culture?

To a degree, yes, yes.

Yes. And it's a worrying thing, you know, because people / I think they don't understand sometimes they have got you know if you look at the training record and if you look at this everything is tick box, you know, everything is right, the paperwork is immaculate, but you don't know what's underneath that paperwork, you know, and that is the worrying bit.

So talking about the agencies here that oversee these new sites, do you think / how would you describe the goal, I mean, what's their aim do you think?

Well the agency / when you say the agencies like for example MHRA, E.U. or FDA or whatever, I think the objectives are clear in terms of quality and delivery etc., but it's more how do we do it / it's the management side of it to make sure that it is fully fully fully compliant and I'll give you one example which, again, worries me is that you know, for example, once I was auditing and I saw drums and drums at 40 degrees outside the warehouse, at 40 degrees. Now I'm asking the question what is this and why is it outside and where is the paperwork. Oh this is only going to be here for three hours and then we are going to put it back, yes, but we don't know what's going to happen, so how do we police that.

Because people start making their own judgement about oh nothing is going to happen in three hours, so we are safe, doesn't matter and this is / I haven't seen that happening here you see, if you see what I mean.

Everybody would be thinking is that right, is that right, is this wrong, you know, everybody will get involved.

If we describe the agencies and there's two terms here I want you introduce. One is a meritocracy which means that the people in agencies and in positions of responsibility to review and approve and authorise, are there because of merit and because of they are the best person to do that particular job? Or the alternative term is an autocracy where people get promoted because they've been there so long or they get put in to positions not because of merit and good experience. How would you view the difference between say the major European agencies and other international agencies?

I think the agencies have a role you know in E.U. or FDA or MHRA, they have a clear role and / but you know it's I guess / I'm not sure whether I've understood the question right here.

Okay, well let me give you an example. MHRA umm you give them a marketing authorisation application, MAA.

Yes.

They go through it with a fine toothed comb and they'll question your analytical method development, your analytical data all your CMC information, they'll question it to a level of detail because they are, as we know, they've come from industry and visa versa, do you feel there's that same level of expertise applied on other agencies, such as you know ANVISA, or the Japan Ministry of Health, or you know other national agencies, do they have that same approach to assessing quality?

I think the MHRA, FDA in Japan, I think these authorities are pretty good, particularly the Japan market and FDS. I think MHRA are as well, so I value their opinion and they're important and the rigour around questioning and quality and all that, so I don't have issues with the other / the regulators as such, you know, because I think also you know this / this / again the culture of you know umm challenging situations, which we have here, is defining the quality, you know, whereas you know, you challenge the people in other countries, it's / you know it goes through layers and layers of management and it just / I don't know what / you know /

So let me ask you a question based on that, so if a product was approved and manufactured in the UK, product licence was issued and then the product manufactured and released.

If there was an equivalent product that was manufactured in India, for example.

Which was released by an Indian company, it had an Indian equivalent, MAA, approved by the Indian regulatory authority, and if there was a mutual recognition agreement between UK and India, would you view that Indian product to be of the same quality and standard?

Oh no, forget it. Forget it. You've got no chance. No. No.

So there / there's a basic in-equivalence there in the agency oversight?

Yes, and mutual recognition, forget it, you are going to flood the market with all sorts of you know / Very high / extremely /

No, no, I think you know having / as I said earlier on, I was born in Kenya, Indian origin and my parents originally came from India, but you see, having been to India many times and also audit all sorts of things, you know, I always have that worry.

I mean I'm sure that / it's going to become one of the big economies in the future, but you know, that difference between the rich and the poor and this that and the other and that creates a culture and all sorts you know, so it's quite deep down, it's rooted in to the whole set

up. I don't have anything against India, I go there every year, or China or anything like that, but you know, like I'll give you a perfect example about China. you know. I'm not going to tell you about the company but I was there and as I was auditing I was walking around the site and I had / which I often do, I had to go to the toilet, and I said uhh I never go to the toilet before I leave the office, when they are walking me around, I say, can I go to the toilet, and they said oh here, and my goodness me, you know, it was disastrous, it was just an open thing, right, and people are walking in and out in to the manufacturing area and they / and I questioned that and I said there is a very very high level of faecal contamination here, which I could see, and I just had to walk back out and it's this sort of thing / I mean don't the local authorities, when they audit it, don't they see this?

How do you feel about imported products? Do you think they are good, bad, or indifferent?

Right, imported products, it's good to have sometimes the generic imported because sometimes it's cheaper and it's good, but the worries are still there in terms of you know umm consistent qualities, multi-national might do a good job of it, but other small organisations will have / who hold the MIA I do worry about them you know. I've seen some issued particularly in India, I do worry about it, you know.

Do you think they're safe?

I / I mean for the / sometimes / no, I don't feel comfortable.

Your gut feeling, your first reaction is you know / and you said there you're not comfortable.

Yes. It's also it's you know it's you might produce the best quality first paid batches, but the ninth one might be you know and that variant is somewhere along the line you know is the worrying part of it all, you know, you might not catch it because how do you catch someone who produces 20 million tablets you know. It's pot luck isn't it.

Yes, it's lost in the noise and that variant's somewhere and where that comes from is, you know, people don't want to stop machine, oh, if we stop machine the managers would say this or the managers would say that, no, you've got to stop it and see how / you know / how you / how you rectify the situation.

So if I came to you with two products, domestically manufactured or internationally manufactured. Which one would you take?

Oh I'll take UK, any day.

The other thing, while you've talking about the products, have you heard of <redacted>, capsules, right, slow-release, this that and the other. Now slow-release formulation demands a lot of understanding and it is quite intensive in terms of manufacture and this that and the other. Right. And I have seen way too many failures on that product coming in to the country and I'm thinking I bet any money whoever is managing this product coming in to the country, right, he is fired by greed and he doesn't want to say anything, this that and the other, and it just comes in to the market place. As simple as that.

So, for example, if you say / if you give me <redacted>, slow-release, from here and from any other developing countries, or whatever, I would take it from here, because I know that I'll get the right dose at the right time, or the absorption would be the same profile, if you see what I mean.

So you are saying that's a financial driver rather than a quality driver?

Yes, yes. sometimes gets hidden underneath.

So in your experience, you've been in the industry for well over 30 years now, has your perception of products and imported and domestic products and equivalents, has that changed or do you think its been pretty constant throughout?

I has changed since / over the last / particularly 15 years.

Why do you think that is?

It's because the market has changed and we are flooded with generics and we have lost the manufacturing here you know, because of the cost obviously, and because of that we can easily lose our quality.

So your opinion of the industry has changed. Do you think that has changed based upon your personal experiences within the industry, or has that changed primarily because of the natural development of the industry, the modification of the industry, so two different approaches here, the more you've been working in the industry the more you see and the more you've learnt, has that changed your perception of what's going on, or is this because the industry has evolved, for example?

I think the industry has moved on and has evolved, but being / you see / being in the / understand/ for example sorry to keep going / I mean having lived in Africa, a degree in India, I'm sorry to keep going back to India and Africa, whatever, but you know it's just that understanding lacks you know and that's a / you know I haven't been in that so I understand the thought process probably of the people who are involved with that industry. You would understand for example you would understand the British way of working better than I would, but I / having lived in the country for 40 years I understand how we work here, compared to how the rest of the world works, you know.

You see what happens is when, for example, when I'm in India, and I'm walking around, I come across so many poor people, I do feel sorry for them, you know, in terms of / but I do worry about the drugs they are taking and the control within India, for example, and the whole you know / whole system and the process / it's / it is worrying you know.

Because the controls are different. For the local market they are different and for other markets they are different, you know, it's like you know when we used to make for <redacted>, now our specification was not as tight as American specification, so if American / if a product fails American specification, then it passes European specification, then we are happy to pass it on, but the difference between the two specifications are not vast, if you see what I mean, so the fine particle mass, which would be delivered in the lung, it won't be / the difference won't be huge, if you see what I mean?

Is it that application of expertise?

Yes, yes.

So what you've described then your current view, as it stands now, 2021, of the industry is a mixture of your experiences, your perceptions, but also the change in the industry and the data that you've seen and the data that you've been part of?

Yes.

So is there anything else that you think has driven umm changes within the industry that we haven't talked about, you know, we've talked about culture, we've talked about expertise, we've talked about umm cost and financial drivers, anything else in your experience you think is a key driver here?

I think / it's just the / the financial and the differential in the expertise and understanding, you know. The / the reasons, <REDACTED>, you know, that's what it is. It's / somebody / I'm

looking at a chromatogram and there is an artefact at the point of interest for example a huge peak is coming out at 20 minutes and that's what I'm interested in, but underneath that, is another peak, which is due to the artefact of the system, so you need to that otherwise you are going to get the wrong results, but people have said, oh, we have done five injection and we are getting a result so we subtract that from our no you don't do that. You can't do that because the response may vary, we don't know, and you could pass a borderline result or this / so yes, I think it's / overall it's / it's just / cultural and financial motivation.

What do you think could change for the better to change the industry and how we approach international products?

I think you know / better umm / we need to police whatever is coming in a lot more vigorously, and put more resources in to the authorities, so that they can monitor that. If its been done, I know its been done at the moment, as we speak, but MHRA haven't got enough resources to keep going to places every three months or every six months or every / at least twice a year or something like that, you know.

Do you think you can help that change? Can you be part of that?

Well I / I am obviously nowhere near the authorities but.

Your role as an industry professional of over 30, nearly 40 years experience here, you're consulting now, so you are imparting your expertise to clients, so do you feel that that is part of / or could be part of the solution or do you feel it's purely an agency responsibility?

I mean if you are involved directly with, for example, the authorities, in this country, then I think yes you can influence and push that forward in terms of you know more vigorous checks and unannounced checks as well, you know.

So you think it's more of an agency responsibility to lead this?

I think what agencies have done is they have passed it on to us in terms of you go and audit them. So they have passed / they have said, oh, this is the requirement, every three years you need to audit this company, this company and this company, or every three years you need to audit them, right, and you go and audit them and the agency asks them that have you / has your organisation been audited and they will say, yes, and that's it, you know, but I mean we get, I don't know, these days we just get a day, how much sampling can you do in a day, when you are auditing a huge company, how can you / I mean you go in to the warehouse, you go in to the manufacturing, you go in to the laboratory, and then you look at the documentation and now you've got the documentation you look at it and they show you / and I don't have time to read the whole thing, but I'm just looking very briefly over the set of data I'm given, you know.

So do you feel then that change in auditing, for example, where you said the agencies have pushed it on to the clients to do more of the auditing, is that a reallocation of responsibility or an abdication of responsibility?

Oh it's a reallocation, yes.

So you're not saying then the agencies are deficient, you are saying they are more looking for more interaction with companies to do their quality auditing or do you think the agencies are relying upon those companies, so what should be an agency responsibility they are saying, well, we're not going to do that, because the clients are doing that policing?

Yes, so we / I mean I / I will go / I mean to a degree agency have passed it on to us, which is okay, they can't do everything, but you know, with us, I mean, as I said, one day of auditing, how much can I do, you know. I really do worry of this statement, particularly when I in India or China you know. I really do, because I'm on my own, and I'm looking at these things. I'm going to miss a lot of things, there's no question about it, you know.

You know they know what I'm looking for. I'm looking for water analysis, I'm looking for microbial testing, I'm looking for warehouse discrepancies, here or there, umm, and they know what the standard auditing process is, you know.

But I think / I mean agencies / you see MHRA, we have got so many people bringing in so many products from abroad, how are they do it you know.

So your thoughts are, particularly for imported products, it's more a case of policing rather than ensuring quality at source?

Yes, policing and making sure that the source is audited. The source needs to be you know monitored very very carefully.

In detail you know and as I said I am more analytical but I've worked in API's so I've been fairly / I've been lucky you know that I / I mean I don't only look at the API, I also look at the stability data and I look at the production and I understand the key variables, I try to, before I call, you know, so that I know where I need to look at things, you know.

And also you need to be aware that when a third party is involved in, for example, China, not so much China, but for example, India, then they will do microbial testing for you there, but what if it fails, you know, what is the company going to do, are they going to ask them to repeat the test? Are they going to follow the procedure? Or are they just going to say, can you just pass it.

Is it more a case of the ethical approach to manufacturing?

Yes, that's it, that's it, that's it, it's between the / you know / you become friends and you say, oh, you know, just forget about it, we should / it will be done though. I worry about those sort of things. I haven't seen it but I worry about it.

So if you had to pick top three drivers for change what do you think would be the top three influences that would or could or should force change on the way we approach global pharmaceuticals?

The first change would be (1) training and encouraging your people to come forward when they see any anomalies, so for example, if it is in China, India or Africa, or wherever it is, outside the Western belt, that you know, the management have a high responsibility of making sure that the people are / it's very easy for me to say this thing, but its got to be done, to monitor the quality, you know, so that training, that whistle-blowing culture is not there.

That's number one, what's would be your second driver?

Second is more authorities also, policing, more rigorously, anything coming in.

So first high level of training, extremely important, and that vocal, that being vocal and encouraging the lowest of the low, in the organisation, to come up with anything they are concerned about. Then the policing part of it. And more of also authorities looking at people who are exporting locally.

So would that be your third priority then, so the second one would be policing, i.e. MHRA policing what comes in to the country, but then the third priority would be the local agency policing their own companies?

Yes, local agency policing their own companies, and MHRA also policing the companies who are importing from abroad, you know so, for example, I told you I worked in very briefly in one of the companies. Now have the MHRA visited them, or have they just done a audit? And have they actually looked at the data more vigorously? They haven't. I know that they haven't.

They would have seen it. They would have seen it because there are lots of companies importing these drugs, you see.

So those are the drivers for change that can influence change. What about your top three reasons for change? Why is a change required do you think?

I think it's the quality / patient. At the end of the day you know if a patient is due to receive 50 mg of drug and receives 25, then the doctor's got a dilemma here.

You know, measuring the response.

If quality is the first, what would be your second driver, reason for change?

Well just to make sure that we have a / global health is the key thing isn't it. Change is / I guess umm / you know / I mean / second reason for change you mean right?

So global equivalents?

Yes . Products being the same across the board.

Yes. It's a difficult ask but it should be that way, if we are going to you know / and more surveillance.

I think if we / if / Governments have more incentives you know to now push the quality, for example and so, for example, local Government you know, they want to work with everybody else in the world, or we want to work with everybody else in the world, so it's more of what we can you know / what we can achieve by putting that pressure on locally and abroad, you know.

A global political incentive?

For example, you know, the local / a local Government can push for a / you know better employment conditions within an organisation and better you know / motivate the people to come up with any deficiencies in the process.

So just to come back then to a previous question then, so for these changes, we've just described the drivers and the changes and the aims, who should be pushing that, who should be pushing for that change for that harmonisation if you like?

I think that push comes from / it should be the World Health Organisation isn't it really, or at least, ours, whatever is coming in here, MHRA should be, or the Government should be you know.

So an international or a global agency?

Global agency, yes, yes. But it has to be done properly because you know in / I keep going back to this auditing business, there were times when people used to go / two of them used to go for three days, or two days, you know, and these days we have one person going, all the way to China, for one day audit. Now where is the / I think it's a false economy you know. It really is because/ you know I don't know, I haven't been doing it for long, but you know these things better than I, but you know /

Do you think a false economy is a good description for it because all you're doing is moving the resource from one area to somewhere else where you have to spend it to try and ensure quality.

Yes, yes, that's / and there will be lapses, because you can imagine I work from here, and you arrive there and the following day, after arriving, you are doing auditing and then the following day you're coming back. You are more tired than / and what I will produce in that time, you know.

And those are the / I think the quality movements are in place, but how vigorously are they applied?

One more thing, you know, I should umm / you know talking about culture and all that, once whilst I was in India, I had a <redacted>

No, this is what I'm trying to say when I'm talking about quality as a whole, you know.

So it's a total health care rather than just pharmaceutical products?

Yes, every sector, you know, has got this you know medicine, oh, this guy, you go to a doctor, he's going a table there, you sit there in this modern world, and he's prescribing you five different tablets, does that mean that you haven't sorted out what the problem is with this patient or what?

You know [laughs] this is what happened to me, that's why I'm / I'm telling you you know. So it's not joined-up health care is it?

No, it's not, it's not. It's not at all, not at all, and you know you get like you know Imodium for example, we get it here for £6 or something like that, over there you get it for a £1 you know, but the differential in quality it has to be that / I haven't tested it, I don't know, but I know that it's going to be that.

And counterfeiting. Counterfeiting is another big problem.

Subject 61855

Do you think the current regulatory process is fit for purpose to give us safe and efficacious pharmaceuticals for every product, that includes generics and new chemical entities?

Laugh! Oh it really is a mixed response. I think in some areas the procedure is overly bureaucratic overly conservative takes up far too much time and resource however I kind of understand why it is that way because not all companies behave in an ethical manner. I think particularly with generic products money is such a big driver, that's money to companies wish to make by manufacturing a cheap generic but also the political aspects of having cheaper medicine on the market provides for politicians and society I guess. The current process can certainly be better.

So would you say that's the same across all the countries? In Europe for example?

Oh no definitely not! In my experience although 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 markets 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 I think some of the smaller European countries rely far too much upon the bigger more established agencies to give them guidance on what is required and I have seen some companies try to exploit that by using smaller countries smaller agencies as their rapporteur agency and causes problems further down the line for the registration.

Can you elaborate on these 'problems'?

That's simple I have experience of a product being registered and reviewed in Portugal, it was a sterile product, Portugal has very limited experience of sterile products and once the approval was then rolled out to the wider European Union it was pretty much torn apart by the UK, French and German agencies and just causes huge complications. But that said it was a similar activity that happened when the clinical trials directive came into force some 20 years ago then some countries would put their CTs into the Netherlands for example because they hadn't ratified the CTD and therefore it was easier to do a phase one clinical trial in the Netherlands and it was any roster in Europe, people would always try to find a loophole and exploit that if they believe it's quicker or cheaper!

Is there pro-active engagement from the agency or from industry?

From my experience in big pharma there is very little proactive engagement with agencies from big pharma. I've also seen very little proactive engagement from agencies to big pharma in fact I'd be hard pushed to think for example where there has been proactive agency in

engagement. This is my perception that virtual pharma companies or biotech how a lot more reactive and willing to discuss with agencies however that is anecdotal and not based upon my own experience.

Would you agree with the description that it's a policing model of regulation rather than an interaction and a joint striving for quality between industry and regulators?

In some countries it certainly is policing but certainly not within all.

Can you elaborate?

Well I think we in United States and Canada it certainly is policing in my experience. In Australasia no in Australia is more of a dialogue and engagement whereas in China and Japan and Taiwan it is almost deferential to the agencies because they wield so much power. And I don't think anyone of these options is a particularly healthy process.

Do you see a difference between big pharma and little pharma with regards how they approach or interact with agencies?

There certainly is, I think 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 so they use the agency engagement process as a form of learning or sort of training.

From the agencies you have worked with and dealt with, are they autocracies or meritocracies?

That's difficult well 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 some cases their autocracy in some cases they are meritocracy does that work?

Have you ever done an audit, a co-audit with an FDA Inspector or another nondomestic agency?

I have with TGA and also with Health Canada I don't have any direct experience with FDA not as a Co audit however I have been an auditee of the FDA and I can only say that that felt very different in nature a lot more challenging!

Do you feel that we have sufficient control over imported pharmaceuticals?

That's a very emotive subject isn't it but I guess that's really what you want to talk about. No I don't think there is. I think the fact that it is more difficult to inspect, it is often more difficult to travel to these sites, replace undo confidence in some of the local Regulatory agency inspections there to conducted which we know in some countries aren't really very good at all and I think it's a bit of a dangerous area for us to we could see problems we can sense promised we often perceive a problem however there's very little information on which to say yes it really is a problem or is it just a perception because we don't have total clarity or visibility of what's going on. Maybe that's it maybe it's just having that visibility at transparency there were more used to hear from domestic manufacture then we would be from overseas?

So that aside, if you were given the option, you had to take a product and are given the option of product manufactured domestically or product manufactured internationally which one would you take?

Within the EU! Every time.

So what about product manufacturing in the U.S.? Would you take that readily?

I would if there was no other option but let's be honest we don't get a choice do we mine only just kept whatever's on the shelf and then off and I was just looking at where is manufactured just out of interest really. I guess it's perceived to be someone else's problem even though I work in this area and have done for decades I don't really think about it to be honest.

So do you think you know is there a political component with regards to regulation?

There is money involved, it raises taxes, healthcare has to be paid for, terminal was bare political components

In the last recorded 12 months Jan to Dec last year there was an large increase in recalls of overseas medicines imported in to the U.S. and that corresponds with the lack of overseas inspections due to covid-19?

Wow <redacted> although I'm not surprised there was a change particularly in the US there is a drive through managed healthcare to always source the cheapest possible option for medication in my experience.

Are you surprised it's high?

No I guess I'm not really.

So then on that basis then, someone once said that politics would always trump pragmatism, do you agree with that when it comes to pharmaceutical regulation?

As I said earlier there would always be politics because there's money the two go hand in hand and they probably always will do healthcare costs money medicines cost money operations cost money therefore has to fit within the budget of a country or the budget of an individual and therefore would always be an explosive subject!

Is there a moralistic component to pharmaceutical regulation?

Within development no but within regulation there often products which can get a faster if you or can get access to greater expertise within agency because of the indication they are seeking or because of a public health emergency such as with covert vaccine that's a very good example. The rolling and review that was conducted during the vaccine development process really highlighted this because the approvals happened so quick in comparison to a normal regulatory review process people start to suspect that there is a quality issue whereas I believe there's not a quality issue there what we saw was a reallocation of resources such that a priority was given to something which had a greater public interest now that would be a mixture of public and political pressure in those sorts of situations.

Do you think it's purely politics and risk-based that are the main drivers?

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

Regards regulations then of the various agencies we've got ICH, we've got PIC/S we've got PDA in the U.S. Do you think there will be any benefit to having a global system, How can we overcome that nationalistic approach?

Absolutely definitely yes. That would benefit industry, it would be simpler for agencies to oversee, it would give patients confidence in the medication now taking, nationalistic drivers I'm not a simple hurdle to overcome so why should I think it's a very worthwhile and worthy aim how that would be done is very difficult to visualise.

Who would lead that change? Who do you think should lead that change?

This would have to be one of the big agencies or the cross agency groups because people just wouldn't listen otherwise. If Norway for example said to Wigan to create global standard that everyone has to work towards you could almost guarantee that Germany and France the United states was Oh no we're not going to cover that we're not going to agree with that we've got a better system for stop a great example is that we have the ICH quality by design process which large numbers of countries bought into and approved of but even up until a couple of years ago companies were being sanctioned because they were taking the criteria in that quality by design process and then using descriptors of their own classifications rather than follow the process which multiple national agencies have agreed between them. why? That just doesn't make sense I think a similar problem could happen with almost any sort of global initiative. Maybe I'm just sounding too much of a sceptic?

On that basis then, from what you've just said, you're effectively saying that politics has a greater weighting than patient safety?

No not always but I'm not naive enough to think but sometimes politics does have a greater influence. Directly agencies are governmental departments affectively and therefore priorities can change and wine based on the pressures put on those agencies. Safety is very subjective measure if you talk about oncology sometimes the drug could be as dangerous as disease almost and that's all part of the risk benefit analysis it's never a straightforward calculation in those types of situations and I think sometimes agencies are put in the middle to make those very difficult decisions I don't think it's naive to think there's always a set process for that.

In your experience, what would be your top priority to change to improve the overall quality of medicines, of imported medicines and domestic?

A single quality standard! One standard for countries for all agencies can only be beneficial. Although thinking about it I'm being realistic a single quality global standard is a great aim but highly unachievable certainly at this point in time but would be more likely something akin to ICH where we have groups of countries that band together to have single quality standards I think that at least would be a starting point other countries could join as time goes on and then it should be on those countries that create these processes to demonstrate a palpable benefit from the process to encourage people to join but that will require a level of confidence within each other and sharing of information which so far has not really happened.

Subject 61290

Are the regulatory systems fit for purpose?

Uhh I think it's a little bit different uhh when I look at it in Europe sometimes the risk that they take is actually lower for the development, depending on the area of / development of which kind of molecule, right, for like in Switzerland I think proteins they actually treat similar way as the U.S. but maybe saline gene therapy in Europe is they actually take very good precautions, in U.S. a lot of people take a lot of risk in that area because it's an upcoming area and also FDA actually give somehow guidance so I think when you compare an analysis of proteins I think both parts of the world now is becoming very similar, but in the saline gene therapy area, it's actually there is a big difference.

And what about the rest of the world, so sort of the Indian market, China, do you view those as equivalents?

In China, I work with China a lot [laughs] all my manufacturing partners are in China and China is not up to par with Europe and U.S. but they are catching up because like us consultants actually basically teaching them [laughs] so it's a good opportunity for them to have consultants like me to actually teach them so / uhh / that's what I see. They are coming up very rapidly but the analysts are not trained. Analysts cannot think, yes?

And uhh so there is issue I think it's a hierarchical in China so they actually wait for their supervisor to make the decision rather than them making a decision.

So it's cultural rather than accurate technical expertise?

Yes.

Uhh cultural plus technical as well because they are rapidly growing the companies I work with, they are expanding exponentially, so they cannot keep up with demand of people that they need to run a proper organisation. This actually comes through project discussions, you know, they have different (03:28) and also it shows that they don't have experience because their proposal that they put forward to say okay to solve this problem lets do this way, but their analysts don't think about what will be the risk at the end, yes, so /

Is there a holistic view of the process?

Yes, it's compartmentalised in China. You are hired to do something that's it [laughs] it's very departmental.

And uhh yes sometimes it takes a lot of time to navigate and actually when analyse some samples because the formulation and analytical have to talk and get the agreement on rather than saying, yes, actually I agreed a long time ago to do this, so / but it's interesting I think China will catch up and beat U.S. and Europe in manufacturing on /

Manufacturing of products of equivalent quality then?

Yes, yes.

Maybe actually over take with another two three years.

So do you feel your role at the moment, when you deal with your manufacturers in China, as an educational role?

No, no, I get uhh what I want for my client, that's actually to develop a drug within certain timeline, that's my goal, right. At the same time if I can teach them I'm fine with it, so I look at it as longer term relationships there, you know, what I want and get what I want and get out, I have good relationships with them, for example, uhh, when U.S. did not have mask for Covid, actually Chinese manufacturer I am working with one of them actually within two days supply me 300 masks [laughs] from China!

Yes, so that's actually you know it's a / I look at it as friendships rather than a consultant the way I want to do.

So thinking about the regulation processes, that you've been involved in, obviously you know the European and the North American ones, the current process we have in Western Europe do you think that is acceptable and fit-for-purpose, or is it onerous, is it not detailed enough?

Could repeat, I missed one part of the question.

The regulatory process we have in Western Europe, so the EMA and the FTA and MHRA, do you think that that regulatory scrutiny is sufficient for domestic products and for imported products, so for example, in the U.S. at the moment, you have domestic inspection of domestic manufacturers, routinely, but are not inspecting overseas manufacturers at the moment.

No, that's not only the Covid issue right, otherwise yes / for me I think uhh when I look at it, I actually look at it in a different way, right. It doesn't matter where are you actually produce, what is required is actually the acceptance of the regulating authorities to allow them to do the clinical trial in their countries. So if they can achieve that that actually that the companies in Asia, if they are actually supplying clinical trial material or commercial material to Europe or U.S., they are on par with the regulatory considerations for analysis and all the activities of GMP. So I look at it as it's actually okay but I think when I think about it I know that U.S. FDA have a branch in China, they actually do inspections, I'm sure the same as in Europe and health authorities there do that, or they combine with U.S. to do some, I think, so yes, I think a lot of people are concerned, for me actually at the final stage what is actually required is actually getting the of the health authority. They are the responsible party to finally say yes or no and if they say yes that means they are aware of the quality systems and you know requirements that these Asian countries actually the manufacturers have and implemented. I'm sure that they know which ones are good, which ones are bad. So I have not been stopped by any health authority / the companies that I work with to start clinical trial is in U.S. or Europe. So it's / so I think you have to pick the good ones uhh and work with them.

We have ICH at the moment, do you think a wider adoption of ICH, and an enforcement of ICH would help across wider markets?

Yes. Definitely, 100% agree on that. Yes. Yes. Because there are some small small changes in / even in Europe and U.S. right, uhh, small differences, how they depict things. It makes very hard for developers right and small word changes [laughs] different requirements but if you can put ICH and actually agree on it, then I think it will be very helpful. But the question is / yes like you say

Would having an available regulatory framework be beneficial?

Yes. It will be beneficial but the question is the uhh national interest right, so you can have all these ICH guidelines and everything, but at national level, if they actually have their own guidelines, you always have this issue of you have to do extra for certain countries, you know.

So when you've had engagement with agencies, any regulatory agency, do you feel in your experience they all apply the correct level of expertise in technical reviews, technical discussions umm have you ever had cause for concern dealing with an agency? They don't really understand what you've been doing or working on?

No.

You've been very happy with that interaction?

Oh yes, yes, yes, my interactions are being very interesting and happy what they provide uhh the way I actually look at it uhh early on in early development pretty nice, I mean, you know, I can give you example recently I'm actually working with a company on an indication where, for example, some physical particles have to be solo for that particular invitation, and when I actually propose the specification I didn't want to you know surprise them with a big number but I actually gave a reasonable whilst I was thinking at that time now I think it should have been a little bit more margin on my side, but they actually said that whatever the number you propose will be very hard to achieve, but we'll be happy to take it, because you are proposing what they say that it will might be very hard and they will be happy to consider if I actually get in to an issue that we cannot deliver. So they were pretty, you know, open about it.

Do you feel that extends to the wider corporate industry or do you feel that the industry is very reluctant to engage with agencies early on?

It will depend on the company and the experience and the mindset, so for example, small companies actually sometimes they really want to go and talk because they think that getting input is good and they also the way I looked at it is like getting input early actually make them aware what to do and also if the discussions goes well they can raise a lot of money because they can say here, my / you know FDA actually told yes you are going to go for Phase 1, or something like that, that's actually helped them a lot, yes, larger pharma, because of experience, they don't go for Phase 1 discussion. I think for like antibodies, you know, they know what to do, they know the expectation, they know the specifications, unless there is an issue, so it depends on your expectations and things like that and who actually work in the company also define it, something that they actually have the expertise and they don't actually ask these questions and what at the end is actually they are getting on this clinical where they could have actually asked something very quickly with FDA and got on, so I think it's to actually kind of thought process, I think, one is the people who are involved in this, some things / they know / some people think I know everything, I don't need any advice, and in that sector I think if they have an issue they actually fail, like hugely right, because they actually (14:53) document, it's a clinical. The other side is asking too much when you are a small company, you know, trying to go and have a Face time. I think the FDA will offer it and actually they treat very nice. I have been with the FDA to very small companies, I'm so surprised sometimes the things they agree [laughs] to you know for these small companies, how they can do their work, so I think it's two parts.

Is interaction key?

Yes.

So talking about drug products now, so established multi-drug products, obviously we have a huge supply of generic medicines in Western Europe. Do you view Western generics, Western manufactured generics, as being of equivalent quality to those manufactured say in India or Bangladesh?

Uhh / if it's registered it should be same quality, right, that's the way I look at / that's the gauge I actually pertain.

So you used the word should there, what do you believe?

Uhh / the way I look at it is it's not my belief that is important right, it's the data driven decision made by the health authorities to sell the drugs in their own country and if they have a standard then they actually see the standard from Western country and an Asian country, I think that's their responsibility to actually say yes or no. But you know it's the question is the same quality uhh is / sure what they are looking at is what they innovate a product, what's the purity profile and what's the impurity profile of the Western generic and Indian generic, right, so that's the way I look at it, things, but if you know, yes, some people say, oh, maybe these are actually different or something, but if like the / my belief, I don't have the data, because I have / I'm not a generics guy, but I think the way I look at it is like if the country allow it to sell their country that means the health authority have figured out their profile impurity.

If I said to you that a medicine manufactured domestically, or you have a choice of a cheaper generic manufactured internationally by another generic manufacturing company they are both licensed products, which one would you take?

Most probably I go with product from domestic source, right. Yes, it's because I know the subject.

Consumer who don't know and who don't follow companies will always think that the health authorities on their own country took care of the safety factor, right, so.

There's an assumption isn't there, there's an assumption on quality?

What about ethical concerns regard manufacturing?

Yes. Yes, yes, I think it's actually uhh if that happens it's actually ethical concerns of the company, how they operate and also I think for me I actually give the argument authority of approval or disapproval of a drug and authority of the importation, the licensing and things like that, to the health authority of their own country, right, and if they don't care about your own people and if this happening all the time, this actually says that maybe there is a broader picture what they see maybe if they don't allow this kind of products we will have an issue of supply, I don't know, it's actually all driven by the decisions of whether you can actually support that product in your own country and how you take care of your own people. So we don't know the background story of it, unless someone actually really go and analyse, maybe another PhD for you? [laughs]

Do you feel that an application of that would actually satisfy a single quality standard globally?

Yes, I uhh I think uhh when I think about it I think U.S. and Europe are close, right. There are only certain things that are different and everybody knows about it and if they can work on it I think you can come to a kind of agreement of quality parameters. I think you can do it if there is a willingness to do it. Yes. I think who leads the discussion and who wants to get it done will be the broader you know discussion I think but I mean for biologics on the side if I look at it I mean I only look at few things if I am actually in the U.S. or Europe, I mean, so / but uhh / how you write it is a little bit different but quality-wise I mean they are very very close.

Yes. So I think they can get it done and if they really want to, but I think the national interest always trump all other concerns, like some peoples can say oh U.S. approved, so we are to use it, and some independent countries don't like that concept, so yes. I'm actually surprised I mean even in Sri Lanka, I would have actually / because you don't have a man power to evaluate you know applications, they should have actually said that okay if this actually approved in the U.S. and E.U. it's automatically [laughs] right. That's / I mean that's the way I look at it.

So you are effectively out-sourcing your quality review process aren't you?

Yes, yes, you trust the people who have the bandwidth and approve it, but they have to actually not go for generics and things like that, but for the innovative products they can approve it very quickly. When it goes to generics I think they should actually really look at it and for example, I mean, I agree with you about the quality and things like that. My father actually, I cannot remember what the drug, I used to actually send it from U.S. It was like always so expensive, don't actually send it, and I'll take it Indian one and he actually became so dark when he took it actually / yes / yes it had some effect on some cells or something on when you go on the sun, he became so dark, but they actually say.

Yes, yes, it's actually sometimes it's crazy uhh to think about like this in developing countries, they approve things without looking at it right, so / or it's a political decision. Politician actually force someone to approve it because he might actually get some you know financial benefit out of it.

Critical drivers, you know, benefit drivers,?

It depends on the companies I think, right, if you are an established company, uhh, most probably they will try to stay in a course that they will not get in to trouble, but they always get in to trouble. It's a money thing I think, financial, it's actually a risk benefit analysis at the end. For me I mean I have good examples, even today, I was actually talking to a client, they actually got in through a due diligence and for a partnership and this is a large pharma and they are doing the due diligence and they are asking why you did not do, why you not do, why you / it's a risk analysis of whether you have money or can you get it done later, right. So in a smaller company I think they value the safety but they don't have money so they have to make very hard decisions but they make the decisions from my way of thinking, they make the decisions, based on patient safety, but maybe they cannot actually get the full profile because they don't have the financial resources.

Yes. And the large pharma, if you actually look at it, I think they actually go find you know investor return [laugh] if they are actually doing cutting corners right. So /

Yes, yes, yes, so that's the issue you kick it out(essential work) until you have to do it.

Yes, there are things, yes. I do it all the time umm / it's a basically a risk the company carries and it should be documented so everybody knows it's actually there, it's this risk that company carries forward.

So if we put those words together, it's having a satisfactory and quality risk management process?

Yes. Yes.

And someone that knows that how to apply that to a process, based on expertise. So thinking about again safety and efficacy, what do you think would force a change in a global quality policy? So if we said right we want to roll out ICH to the entire world, every country wants to supply to other countries as this common standard, what would be the top three drivers to make that work?

Oh the top three drivers to make it to work, if you can actually show the benefit of cost, right. I mean I think if you have that concept and the companies will actually allow it, because you don't have to have different testing parameters, you know, if you have global alliance specifications, it's actually very nice, and what I think is the most important is one submission package globally, yes, so / done, yes.

Please elaborate

So I think that's I think the one. If you have it I think it's very good for financially, for pharmaceutical companies, and actually for consumers it will be also good because it will be a cost will be reduced to go to the market, yes, so what else? I think it's actually if you have it then people will learn quickly in other parts of the world what you have to do because now they are confused, different markets have different requirements, then they actually don't know what to apply unless they have the people who actually done this studies in different markets. So they also can actually save a lot of money because sometimes they start with actually just supply my country and then I'll expand, but if you had a one global standard, they can go anywhere and sell it, so it's actually will open up a lot of opportunities for developing countries I think.

Is cost a big driver then?

Yes.

I think actually for that reason I say no, because I don't want a poor quality drug coming in to the market and I might be a consumer or somebody.

Yes. I think uhh / I don't think this will shift much. It will take a long time to shift. Because it's also it's not just \$6 million right. If you have a global standard and if you basically uhh have that standard that everybody apply, then the countries that have the low-paying jobs,

will dominate the industry and it will take out the quality jobs that we have [laugh] right after five years.

No, no, it's actually you had to think about what (35:04) will think, right. It's actually the giving out the power.

A your employer, you know, your people actually get employed, so it will drastically change. I think that's why you don't see this kind of thing, you have to have that power to control.

And does that come back full circle then to what you said initially about nationalistic interest?

Yes, I think so. That's the issue right, I mean, this is actually started from France a long time ago, Brazil, I mean, you know, testing requirements and things like that, because they want to have their people to have jobs.

Yes, I think / I mean / yes, I think it's not going to happen for a long time, uhh, unless you know the shift of financial power changes, right, so yes, I mean, but it's changing, for example, uhh, I can actually now / the money I paid, I actually transferred a project because of that. I transferred a project from China to Germany because in Germany I can do it cheaper than in China.

Because they were asking me so much money we just went to Germany and it was actually cheaper [laugh] so uhh as China is actually becoming expensive to be there, but people have not made their mind yet to say we are to go, yes, so I think this is what is actually going on, uhh, I think China will saturate and literally dominating production, but uhh, they will be 80% cost structured when you compare to U.S., so then you ask the question why not use just say in U.S. because you have so much headaches.

Why do you think that?

So they actually realise I can tell you I actually work with a company in China, one of the largest, now they realise this issue and they are now actually building facilities in U.S., Germany, Ireland, I don't know whether England, they are actually building facilities all over the world because they actually come to realisation their cost structure and everything will be similar very soon.

Yes so that's why I think it's actually come full circle I think, U.S. will get the manufacturing jobs again, uhh / and also you know politics helps [laughs] sometimes [laughs]

Subject 57127

Do you feel that there is a level of equivalence between those markets as to how they assess product quality?

No [laughs] Umm / I don't think it ever has been known. It would be nice to have equivalents within the E.U. alone wouldn't it? I mean that's one of the biggest problems in Europe is you've got / well now only 27 member states, but you know, you've got almost as / well you've probably got more than that many interpretations because you've got places like Germany that have, with their federal system, have very different / they can't even meet / agree amongst themselves in Germany, their different they all have their own regulators, so no, unfortunately, it's not a level playing field at all umm / I think some uhh / certainly at least in Europe we try and strive for some harmonisation, don't succeed too often, but at least we are trying. 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, so I think my experience of what I've seen in India is, certainly the big multi-nationals, or the larger generic companies who want to supply to the U.S. and the E.U., by and large, take their cue from the regulations in those areas rather than their local national Indian requirements, for instance, because they will be far more stringent and far more effectively umm inspected and enforced, both in terms of the

review of the marketing authorisation applications and in terms of GMP's. I'm pretty certain if you talk to an Indian company they would say that they get far more / or 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. And I think the similar probably applies / the same applies in China, although I think the Chinese are genuinely trying to up their game and become international players. The Japanese are an odd one, in that Japan is still, as a culture, obsessed by appearance of things, that includes medicines, as opposed to the actuality of how they are made. I remember auditing about 10 years ago now and more an API facility in Japan <redacted> and it was you know beautiful, it was spotless, but some of their validation activities were just ludicrous [laughs] They'd validated their stability chambers by monitoring them for an hour [laughs] you know and had got, you know, that was perfectly acceptable, you know, so no, I'm afraid there are differences.

Are you referring to the tablets have to be round and white etc?

Oh absolutely, yes, everything has to be perfect, yes, it has to look perfect, so yes, yes, the Japanese are odd in that respect, but even again the facility, you know, as I say it was spotlessly clean, very well maintained, but some of the health and safety things they were allowing would never be allowed in Europe. I mean they were dealing with a high potency product and umm it got to the point where myself and my fellow auditor we refused to go in one manufacturing facility because we just didn't think it was safe [laughs] not because you know / it was to protect the product from us, it was protect us from the product.

Do you feel these international / or some of the international players are being proactive on regards to quality or is it more a case of the agencies policing them in to a quality state?

I think fortunately it is by and large being policed in to a quality state, umm, you know, in a lot of cases, in places like India and China, the police are also big pharmaceutical customers, you know, the big players, both in terms of branded medicines and the big generics players, they realise they have to make / you know meet the requirements in their market areas, for E.U. and the FDA, so they police their own suppliers, obviously not as well as perhaps they should do in some cases. We all still read about some of the horror stories that FDA find.

We get chapter and verse more on the FDA findings overseas than we ever do out of the Europeans. We get little bit of snippets of information, if they issue a notice, a non-compliance in Europe, but we don't get the detail that you get with the same / if you can read an FDA warning letter.

If I tell you that last year, and given it's Covid at the moment and it was last year, when the FDA scaled back hugely their overseas inspections, well pretty much stopped them anyway there was a huge increase in umm imported medicines being withdrawn from the market because of defective of quality issues. Are you surprised by that?

No, not at all. No. Sadly. I mean I think ICH over the last five years have been morphing in to a much more international body other than you know / for 25 years it was just the Americans, the Japanese and the Europeans, and now they've added, you know, places like China, Taiwan, Brazil, South Korea and a whole host of you know new members and they are genuinely trying to promote global standards, but again that's only half the battle, it's all very well having the standards, but unless they are enforced, it's kind of you know meaningless exercise, you can have / just like in a company, you could have the best in the world, but if nobody's following them it hasn't actually translated to reality on the ground.

So the agencies have a key role in this, either policing, or from a being proactive and engaging with industry, but do you feel that the people on the ground who do inspections, review dossiers etc, that those people/agencies are meritocracies or autocracies? Are the right people doing the right jobs?

Ooh / and again I think it's very much a mixed bag umm even within Europe you can see / I mean I think agencies like the MHRA, the Swedish agencies, some of the agencies are very good, umm, and do have the right people. Others less so and again there's a mixed bag. Obviously PICS has been for nearly 40 years trying to harmonise standards amongst inspectorates, amongst their members and, again, they have been expanding in the last you know several years, so it's very hard to drive standards, umm, FDA, I would have said, have made good strides in the last decade, but again, umm, it's again a very much a mixed bag, particularly when you get an agency the size of the FDA, with thousands of investigators, you're bound to get variations. They've got projects ongoing like the <redacted> is trying to harmonise standards and you know give each of their investigators a template to follow for particular dosage forms, which might help, but I always worry about checklists is that people turn off their brain and just follow the checklist.

[laughs]

So from the agency perspective then, and accepting inherent variability and assuming you don't see an east west difference, is it more a case of a more scatter-gun approach from what you've said previously?

I think so, yes. I mean / I think 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, that they were coming to learn, whereas now they are known as one of the tougher agencies, you know, you're going to get an inspection so you know it's going to be a pretty tough affair. So you know people are / there's always this, you know, the nationalist approach, obviously clearly agencies would much rather you made the product in their jurisdiction than import it, because it provides local jobs.

Are you saying there's a political/economic consideration here?

Oh there always is, I mean, look at the retesting on importation in the E.U. I mean that's / you know in some instances it might be partially justified, but we all know that testing a tiny little sample on importation really doesn't tell you much about the quality coming in. It / that's purely a trade barrier and of course its been demonstrated amply by the Brexit, you know, now you have to test products coming from the UK whereas the last 40 years you haven't you know, there's no science in that, that's purely political. So there is a lot of politics still and you know all of the agencies of course are agencies of national governments and so they are you know / he who pays the piper calls the tune.

You are talking about national agencies, when industry write a submission for North America, i.e. for a tablet with Mannitol, and we'll put Mannitol NF, BP USP JP, we put all the grades, and for the most part those grades are equivalent. There are a few minor differences. Do you feel that nationalistic monographs are not helping either? Would a single quality be more acceptable?

Yes, I mean I think the biggest problem with pharma harmonisation is USP because they are a law unto themselves, literally, umm, you know, it's a convention in the States. They are not part of FDA at all umm they are not really a government agency, they are a bit like NSF, they are a not-for-profit umm group who will certainly try and make profits in my experience [laughs] So yes, I think umm / I would say that / because / I mean you've only got to look at ICH Q4 and it / you know / it took them something like seven or eight years to harmonise the monograph for sulphated ash or loss on drying, I mean [laughs] it's just nonsense and so, yes, definitely there's protectionism there.

So if you had to pick a single approach, ICH have tried, PICS tried, if you had to pick ICH or PICS which would you pick?

Oh. As an approach, there's pros and cons. PICS is at least the inspectors trying to harmonise themselves but it doesn't of course involve the industry.

The unique thing about ICH is it's a forum where industry and the regulators participate, at least at the start of the process, on an equal footing and so it is the only formal forum where industry and the regulators get together to work on guidance, so for that reason alone, I think ICH has to be you know the primary one. PICS has the advantage of trying to raise standards amongst the regulators and because they don't involve anybody else, they can be presumably more honest in their meetings and uhh / and so / I think you know there's a place for each. I think you know if you look at the PICS website their aide memoires are really good but you know they are aide memoires for inspectors, so umm / some good guidance there. The PICS GMP is almost identical to the European GMP, although it is now diverging with ATMP's, so I think there's a place for both. There's another organisation as well that is ICMRA, which is the / I can't remember what it stands / International Coalition / it's the heads of medicines agencies from around the world.

I can't remember exactly what the acronym stands for. Yes. Again they can take more strategic decisions for the agencies because you're generally involving the heads of the agencies, whereas obviously PICS, typically, is just at the inspector level, maybe the senior inspector, but you know, it / so, yes, I think all of these actions / I think the good thing is, over the last 20 years, all of those / well ICMRA is new, they've only been around about 10 years, or less, PICS and umm ICH have tried to expand in terms of their coverage and the number of members they have so, again, I think that's all good. I think ICH / the problem is going to come in ICH as they gain more members is how they set up the expert working groups, as you know, you're trying to write a global SOP is difficult enough, and you're trying to write an international standard and then you've got 40 people in the room, it's not going to work.

So would take a long time in your opinion?

Yes, exactly [laughs] so how they get around that you know is something that is going to challenge them in the next / over the next few years.

With your EU QP experience, if you were given two products to release and you had, for argument's sake, Lansoprazole, that is manufactured by a domestic company, or Lansoprazole manufactured by an international generic company. Would you spend more time reviewing one or the other? Would you have a gut confidence in the supply chain for one over the other?

I was lucky, in my time as a QP, I was working for one of the branded companies, and only had to release our products, which even though they might have been made elsewhere in the world, I knew they were at least following the same corporate standards. Umm / it's a difficult one because I hate to generalise too much, you know, there's good sites in the East and in the West and there's bad sites in the East and in the West and my father, 30 odd years ago now, was an MHRA inspector, one of the first inspectors, worked with <redacted> and he said some of the worst sites he ever saw were in America, so you know, and I've heard similar tales since. Now we all think the FDA is you know all singing, all dancing, but again, they / there's good and bad wherever you are and so I don't think you can generalise on geographical grounds. I would be worried about more so an Indian company, or even an Eastern European company, that had never really gone outside their national borders. I think they are the ones that are particularly vulnerable. I think once they become multi-national they get the extra pressures put on them by both their customers and by the whole range of regulatory authorities, that they pretty much have to knuckle down and umm you know get

with the programme, whereas if you know some of the enforcement, even in places like Eastern Europe, their national agencies are not that good at enforcement because, again, there's always that other pressure that government agencies and the governments want to keep down the cost of medicines.

Well that's an interesting point you raise there, so what do you think are the biggest drivers then for harmonising quality? To give you a statistic behind this, in the previous two years, in the United States, 600 million dollars worth of product was destroyed.

Yes. And I'm not surprised and you know we all know drug shortages have been a problem around the world and you know that's not new. Did you see the <redacted> study that they did in the U.S., as to causes of shortages? It was a study commissioned by the FDA umm / umm / bring up some of the things that they umm came up with. They / umm / were asked by the FDA to look at what they thought was the drivers for drug shortages and it's obviously just domestic with the FDA, and they came out with some interesting factors that I wouldn't have thought of and it was an / you know a different take as / because they saw it from the outside of the industry looking in, whereas I've been you know an insider for 45 years now, so umm clearly my vision is umm / umm / I won't say tainted, but umm, my perspective.

Do you mean an unconscious bias?

Yes. That's it. Yes, my perspective is shaped by my experience which is umm / so / I'm just looking / oh come on / I've got too many things open in my computer and it goes on a go-slow, ahh, I'm out of memory! A bit like me [laughs]

[laughs] Yes. Umm / ahh / it's just thinking about opening a Word document, it's / right / drug shortages / right, so they have listed the top 10 quality system / they were asked to look at what would give you confidence in that they had a mature quality system in place, so they were looking at markers for a mature quality system and this is what they came up with. Optimised set up and cleaning procedures are documented as best practice and rolled out throughout the plant. A large percentage of equipment on the shop floor is currently under statistical process control, which is something that our industry is useless at, every other processing industry has done it for decades.

You know <redacted> is spinning in his grave I'm sure. Umm / the firm has standardised tools to get a deeper understanding of the influencing factors for problems in conducting root cause investigation, so no surprise there. Goals and objectives of the manufacturing unit are closely linked and consistent with corporate objectives and the site has a clear focus, so that's the balance between you know just get it out the door and lets make lots of money.

Manufacturers have joint improvement programmes with suppliers to increase performance. All potential bottle-neck machines are identified and supplied with additional spare parts. For product and process transfers between units or sites standardised procedures exist, umm, charts showing the current performance data, such as the current scrap rate and current up times, are posted on the shop floor and visible to everybody. The firm regularly surveys customer requirements and the firm ranks its suppliers and conducts supplier qualification audits. So some of that is already in GMP.

Do you mean some of its QBD QRM?

Yes, exactly.

The FDA looked at this in / uhh at the end of 2019, they set up a task force, umm, and they've proposed umm creating a shared understanding of the impact of product shortages on patients, which makes sense. Developing a rating system to incentivise drug manufacturers to invest in quality management, so I guess that's / it's a bit like hotels isn't it, you know, you want to / they want manufacturers to be you know / to be / literally have a star system and

then promote sustainable private sector contracts with payers purchase and group purchasing organisations to ensure that there is a reliable supply of important / and one of the things that's interesting / have you heard of an organisation called / I think it's called CIVICA?

Please elaborate?

It's umm <redacted> who used to be the global head of quality at Amgen.

Umm retired from Amgen and has set this up and he started off just as a purchasing organisation and they set it up as a not-for-profit body, so they started off just buying contract manufactured drugs, that were in short supply, and selling them at cost, you know, and now they are building their own manufacturing facilities in the U.S. to make generic drugs umm that are you know key generic drugs that basically / and sell them at cost and they are not aiming to make a profit, because you had that awful guy that got jailed for tax fraud or something, that bought up umm generic medicines, you know and increased the price by 4000%.

Yes I was aware of that.

And this was as you know / this is a direct response to tackle that sort of abuse of market power.

Now going down the route of changes then, you talked then about changes in supply and people taking a more altruistic approach to drug supply, given there have been so many initiatives in areas such as patient centric and value for money and the various managed health care schemes, particularly in the U.S., what do you think are the biggest drivers that could push a change in the pharmaceutical market, with regards to quality?

I think the FDA are on to something. I think it's because, as a consumer, these days, I have to take medication every day. I have no choice, no say, over what's prescribed to me, so that's one thing, and secondly you know the incentive on the health service in the UK is to buy a cheap as possible. There is no real incentive, other than the regulators inspecting them for non-compliance with rules, for companies to invest in quality. Now the enlightened ones understand that if you drive down your umm you know costs of failure, you'll be driving up your bottom line, but not many companies see it that way, particularly in the generic, because they don't have the margins that the umm the big boys have and that's the other problem, you know, the branded products can sell it / can pretty much / well certainly in America, they can name their own price, less so in Europe with bodies like NICE, you know, deciding whether it is good value for money. But there is nothing / there's no real driver on the industry, other than, the threat of being closed down for non-compliance, to really invest in quality. You're reliant on umm enlightened management understanding the benefits of getting quality right, versus, oh lets just get it out the door as cheaply as possible.

So on that internal element within a company, would you agree with the premise that the bottom line is the cost to the company, if they are manufacturing products, sub-standard product, which they can't sell, or they lose because it's not approvable in some shape or form, the demonstration of a financial gain or at least no financial loss, would be a driver for the companies to do that?

Yes and again it's something we / you know a bit like the statistical process control, umm, as an industry we have not really embraced understanding the costs of quality, very very few companies I come across have any idea of their quality costing, whereas if you are going to somebody making nuts and bolts, widgets, you know, which the margins are very low on, they have to understand the cost of quality because otherwise they'll go out of business, and so by and large the industry benefits from having large margins, but it also induces some poor habits, shall we say.

Therefore if I was trying to propose a new process, or a closer interaction between agency and industry, to actually demonstrate a financial benefit to the industry, to some players anyway, would there be a benefit to do that?

Yes, I think so, I mean, let's face it, at the top of most companies, the most / the thing they talk about most is share price and umm you know umm what the profit margin is, and so you've got to help senior management understand the impact of poor quality, if you like, on both of those things.

So do you think that a financial benefit would help some companies understand that cost of quality?

I think so. I think it / I think it's a real weakness in our industry is that they have very little understanding of the costs of quality. They see obviously the obvious cost of labs doing testing and you know QA people umm being employed to do quality stuff, but what they don't see, and what's generally hidden, is the costs of poor quality, the costs of deviation investigations, the costs of umm / you know umm failures, you know, because often it's cheaper to throw it away and start again then bother with it.

Umm so yes, I think, you know, the lack of understanding of quality costing, and some of the statistical process control tools and techniques, which can help you spot issues before they become failures. Again we just don't do it. I mean I've taught Math and Stats to trainee QP's the last 15 years and it / it's hardly any more prevalent in the industry for people actually before they come on the course to be using these tools and techniques, than afterwards, and again, you know, it's not rocket / given the amount of investment it would take to equip a few people with a decent statistical software control package / and implement it, it's peanuts, compared to what they spend on a load of / on marketing, for instance [laughs]

So what you're saying then comes back to a process understanding?

Absolutely, I mean / yes, I mean you've only got to look at what is currently imposing a huge cost on the industry and that is the Nitrosamine risk assessments. I mean that's due to a quality system failure to understand your API supply chain and you know we've outsourced all of that for generic medicines to places like India and China and not only outsource the actual production, but by and large, outsource the controls and really you know the old adage, you can outsource tasks, but you can't outsource responsibilities.

And, of course, now everybody's having to do a risk assessment to / to just check that there isn't Nitrosamine's in their products and /

And that's a massive cost to do that. But, again, it's a failure of management of your supply chain because I bet you now, well, I can tell you for a fact, in many of the companies making the products, they have little or no understanding of the process for manufacturing the API's they are purchasing.

Do you think there's enough transparency in the industry, between industry and regulators?

That's an interesting one. I mean / I think it has got slightly better in the last 20 years. If I go back to the late 90's when / just after the generic drugs scandal in the U.S., we were told very much in quality, you know, don't tell the FDA anything, unless they absolutely specifically ask for it, umm, and we never quite got to those levels in Europe, but again, there is still a tendency not to share everything, shall we say, with the regulators. I mean I know companies who umm try to almost implement things like semi-continual manufacturing and PAT by the back door, because they were so afraid of what the regulators would make of it and certainly when we were you know / I was in ICH discussing Q8, Q9 and Q10, industry's feedback to

the regulators that you are one of the biggest blocks to continual improvement because, you know, once we've registered our product, it's fixed, we can't change it, costs us a small fortune to make Type II variations or whatever, so you know, the process on the day you first file it is the process that you use for the next 30 years possibly which completely goes against other manufacturing industries.

That try and do a continual improvement.

What about full disclosure audits, do they exist?

No, I mean, no, no, I mean I used to be told, when I was you know Head of Quality and by you know the powers that be, because I worked in an American company, so the culture was very much American, that during an audit you answer the questions you're asked and you don't volunteer anything.

In some companies, in my experience, it's almost visceral gut reaction, you want to talk to the FDA, it's the absolute process of last resort, everything else first before you even talk to them. Even if it's just a briefing to bring them up to date of where you are with products, is that helpful?

I think, you know, some of the quality by design stuff has helped because that had to have a dialogue between the industry and the regulators to get it through, but again its never really taken off because that dialogue occurred between the major players in terms of industry and the regulators, but if you're talking about you know trying to talk to the Indian authorities, or the authorities in Colombia about some quality by design process and you submit it, they probably wouldn't understand what the submission meant and so that's always been a blocker on it, this / you know that lack of international harmonisation.

So that comes back to one of my first questions regarding expertise and autocracy and meritocracy?

Yes, exactly, yes.

So can you link that to the scatter of quality issues?

No, I mean, that is 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 and so it allowed that to happen. Unfortunately umm about 40% of their expertise left when the MHRA left [laughs] so that you know that is one of the strengths of the European system, whereas I say, if you go to you know other parts of the world, you know, I mean lets face it, how many experts in you know in quality by design does Malta or Slovakia probably have, very few, but they don't need to, because those products in Europe go through the centralised route. It's not the case elsewhere.

We've been talking mutual recognitions then. Do you feel that's something that's still going to help, or do you think they will be over run by nationalist interests and politics basically?

I think its got to help and its got to continue. ICH is probably the best forum for that, although you've got ICMA and others umm around the world, but it's always balanced by product / by politics, because those involve the regulatory authorities who are themselves agencies of various Governments, and so what they can and can't do / ultimately the MRA's are Government to Government negotiations and as we have seen [laughs] very recently with the Brexit negotiations, you know, politics / somebody told me very early on, when I was

getting involved in these international negotiations, you've got to remember politics always trumps pragmatism. [laughs] And it's true.

I don't think, you know / it's almost like asking you to overcome human nature isn't it, it's you know / you can't. All you can do though is not give up and keep trying to chip away.

We've talked a lot about sort of pharmaceuticals of the products and the quality from that perspective. Just want to talk very briefly at the end here about efficacy, particularly with regards to generics development. Now there are very clear guidance's on how to get a generic approval compared to a referenced product. In your experience have you had much experience with that and do you feel about it?

No, I've never worked for a generic company. I've always worked on the branded side of products, so my experience with new products is new products we've developed coming to market. I've no experience of trying to bring umm to market.

Oh / within companies, sometimes politics, but I certainly can tell you as a practicing QP and I still teach this to trainee QP's today, say look you've always got to look at two things, you've got to look at the impact on the patient and you've got to look at the impact on compliance and I always look to them in that order.

It was always the patient impact first and that's why I think the stupidity sometimes of rejecting perfectly good batches because they is some non-compliance you know / and again I think we've probably gone backwards on that over the last 20 to 30 years. I think QA and QP probably had more leeway. There was less emphasis on compliance on the regulators back in the 80's than there was you know / certainly through the 90's and the 2000's, we got very much in to a compliance driven mentality. The idea behind QBD and the science and risk based approach was trying to turn that back to being, look, it's about patients, and it doesn't help the patients throwing away perfectly good medicines.

So do you think there's enough support for QP's to actually make this decision?

Do you feel there's enough support for QP's to make these difficult decisions, bearing they sit within a company?

I mean, on a day-to-day basis, it is down entirely to the company. I mean ultimately, as you say, they can vote with their feet, they could shop the company to the regulatory authorities and / but again what I see is the regulatory authorities around Europe, the support they give to the QP's is very variable, umm, the UK is not the worst, by any means, umm, the MHRA certainly / they certainly pick on QP's first if there's something wrong, umm, and so it's very much I've helped a QP who actually left the company and the MHRA went in six months later and gave them critical findings and wrote to all of the current and former QP's and this QP basically turned around and said well that's why I left, the MHRA turned around and then said well you should have told us then.

But equally we've been asked as a company to do some basic / I mean basic one day of basic training in critical factors for biotech to a group of QP's who have only ever experienced / or solid dose and who are releasing biotech products that were imported in to an E.U. country and the regulators had allowed them to put that on the licence. Now the MHRA would have challenged that.

This was another European country and it had never been challenged and I was appalled. I mean I think those people needed their / you know a six month course on the critical factors for biotech and not a sort of seven hours.

What is your role in the industry and how it's evolved from when you first started to where you are now?

Okay, I mean, currently now I'm consulting, umm, in the interests of candour, I don't know many other consultants, the pharmaceutical industry, but I also consultant in to the tobacco industry, but not in terms of cigarettes, cigars etc., more in safety profiling their electronic devices. So the niche area I operate under is what's known as extractables and leachables, which is basically where we are evaluating the materials that comprise for instance a container closure system for a pharmaceutical product or umm an electronic nicotine delivery system, e-cigarette, for instance, just to make sure that these materials don't leach harmful substances in to what's delivered to either the patient or the consumer, depending upon which industry we're talking about, umm, how I've evolved through the 35 plus years I've been in industry, which is a terrifying thought, I started in the mid 80s before the days of regulations such as COSHH for instance. It was a GLP QC laboratory in Dagenham in Essex <redacted>, I was a QC Technician and I think since then there has been obviously an increasing emphasis on the control of the quality of product that's being delivered to patients. I think from my perspective it's a rather unfortunate issue that Europe, the U.S. and other territories, have different views on how this control should be carried out. Now obviously we have ICH in place which helps to harmonise many of the regulations, but there are still areas where there are differences and my area, extractables and leachables, is a class example where the U.S. is very much more conservative than the E.U. which has a much more, for want of a better expression, a much more pragmatic approach to the subject. The U.S. it's very much a case of you have to test almost for testing's sake, whereas in the E.U. it's much more a case of a risk-based approach. A well constructed scientifically robust risk assessment will often be taken as a justification for no further testing, if that's what the risk assessment tells you, whereas the U.S., you can still provide that information but I hesitate to use the term, tick box exercise, but it sometimes feels like that with the U.S. and whether that's because there's lack of understanding of the subject, or whether it's the litigious nature of the U.S., whereby they're just not willing to take any chances, I think that's / for me the biggest problem at the moment is this, are these differences between the different territories and the good news, in terms of ENL, is that there is an ICH initiative under the Impurities Q3 group of guidelines, whether that comes on board within the next five years, we will see. I hope that makes sense?

Throughout your career, have you predominantly been product development or commercial products or how would you break that down as a split?

My early career, I'm talking here about the first five or so years, was very much production, quality control, but my experiences in the pharma industry for the last 20 years, have been very much in development, not so much early age, but more I would say umm / just prior to Phase I up to post-approval.

Ethicals or generics or an equal split or other?

Uhh I would say the majority of that would be in new products.

What about dealing with third party manufacturers, either domestic or overseas, have you much involvement with that?

Umm I've had some involvement, both in my time in my previous role at <REDACTED>, which was an ENL role, and actually, take a step back here, when you say manufacturers, are you talking about contract laboratories, in general?

Have you partnered larger supply chain.

Okay, yes, so yes, I / I've been out-sourcing work for well over 15 years now. It was one of my main roles at <redacted> in the extractables and leachables group. Because we had a small group but a huge portfolio of products to cover and to support, there was physically not enough people within the team to do the practical work, so I would say 90% of our testing was out-sourced, so that would have been both extractables testing, which is the / which is forced / what's a good way of describing it / taking a material and cooking it up to extract as much out of it as you can, that's a very specialist role. There are not many laboratories that do it very well and so there was a very limited number of laboratories that we used to work with and indeed I still work with. There are only probably two or three that I really trust.

Can you expand?

Leachables testing is much more stability testing, in which case, you're talking about developing a method to the ICH guidelines, sorry, validate / developing and validating a method to the ICH guidelines and operating it in a very similar manner to a conventional stability protocol, so there's many more laboratories who can actually achieve that. The / I would say the bottle neck there, that's probably not the right term to use, but we'll use it anyway, would be on their ability to conduct trace analysis effectively because many of the products we're talking about now will be aqueous-based and so there's a lot less affinity for organic molecules to leach out of rubber stoppers, plastic washers, whatever in to an aqueous phase, so anything that does will only ever be present at trace levels, so in that case then, there / you are talking there about much more specialised equipment and specialised operators, experienced operators. Whilst there are more of them than for the previous case, there are still a limited cohort, for want of a better term. Fortunately, because I've been doing this for 15 years, I know who can do it, and who can't do it. But having said that, sorry, just to expand a little bit further, these laboratories have a high turnover of staff and that's the biggest challenge we have because with that turnover of staff you can have a method that's been working absolutely brilliantly for 12 months and the guys who have been operating that method suddenly move on and then that CRO has a challenge to bring their new staff up to speed, if it's a challenging method.

So, again, I hope that makes some sort of logical sense?

Talking about these CMO's, so where you've dealt with third parties, and you said there's a few, only a few, particularly in the E&L world that will do what you want them to do and do it properly, do you see differential between domestic and international CMO's and if you do do you treat them differently?

Umm of those that can do the extractables testing umm effectively, the only discriminator I would say at the moment is price. That's not quite true. There is a party in mainland Europe, in the E.U., and there's a party in Northern England, and these are probably the two best at the job at the moment. I would say anyway. The parity in the UK, the organisation in the UK, umm, is more / is cheaper, is more cost-effective, but they do a good job. The laboratory in the E.U., they are based in Belgium, they've been doing it for a bit longer than the English company, so they have a database, a larger database, of molecules that could potentially be leached out of plastics, rubbers, whatever and the reason that's important is because when you cook up one of these materials you're going to get a sea of peaks in a chromatogram and you need good quality mass spectral data or more correctly a good quality mass spectral database to search against so that you can identify each of those peaks and because the company in the E.U. has been doing it for a little longer, they charge more.

Yes.

In terms of their quality perspective there isn't a huge amount of difference. The laboratory in the E.U. has a GMP licence. It can also operate under GLP, it has both licences. The

laboratory in the UK has a GLP licence at the moment, is seeking to get GMP status in the next six months.

So that's a very niche role. What about more general analytical testing?

More general analytical? Umm /

The differential there between domestic and international?

I think it's an interesting question. I would say, in my experience anyway, there's / it's a mixed bag, and I know you don't really want to hear that, I'm sorry.

But / I've had a lot of experience now working with a couple of organisations in the Republic of Ireland and they are very very strict with their quality, with their QMS, or the implementation of their QMS. They are not very flexible at all and this goes back to my days at <redacted> and I'm still experiencing it now, and the theory we came up with was that during the Celtic Tiger years, a lot of ex-pat Irish people graduates who had gone to the States to seek experience, had if you like matured within the pharmaceutical industry, under the FDA, and have come back with this very conservative approach to how regulations are implemented. Within the UK and mainland Europe we find again it comes back to this term pragmatic. They seem to be much more pragmatic in the way they apply the regulations and I'm not talking here about being loose, I'm talking about working with their clients to solve problems, rather than letting the QMS tail wag the rest of the dog so to speak. That's the only / I've found the most issues with in that respect.

Okay, thank you, that's great. Lets move on slightly to the wider regulation now and the product approval process and the MAA approval process. Do you believe the current process works as much as it ensures a safe and efficacious product for everything we take in this country?

If I'm being honest with you, I've only had experience with a limited number of MAA's, probably half a dozen and either the rapporteur or the co-rapporteur in Europe has always been one of the big four or five if you like, so there's always been a member of MHRA in there, there's always been a member of the French regulators, German regulators, uhh / experience with Sweden, and those submissions umm / what I've seen of those submissions have been quite robust. I've not had any experience with any of the, if you like, it's not meant to sound pejorative, but some of the if you like the more minor regulatory agencies across Europe, I've not had enough experience to say what the quality of their review process is. In terms of Phase I I've found Spain to be quite challenging, not lacks at all, actually quite umm a little bit over-bearing shall we say in some of their questions, but apart from that, I'm sorry, I can't really go any further.

Do you have any experience of anything further afield, China, Far East, Australia, India?

Only really what I keep up-to-date with in the literature and the concerns around some of the issues that have arisen in India and China for instance.

So that's third-hand information rather than primary experience?

Yes, it's not experience.

So do you feel / your gut feeling for the current regulatory process we have in this country in Europe and the West, is that really for the common good or do you think it is too prescriptive?

Oh wow! [laughs] Umm /

Do you think it's a good process or do you think it's a stop-gap measure rather than actually a final finished polished process?

I think the way it works at the moment is probably as good as it can be at the moment. I have some concerns or what's happening in the UK post-Brexit in terms of the ability for the MHRA to cope with the amount of work they're going to have to do going forward, because they won't be able to rely on their European partners any more. If anything I think in some places it's probably a little bit over-the-top.
For want of a better expression.

Regards the European Agencies, (including MHRA) and North America, would you describe these agencies as either a meritocracy or an autocracy?

Umm / you'll have to define those for me <REDACTED>

Okay, meritocracy is the people who are involved in the review and approvals for the MAA for example are the absolutely best person to do that job based upon their experience and their background, or are they people that have been, for lack of a better word, 'promoted out of trouble' and put into positions that they can't necessarily have the experiences or the expertise to fulfil? Are the right people in the right job at the right time?

I think there has to be / I think there's undoubtedly / my experiences is that there have undoubtedly been people in the latter group /

For the autocracy?

Yes. Yes. That really shouldn't be reviewing documents because they don't have / they might be experienced in parts of the process, but they are reviewing parts of the process that they shouldn't be.

A jack-of-all-trades, master of none, in some regards?

Yes.

Okay. So just talking about feelings and perceptions now, if I gave you two products, Omeprazole and I gave you Omeprazole manufactured in the UK or Western Europe, or Omeprazole manufactured in another market, which one would you take?

I'd prefer the European one.

Why?

Primarily because I would have / I would / I would expect that the regulatory rigour that that product has been through would be / what's the word I'm looking for / more effective, more / more rigorous, I've used that word twice in this string, sorry / umm /

Are saying you believe more in the European process as opposed to the non-European process, to ensure safety? Can you clarify?

Yes.

Would you assume, because they are the same product, effectively, that they were equivalent efficacy?

Umm / I suppose gut feeling would be I'd have doubts.

And what drives those doubts?

Again it's umm / it's / you mentioned the term earlier of third party information, it's the stories and the whispers throughout the industry about the issues, particularly in India and China, about whether it's a counterfeited product, or an inferior product, umm, and umm certainly some of the documentation I've reviewed for some of my clients, for instance, there are holes in the quality documentation that they provide. They claim food standard grade material when it should be pharma grade material. Why are they not using the correct grade of / they are not using pharma grade excipients? for instance, just as an example, so that / with that sort of hole in the process, umm, is there something else that's not quite under control, umm, has the tablet been manufactured properly, is the bio availability / these are not the sorts of thoughts that are going through my head when I'm looking at these two tablets of course, but if you dig down deep, and you think to yourself well what could be wrong with this, these are the sorts of questions that would come to mind. <redacted>

Okay, thank you. So your background is analytical chemistry, involved in method development, product testing, looking after contract laboratories who have been doing analysis for you. Is your perception and your views of the industry changed throughout your career or has it remained pretty constant throughout?

Umm / I'm proud to work in the pharmaceutical industry. I think we provide a positive benefit to people, umm, I think undoubtedly / well as I've matured, as I've become aware of the wider industry, umm, I am concerned about some of the practices. You've just mentioned China umm certainly there is a problem in the U.S. with certain smaller pharmaceutical companies. I think much of the opioid crisis in the U.S. is driven by you know unscrupulous characters in the industry umm / I think the larger multi-nationals for the most part operate in a reasonably ethical manner. Again there have been problems in the past. Those have been highlighted in the press, certainly with regards to payments to GP / well not GP's, to doctors in the U.S. again, but I think the industry is trying to cut down on those sorts of practices, but again, umm, I come back to my initial point, for the most part I'm proud of my industry and you've only got to look at the effort that's been made in the last 12 months over the development of the three vaccines that are now approved in the UK, uhh, which is an unheralded / it's an unparalleled umm achievement by the industry. So umm / has my opinion changed? I think only in my appreciation for umm both the good and the bad side of the industry, but that's just really important just because I've got older and I've got more experience and I've been uhh exposed to the.

Exposure to the wider industry rather than local?

Yes, absolutely, yes.

Thank you. So you mentioned earlier that some of your views have been swayed by things you've read and sort of the background noise from the industry and from the regulations. Do you feel that the industry is doing enough from the industry side to ensure quality for the products that we either use or we import, or should the agencies be doing more, for lack of a better word, policing of the systems?

Uhh / that's a good question. Umm / I think it is incumbent on the agencies to keep an eye certainly on umm API manufacture which has been shipped abroad a lot in the last 10, 20 years, to / again to India and China and some of those decisions have come back to bite umm some of the umm some of the decision makers, shall we say, quite severely, umm, now whether that's just down to uhh poor practices in these countries, that's what the regulatory authorities need to police. However, I still think it's also part of pharma industry's due diligence to ensure that its suppliers meet certain standards. I certainly don't think it's all down to the regulatory agencies. The internal policing systems in my opinion should almost be tighter than the regulatory agencies themselves, so that by the time it gets submitted to a regulatory agency, a file is / well there's no such thing as a perfect document, as we both know, but what I'm saying is anything that the regulatory agencies pick up should be serious enough to cause certainly safety concerns anyway. My experience of <redacted>, I don't know what yours was <redacted>., but I almost thought that our QA Department umm / they were stricter than the regulatory authorities. They were zealous in their applications of the regulations. Their auditing procedures were second-to-none and I certainly get the impression from colleagues from other companies within the industry that it's similar at <redacted>, whether that's true or not I'm relying on third-party information again, umm, but that / there is a / there's a role to play by the regulators and by industry.

And what do you think that sort of over-zealous or that zealous approach is driven by? Is that driven by a fear of censure from the agency, or is it driven by a quality first approach?

I would love to say it was the latter <redacted>. but it's undoubtedly an element of the former in there as well.

So does that comes back to policing by an agency and maybe the autocratic approach to policing by an agency, influencing the decision?

Yes.

In the industry, looking at the wider regulations, what could change to make it better?

Ooh umm / I certainly think umm a more harmonised approach globally would be helpful, certainly within the major uhh territories, so the obvious case there is ICH, umm, certainly umm expanding ICH to further areas and I mean obviously that / there are a lot of / I can't remember what they're called but third party countries that buy in to ICH and I think indeed the UK will be one of those going forward. For me that's / that would be the key and in that manner, sorry, that's not the right way to put it, in that way, a global approach to quality would then hopefully be able to police the India's or the rogue operators in India, in China, in other less salubrious countries, shall we say, the policing would be more effective because it could almost be shared.

So is that a role for industry or for regulators?

Again, it's both. The regulatory agencies have got to recognise the best parts of how other agencies do things. You've very much got the not invented here approach in America and indeed, just as an example, when the ICH initiative on extractables and leachables was announced, there were three or four comments that came back within 24 hours from key players in the U.S. who just basically turned around and said, we've already got USP guidance, why do we need ICH?

And that's disappointing. There are other words we could use of course but / recognising the best parts of each other's ways of doing things is the key to making the industry more effective because we're not an industry devoted to regulation. We're an industry devoted to bringing medicines to patients and anything that can make that easier, i.e. 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.

So do you feel you could be part of that change? Can you help that change move forward?

Well I'm starting to feed in to the ICH process that I've already discussed on a number of occasions and other guidance's that I feel I should contribute to, I try to comment on via the usual channels and I would very much encourage anyone in a similar area to myself, well, not similar / in a similar situation to myself, in niche areas, where there is little understanding, apart from a few key individuals, that they do the same in their fields. For instance, yourself, anything that was uhh applied to microbiology, I almost know for a definite that you would be shouting from your soap box about how things you know should be done in your opinion, that's what I'm doing in my field, because if we allow these / if we allow, for instance, extractables and leachables ICH guidance document to be written by people who really don't know what they're talking about, it's not going to work is it.

Does it make any sort of /sense?

Do you feel empowered to support that change? Do you feel that your contribution is being considered appropriately?

Uhh well that's difficult.

Is it a process for process sake or is it something that actually is being reflective and responsive to the information its receiving?

Umm from / I can't speak personally but from feedback I've had from colleagues ICH umm is usually quite good at reviewing as many of the comments that come in about a guidance document as is possible. FDA can be a little less collaborative shall we say. USP aren't too bad, if I'm being honest. I remember making some comments on the heavy metal guidance from a few years back, the revision of 232 and 233, wow I can't believe I know those numbers off the top of my head [laughs] and again that was really driven by some of our experiences from ICH Q3D and changes were made, not necessarily based on my comment, but I was one of a number of people singing from the same hymn sheet, so that / when those changes were made ultimately that / I don't know about feeling empowered, but you think to yourself, well at least it was worth me chipping in and at least I helped with the band wagon so to speak.

You've mentioned USP a lot and / but then we have USP, we have NF, we have EP, BP, JP, so on and so on and so on. Do you think that nationalistic approach to pharma helps or hinders now because a lot of those monographs are exactly the same in many instances? In some there are subtle differences. Would there be a benefit in having a harmonised, like an ICH monograph?

I think that's an absolutely superb suggestion. I've been saying this for years. I mentioned starting off in a QC laboratory in 1985 in Dagenham running BP methods and one of the comments that was made back then [laughs] around some of the methods, shall we say, which can't really be repeated in polite company, still applies to some of them now <REDACTED> Some of them have been dragged into the 21st Century, and heavy metals is a classic example of that, which until you know not that long ago, relatively, they were still using lead precipitation experiments and its obviously now been put on to ICP instrumentation, but umm, a harmonised / would be under the ICH umbrella. A harmonised pharma across the world would be something really very very helpful I think. I can't see how anyone would argue against that, apart from the employees of the individual organisations because obviously that's / there would be a lot of people impacted by that. But I think from the industry's perspective, at that point where you're starting to apply controls, what a wonderful idea, why don't you suggest it P.? [laughs]

The industry has over decades undergone organic change, sometimes there's been a bit of a step change where regulations have changed or there's been a major problem that's had to be resolved, but in your experience, what do you feel are the top three drivers for change in the industry? What drives change?

Umm / okay, I think undoubtedly one of the biggest is / I'm not sure how you would term this but it's when something happens, when something goes wrong.

So a responsive change?

A responsive change. A couple of examples umm there was no extractables and leachables industry in the early 90s and when someone found that <redacted> / the reason <redacted> wasn't working after a few puffs was that the rubber washers were degrading. Then somebody started thinking well where's all the plasticisers going, where's all the ingredients to keep the rubber going and of course it was going in to the drug and then going in to patients and when they started to investigate what those chemicals were, the sorts of things they found don't bear thinking about. That started a whole, I wouldn't say industry, that's a bit ridiculous, but it started a whole field of both quality regulations and analytical chemistry and certain areas of packaging are involved in this and the most recent example of that <redacted>. is the Nitrosamines issue, that's / I think that's / I think that's an example potentially of the regulators going somewhat over the top because I don't think they are thinking about the science in some of these issues. I attended a number of presentations, a

number of conferences and presentations on the topic and there is a lot of work going on in the industry, a lot of very very good work and a lot of its been headed by the UK. There's a couple of players in particular that are leading the field and they are taking very much a science-based approach to the problem. The regulators are taking a conservative safety first approach. Obviously it's going to be somewhere in the middle that's probably the most appropriate, but again, this wasn't an issue, until someone went looking for it.

Yes.

And now there's been various product recalls and in a couple of cases withdrawals.

So what about additional drivers for change? We've got responsive change to occurrences.

Responsive, umm, I think umm / technology improvements and I've already mentioned heavy metals a couple of times. The updates to the various guidance documents dealing with elemental impurities and what used to be termed heavy metals, much of that has been achievable because of the improvements in technology. When I started in 1985 the HPLC's we had in those days were 50 ml burettes and it was all / a UV detector was methyl red [laughs] changing colour.

It looked like a proper chemistry lab. So obviously a lot of instrumental step-changes in technology has allowed much of the analytical chemistry world, for instance, to move over in to instrumental analysis. Now there's good and bad behind that and that's a topic for another day. But responsive changes, technology changes, the third one, ooh umm / I'm struggling.

Being devil's advocate, you haven't mentioned cost. Do you think cost is a driver for the industry or not, or a driver for change anyway?

I think there's undoubtedly 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, whether that's a good thing or a bad thing, well that's a business decision for the company involved.

To turn that question slightly on its head, so you're talking about cost, so reduce cost, should a company, any company this is, give out the best possible product it can or should it develop a product which is fit-for-purpose and also being cost-effective?

I think, just to expand that further, I think in an ideal world, a company will develop a product that can be provided to patients as cheaply as possible and obviously that will involve the payback time, so if they can produce a fit-for-purpose product, that's efficacious, and safe, and then the health authorities involved can be delivered to patients without breaking that country's bank, that for me would be the ideal way of / the ideal scenario, so you're getting the best of both worlds and the pay back period there would be hopefully sufficient for the company to make money and reinvest.

Do you think there is an issue within the global pharmaceutical markets for equivalents of products, so generics versus originators products, third party manufacturers versus domestic manufacturers, countries versus you know countries you trust, or may not trust?

Yes. Umm / I think umm / my experience, for instance, in the inhaled industry, is that it's quite difficult to produce generics because the regulations of equivalents are quite hard to match, quite hard to achieve, sorry, that's probably the right way to put it. Now whether that's a good thing or a bad thing, again, that's for the regulators to decide, umm, it's / I mean, for instance, the best-selling asthma drug for a number of years was <redacted> and it's only recently that generic products have been approved in North America, in the U.S. and there's

two now, but umm / Advair has been on the market for years and its been on patent now for five or six years something like that, I can't remember, so it's surprising its taken so long.

Do you feel that is purely a technical challenge or is there a certain amount of, for lack of a better description, protectionist policies by companies?

There is undoubtedly an element of the latter and to be honest with you some of the development projects I worked on at <redacted> it was clear that the reason we were / I mean / just to expand further on this , there was the / <redacted> would have a mark / a product on the market and they would be looking for a product line extension and the product line extension would obviously be looking for some improvement over the original product but if they could add something unique to the product to make it harder to replicate, they would be / we could be encouraged to do that, but I mean that wasn't so much me, but it was the guys developing the line extension, so whether that would be a controlled release tablet, whether that would be a nasal spray in a <redacted> bottle, so obviously that bottle has its own unique spray pattern, so it's very much more difficult to reproduce, hence the generic would be harder to reproduce and similar with / it's very very prevalent in DPIs and DPIs, <redacted> nasal sprays in inhalation arena, not so easy to make a tablet, not easy to copy. Or an injectable for instance. But yes talking about parenterals, yes, putting them in to auto-injectors was another way of trying to make them harder to replicate.

Is there anything else in the industry or agencies that concerns you, that you think is something that these areas are falling over on?

Uhh well I mentioned it earlier on. I think umm / I think the industry itself could do more to police some of the practices in America, as I say, there are smaller family-run pharmaceutical companies over there with very protectionist policies and less than, in my opinion anyway, less than ethical practices, as I've already mentioned, I'm firmly of the belief that one of the drivers of the opioid epidemic in America is some of these companies and they are getting away with well / I won't say it in polite company, but some of their practices are dreadful and so I think it's / I think the industry itself / what the industry could do I'm not sure, I'm not involved in some of these industry bodies, but I can't help thinking that something could be done and umm that for me is one of the key points at the moment.

Subject 25936

Do you feel that our current regulatory framework is fit for purpose?

I think it depends in what context you are asking the question. So I think in the context of overarching safety of I'll call it an investigational product and when I mean safety I mean safety at all levels, so human safety, which is the ultimate arbitrator I guess, but the assessments that go in to figuring out what is considered to be safe. I think the Western regulators are pretty key on that. I actually think 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, so whilst I can completely understand why there will never be a global regulator, I do think that from an overarching safety point of view, I think the regulators do a very good job, because my understanding, when I think about it, is that the job of the regulators is to assume that you are there to harm their citizens and their job is to stand between you causing harm and them causing benefit, so their concern about safety is paramount. But there is something about the global interpretability of that.

On the basis then then that you feel that the Western approach is a very safety conscious, safety centric approach, do you feel international parity actually sits within the existing framework?

Well I think there should be. I think there should be because I mean if you / I think ethically there should be. I think / I believe strongly it's completely unethical to give a medicine to somebody in Sub-Saharan Africa who is desperate for medicine if the Western kind of traditional authorities have considered that the safety profile does not meet their requirements. So I think there is an ethical issue. But then it also comes down to an overarching benefit risk. So I think where that argument can be torn apart a little bit, just thinking about what I'm saying, is that safety is always a judgement ultimately between benefit and risk and in the Western countries they may have other optionality which affects that benefit risk proposition, which is not present in some of the developing countries, so I think / just thinking this through a little bit, umm / you do need to consider safety in the context of kind of what your country and what your citizens actually have access to I think as well, but there / it's that transcending between what ethically is right and then understanding the benefit risk proposition as it presents itself to the people in different parts of the world.

Do you feel there's a moral component within the industry or within regulators as to how they approach drug development and manufacture?

I think it has to lie with the regulators. I wouldn't trust industry.

Can you elaborate?

Because I think the industry / I think there are some very umm / ethical industry bodies and I think there are some who will look to cut corners wherever they can.

Do you believe this is driven by a quality first process?

I think it's a combination / it's almost like the push and the pull. In the ideal scenario it would be a constant push but I think there has to be an element of, if pull's not working, there has to be a push, so there has to be an element of policing if the by first intents not there. I think it's too important not to be.

Do you feel, in your experience, that agencies are equivalent or inequivalent in how they approach DP approvals?

I don't think they are equivalent. I don't think they are equivalent at all. But do you know I think the umm / the longstanding regulation authorities that have many many many decades of experience, like the European authorities, mostly European authorities, I mean if you look at MHRA, if you look at the FDA and I think sometimes the way even the agencies behave gives an indicator because of course many agencies will follow the lead of what is approved and decisions that are made, either by the major European regulator or by the FDA, so there are many agencies across the world that by first intent will become a surrogate to the FDA or to the EMA. I don't think it's that these countries can't do it, but I suppose it depends where their priorities are. I mean if you look at the agency in Japan, Japan is an interesting one isn't it, because very 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, as I think at some point it has been termed!, although that being said there are genetic differences in some ethnic groups, but you know, that's / it's probably a minority of / there's a minority of differences, rather than majority of differences, so I think it's probably a combination of some countries maybe don't want to invest the sort of rigour that the likes of the FDA and the EMA have got. Others are happy to play surrogate to those bigger authorities, yes, I'll leave my thoughts there.

Is there a country of nationalistic component to that?

I think, you know, the more you delve particularly in to / I'll start with China, China's a really complex situation because I mean the nature of what they want for approval in many instances becomes illogical and you've also got the backdrop of very entrenched beliefs in Chinese medicine. Now I'm not saying Chinese medicine is not efficacious, but so you've got a very different sort of playing field in terms of cultural acceptance, cultural norms of what people will and will not accept. The same can probably be held as true in parts of Sub-Saharan Africa in terms of what they believe, because we know are huge, so I think there is something there about cultural differences as well, but again that / in theory that is what the regulator should be able to overcome, but of course, China where it's controlled in a different way, it will never be either or, it's both and when you get in to Sub-Saharan Africa these infrastructures don't exist.

Do you feel the agencies, in your experience, are meritocratic or autocratic?

Explain a little bit more of what you mean, sorry /

Autocracy is a position where someone is put in to a position to review a dossier, or review some data, but doesn't necessarily have the skills to do that, but they have been promoted up through the system for years.

I think there probably is more of a meritocracy in the established agencies in my experience and probably more autocratic in some of the / like in China, although that being said, I mean, it depends / getting access to agencies and people who actually know what they're talking about in agencies, can sometimes be problematic and then you do need to get through the autocratic post box, and that in itself can be problematic. They all say X and therefore you can only do X and you can only be seen by X plus one, so it means / they are very rule-driven organisations. They are very top driven, even the / the FDA is a very top driven / a top down driven organisation. Yes.

What's your view of agencies being driven by science rather than guidelines? Do you feel that they are rule or regulation driven to the extent that it excludes the scientific challenge or scientific rigour?

I think they can be. I think they can be and I'll give you a specific example of why I say that, so I was involved in an FDA review of an NDA and we knew we had an impurity in the drug substance and it had gone through various qualifications. It was named / was it / I can't remember actually whether it was positive or negative, but the challenge with this impurity was the level of qualification that the FDA wanted us to go to. So / and it was an area of very active scientific debate and the FDA were outliers actually compared to other regulatory authorities in terms of accepting the lower limit quantification for / actually it was named as positive impurity / accepting the lower limit of quantification for this type of impurity and we were involved in multiple discussions with the FDA and the toxicology reviewer was there as well and the Head of Division who was at the time, it was clear that he was of the view that the data we had supported approval of the drug and / but he did always say to us, but I will have to be guided by the toxicology reviewer and lo and behold at the 12th hour we got a non-approvable letter in the U.S. and we got an approval in the / with the EMA. The EMA never once raised any issues about the qualification of this positive impurity because we had gone down to such a low level of quantification, but the FDA, in their view, was could try harder and we could get a lower level of quantification down even more and that's what this was all about. It wasn't even about absolute eradication of impurity which was at tiny tiny levels, so I think for me that is an example of where it was rules-based, not science-based and yes.

Do you feel that the scrutiny given to domestic products is the same as the scrutiny given to imported products?

I don't think I know enough to answer that question. sorry.

What about the role of the QP, do you feel that the role of the QP in Europe , does this support regulators?

Umm in my experience it's a bit of a non-role. Yes.

Can you elaborate?

I'm not sure what teeth its got. I'm not sure what / how it actually influences decisions, thinking about how we interacted at <redacted> and the role of the QP and umm / yes, I'm not / I / I mean it's a role that has to be there, but my experience / whether or not that was the way <redacted> operated or whether or not that is true for that role, but my experience was certainly at <redacted> it became a little bit like a non-role because / and it may be because of the other sorts of infrastructure that was round about groups like safety board, for example, which / I mean <redacted> safety board was all powerful, as you know.

Talking about supply chains then, if you were prescribed, Pantoprazole, and were given the choice of Pantoprazole manufactured domestically or Pantoprazole manufactured in Bangladesh, given your experience what would you choose?

[laughs] umm / if I was given the choice and there was no difference I would take the one from domestic supply.

Can you elaborate?

Yes, yes. I know. I was hedging my bets about being honest or not. Yes, so why? It's all about perception and you know / and I know what I just said is illogical, so I take statins and I don't care where the statins come from because I know the statins are manufactured according to the highest guidelines to gain approval for use in the UK, so when I'm sitting in the UK, when I'm sitting in the U.S., I have no concern about the quality of a pharmaceutical product and I tell my relatives not to be concerned, because they are sitting in a country where the regulation / it doesn't matter where it's manufactured, the regulator overseas the quality of the product they are looking at, but given that you asked me the binary question I had both and which would I choose, I would say Ireland and that is about perception, it's about perception of where the greater quality sits, and that's a terrible thing to say, I know, but that is / that perception is what pushed it.

Last year, when the FDA suspended their overseas inspections, there was a huge increase in defects from imported medicines, are you surprised by that?

Actually it does surprise me it's as high. It does surprise me. I thought I knew / I'm not / I am surprised it's as high as it was.

Are you surprised that there's an increase when there was no policing as a term of enforcement?

No, I'm not surprised.

Is this policing quality in rather than the first intents?

I think how I answered the question was you need both, it's the push and the pull, you need both. In an situation you wouldn't need them but I believe you do.

On the industry side, is there a god incentive to push quality first globally?

I think umm / I think in many ways they're lip service, but you know, I think big organisations it's a / it's important for them I think to be able to conceptualise what it is they are doing in relation to the quality and the reason that sits behind the quality being at the forefront of everything we do and I guess / I mean my views and opinions that have been

expressed here just now have grown through my experience primarily at <redacted>, in fact, through my experience at <redacted> and that's what I will continue, so it's lip service, but I think it's with an underlying intent that / I have always believed that quality and actually through, again, through experience, transparency / you'll see me banging on about this as well, transparency is absolutely critical to what we do. I never ever want to be caught in a bunker having to dig myself out when it comes to data and information and you know for me and some of the kind of sort of slogans that you see at <redacted>, for me at the end of the day, the person taking that tablet could be me, it could be you, it could be my mother, it could be my brother and you know / I think human beings deserve better.

And I think, you know, I remember having a conversation, I can't remember who it was with now, several years ago, it was when I was on the whole / because I spent a lot of time on working through suicidality things and on risk management teams and all that kind of good stuff and I remember having a conversation one day with somebody about something and the comment that sticks with me was they said, L., people matter. So for me actually it's less about the campaigns and less about the slogans, but through my career, there have been a few people who have really brought it home to me and I think some of it is that comment that, actually, people really matter and I also remember discussions with. <redacted>

Umm / and you know we were / I was / <redacted> was heavily involved in all the suicidality stuff that I got tied up in with and I remember saying to him one day, I said, why on earth do you keep coming back in to this nightmare situation and again, one of the things he said to me, was he said because I actually believe that what I do and my decisions make a difference. Now actually at the time he was the QP.

On that basis do you feel as an industry we always develop the best possible product for patients or are there other drives that impact that?

There's other drivers.

Such as?

Which is why you need the regulators. There's other drivers. There's commercial drivers as well.

So how would you balance that?

Well I believe that my role, working in R&D, is to put forward the arguments and to drive the conversation around the best product and my rationale for it, accepting that there may be other views and other opinions, now the other views and other opinions would not take you in, I believe, in to the realm of looking at options which are not safe for people, but / and again you've either been directly involved or you know of the whole thing I'm thinking about, <redacted>. Now the <redacted> was smoke and mirrors wasn't it, so was that what was best for patients, no, it was not to do with patients, it was all to do with profit, and I actually believe that there was nobody in R&D who thought it was best for patients, but that was a decision that was made and so, again, you know, but my view is I'm paid, I'm employed, for my judgement on R&D related topics. I will not shirk from that but I will also accept that there are other drivers sometimes. So I think as long as it doesn't harm, but not necessarily in the best interest, and that was just a commercial gimmick.

But do you feel there should be almost like a pharmaceutical component like the Hippocratic Oath, do no harm as a first intent?

That's an interesting one isn't it. It's an interesting one. It would be nice to think that people who work in the industry actually subscribe to it, but it's an interesting / it could be an interesting experiment to do couldn't it?

You mentioned about transparency and I want to move on to that now.

Yes.

From a transparency perspective do you feel that there is enough interaction between industry and regulators?

Well umm / I'll personalise my answer first and then we can maybe think about the broader context and my personal experience is because I've been bitten and I've been bitten by now engaging with regulators soon enough. So if I fast forward to where I am today and what I'm doing here at <redacted>?, as you probably know, I'm instrumental in driving the FDA interaction on the <redacted> and my reason for that is you're better to know soon rather than later what your potential issues are and the earlier in the development pathway that you are transparent and open with the regulators about what your warts are, the more you can actually work together to actually place them in a context which is going to be meaningful and although the sponsor is always accountable and responsible for designing the development plan, it is a partnership with the regulators, so we all know what the guidelines are, we all know what the framework is, but of course, each medicine needs to fit in to that framework in a nuanced way, so that's where I have ended up and you know my experience taking me to that point has also been formed through direct exposure to working with the FDA, in particular, actually as we go through reviewing pre-IND situations. I have always found, certainly the neuro division, which is the one I've interacted with most, I always found them very collaborative. You know the FDA would contact us and jump on a call with us. I also remember when we were preparing for the adcom with an anticonvulsant drug, and we had one of these consultancies working with us to try and get us pitch-perfect, which seems to be what you need to do these days and I also remember fighting tooth and nail and almost sacking them because they wanted us to spin data and myself and <redacted>. who was Head of the Neurosciences team at the time, we were adamant that we were going to give them what it was. Now interestingly the thing that happened with that adcom it is normal at an adcom, as you're probably aware, for both the sponsor and the FDA to make a presentation to the advisors. On that particular occasion the FDA withdrew their option for presenting because their view was that the sponsor had presented the data in an adequately transparent and warts and all way, that there was nothing frankly else for them to say. Now I think that is the / that shows, to me, that you can / I mean we still got non-approvable, but that was nothing to do with the adcom! I think it shows that if you work with the agencies, the reviewing agencies as partners, they're coming at it from different views. Their view is that they're protecting the citizens, our view is that we want to get a medicine in the market. I think you can do it in a much more collegiate way. I've also worked a lot with the FDA related to suicidality ratings and that type of thing and you know the devil you don't know is always more scarier than the devil you do know.

Do you think critical mass with regards experienced professionals is something companies are suffering from?

I think this is a real / and my thoughts are forming on this, I've only been with the bio-tech for four and a half months, or is it five and a half, it's five and a half now, doesn't time fly. I think / I think the enormous benefit that you get with working in a bio-tech is you can move quickly. You can move quickly. You can move swiftly. There are not as many checks and balances in place. I think as a consequence what they rely on is having people with really deep expertise and knowing when to call stop or when to call actually this is not right and the challenge I'm noticing is is for those people to actually have a voice. So there are some people, again, if we just personalise it to <redacted>?, I've noticed that are some people whose voices are much louder than others and I think part of the role of the leadership at an organisation that <redacted>? is to make sure that they are listening to the people who have

not necessarily got the loudest voice, but listening to people who have got depth of experience and they rely on building an organisation through trust and it's a difficult balance to get right. I was also shocked and abhorred at some of the things that I saw when I first came in and I could have continued to be shocked and abhorred at it, but I've taken the view that, well, it's a fledgling organisation, no harm has been done, but let's make sure we do differently going forward.

Do you think that is good for the industry to have companies only focussing in certain development aspects such as to FTIH or Ph11?

Well I think that's where the industry has got to watch a little bit and I think that's where mistakes get made because the reason I have the views and opinions I have today is because of what I know that happens in the totality of the whole, so I will sit and I will listen to a conversation now, on a molecule that is still in Phase I, but I am thinking about where it's going to fall down the holes in Phase III. If I only worked at Phase I, I would not have that kind of lens to look out and I think the challenge for bio-techs is that they need to surround themselves with enough people who have got a variety of experience. It's not that one experience is better than another. I mean one of the things I was really really keen to get was a strong regulatory consultant working with us. We have that now. I don't have that experience but we need to have that and it needs to be somebody that I feel I can work with and I'm just saying that because, you know, if I'm brought in to do a job, then you get it the way I do it, if you don't like it then don't have me. I'm a bit like you now, I'm not worried one way or the other. Equally I felt recently that we just were not getting the depth of toxicology input that I felt we needed and I knew somebody, you know them as well, who I brought in and I'm getting quite a different steer now. Now it becomes self-fulfilling because I'm now starting to become more comfortable with some of the sorts of views and opinions that I'm getting, but that's not to say I'm right, so it's you know it's / but I think there is a challenge, if a bio-tech only deals with a small segment of drug development, then what / it's a bit like at <redacted>, you're potentially going to pass more and more rubbish over the wall.

How much of an impact do you think politics has on pharmaceutical development and manufacture?

What sort of politics are you talking about, just so I answer the question?

Company politics, the general governmental politics, so managed healthcare in the U.S., NHS costs in the U.K.

Umm / I think it's mattering, increasingly mattering, because it's no longer good enough to have a medicine approved. A medicine has to get through the / it has to get through the reimbursement hurdles as well. So again I have been involved with medicines who have quite successfully come through the regulatory process and they have sat on the shelves, but that's no use to anyone. So I think increasingly, absolutely increasingly, then there is / has to be attention paid to / again this gets back in to the environment in which you are launching medicine, it gets back in to understanding the totality of the benefit risk proposition and the benefit risk proposition is informed by partly by what else is in the market place. One of the things that perplexes me a little bit at the moment, with <redacted>, is I am seeing over and over again a belief that an anticonvulsant drug is going to kind of reach the skies in terms of value. I remain to be convinced that reimbursed, even in the U.S., and I think as the U.S. paying structure and I know it's a victim of Democrat Republican kind of tussles, but you know, the U.S. is still the biggest single market for pharma. At some point some of that market's going to get blown apart. We're already seeing it, when we get a company like Amazon who are starting to sell drugs to consumer.

So I think it's huge. And I think you miss it at your peril.

Do you think there's a nationalistic component to this as well? For example for worldwide use, its got Mannitol in it, but we have to list Mannitol NF USP BP EP you know all the various pharma / JP / and they're all much of the muchness but change is very subtle characteristics. How much do you think that hinders or helps?

I think it's a nonsense. I think / as you know I'm all for differences that are real. I'm still processing the back of my head that shocking statistic of an increase in manufacturing failures from overseas in the U.S., but in theory I think it's a nonsense, because if there's nothing scientifically different in real terms, then it's just a cost-generation process and you know you're looking / yes / it's / why would the cost-basis be so different on it, so I think in principle I think it's a nonsense.

You said at the start of the interview that you didn't believe we'd ever have a single global quality standard or a single quality way to review dossiers. We have PICs, we have ICH, we have EudraLex, we have all the other various local guidance's as well. What would you change for the industry to give a satisfactory global health care system that could take a product from any market and use it what would you change?

You know when you're / we've got the perfect situation to think about it just now haven't we, with a global pandemic going on underneath us and you're seeing different regulators across the globe approving things in different ways, looking at different standards, so in China, they are only interested in approving Chinese vaccines. In Russia it's a Sputnik vaccine. We're seeing some Eastern European countries their local regulation authorities, their national regulation authorities are approving the Sputnik vaccine, so they can get it. The EMA and the FDA won't go near it. That's got to tell us something's wrong somewhere. You know these medicines are fit-for-purpose or they're not, so it just / I think it just talks, going back to politics, and I mean global politics, not internal politics, it clearly is getting in the way and it is getting in the way to harm peoples health and that / and the WHO can clearly do nothing about it, nothing, it's / in some ways, at the moment, its got its hands tied behind its back, it is itself / doesn't do or mean anything.

And more of this will happen so I think if we don't get another pandemic my prediction is the next big thing that's going to happen is we're going to be overtaken by antibacterial / resistance / antibiotic resistance.

And they've been banging that drum as well for a long time and no one's listening and it will happen. It will happen and it will happen and it will hit the developing world first and the West will continue to do what we're seeing it doing in the pandemic, but I think you've got one actual example and one I think emerging issue, which talks to the need for more globalised view on these human issues, but I think we're a long way off.

Do you feel then, either the industry or the regulators, are they reactive or proactive?

I think they are largely reactive. I think there might be pockets of pro-activity but I think they are largely reactive and you know rightly or wrongly I think big pharma reacts to money, there's no question. There's a reason why they are not looking at new antibiotics, it's because there's no money in it. There could be money in it but at the moment there is no money in it.

Is that the role you think that smaller start-ups, bio-techs could develop in?

Yes, I do. I do.

Is there a role then for big and little pharma?

I think there is. I think there absolutely is and of course big pharma will jump in once the programme / I think that absolutely is a role for partnerships and you know again, off the record, umm, I would not have chosen to work for <redacted> if it had not been for the

people I'm working with, because I would not choose to work and spend so much time on what I consider to be medicine which is what / certainly 155 is, I'm just getting up the learning curve with ,redacted>. If I was to move to another / but it's about a learning for one's own experience as well isn't it, so I left big pharma, I said I would not go back in to the pharma industry. I'm now in bio-tech and I'm actually enjoying it but I think if I was to continue long term in bio-tech and if after my services are no longer here or we part company for whatever reason, I would be more choosy about which bio-tech I worked for and I would be more inclined to work for a bio-tech which I think is really going out on a limb because for me it's not about the money I can earn, I don't need that any more, I've been very well provided for, for me it's about actually being involved in developing medicines that are perhaps a bit more risky, are really going to tip the balance in terms of if they're actually successful.

Personal ethical decisions?

Yes. I would actually like one day to work in rare diseases. I think people who / and I have noticed a lot of people who have worked at big pharma will go off and work in the rare diseases area. The only way that rare diseases are really going to get the attention they need is I think in bio-tech and rare diseases and also novel methods of delivery and that type of thing. I mean the big pharma tries it on every time they've got a big cost cutting measure coming and it's the rare diseases that get axed.

Subject 22648

Do you think the current process we have within the UK and in Western Europe is fit for purpose to give us safe and efficacious pharmaceuticals for every product, that includes generics and new chemical entities?

No I don't I think it's mainly based on dogma it's based on policy is not always based on science.

I think efficacy and safety are totally different items as far as agencies in India and 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? In my experience I've never seen this.

So would you say that's the same across all the countries in Europe?

No I think 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. I've worked in a number of countries within Europe and dealt with many others that I haven't directly worked in and I can tell you they are not the same the basis for approvals or the basis for assessment are many times very different.

Is there pro-active engagement from the agency or from industry?

From neither. It is totally on an as required basis and sometimes even then even when it is required is he ever not done properly or done in such a way as to gain approval for something which is really not quite right.

Would you agree with this description that it's more of a policing model of regulation rather than an interaction and a joint striving for quality between industry and regulators?

Oh it's definitely policing! And that's just within Europe. if you ask about United States of America the FDA are even more aggressive at policing regulation and less likely to be

willing to engage in a dialogue to understand what you are trying to achieve even if that is with the sole aim of improving patient safety or compliance or even to have a brand new medicine.

Do you see a difference between big pharma and little pharma approaches to regulators?

My experience to date is there is a difference I have some experience of big pharma in situations you really did not engage with an agency until you really had to, the last 20 years of my experience has been many in small pharma and biotech companies and they are a lot more ready to engage and discuss and seek advice or just a conversation to agree a path forward that will help everyone. It does appear to be a totally different mindset

Do you think agencies are autocracies or meritocracies?

That's tricky, I don't think I can answer that on the basis of an agency I think it's a mixed bag of good and bad I think there are known inspectors who are extremely diligent and have the background and knowledge and flexibility to engage in a dialogue which is very helpful there are others who are shall we say less so, is that any different to industry? I don't think it is. I can't comment on the agency approach but I do think there are some people who are in those organisations, in those positions based on merit and some who are not however

Have you ever done an audit, a co-audit with an FDA Inspector or other non-domestic agency?

No I have not. I have only done auditing within the UK and Europe and that was with European inspectors

Imported pharmaceuticals, something that's manufactured outside of the current EU structures.

Do you feel that we have sufficient control over imported pharmaceuticals

I think it depends where you're talking from. In total market importations between countries within Europe I think have quite a good level of parity however we do seem to spend a lot of time looking at products from America which probably don't deserve the scrutiny that they end up having and then also products we get from other manufacturers such as India and China which we don't look at too closely and probably should look at that in more detail but those importations are really in my opinion based upon cost and price. Also I just want to say that I think you might experience countries like Australia and New Zealand we tend to import from quite readily because we believe they are very much akin to our own systems, whether they are or not I really can't say.

If you were given the option, you had to take a drug and were given the option of drug manufactured domestically or drug manufactured by a company in India for example, which one would you take?

Oh I think that would be very difficult and I think I'd have to say it would depend upon who the actual manufacturer was and if I had any experience of them personally then that may sway my decision but face value I can't pick one over the other.

So what about product manufacturing in the U.S.? Would you take that readily?

Yes

Why?

Because my perception is that I trust them I don't know why it's just gut feeling

Is there a political component there with regards to regulation?

drugs cost money and therefore there will always be a political component. Medicine costs in my experience in almost every country is the political football that is used to win or lose support. Whether that's good or bad well I don't really have an opinion.

Are you surprised on that basis that the last recorded 12 months Jan to Dec last year there was a huge increase in recalls of overseas medicines imported into the U.S. and that corresponds with the lack of overseas inspections?

Not at all!

Are you surprised it's high

Nope

Someone once said that politics would always trump pragmatism, do you agree with that when it comes to pharmaceutical regulation?

As I said before politics always get involved in medicine and the cost of medicines and the general cost of healthcare therefore it's hard to distinguish between what is done from a purely patient benefit perspective and what is done for political gain or political manoeuvring

Is there a moralistic component to pharmaceutical regulation?

as a general rule I don't think morals should come into it. Redevelop drugs and we sell drugs to make patients better that's the aim there would always be occasions where a drug gets a higher profile because of the type of disease that you're trying to treat but we are scientists so this should be a day to and knowledge based decision-making process it's hard to then pull in and define a moral component.

Do you think it's purely politics and risk-based that are the main drivers?

From an agency perspective yes they are very risk averse, very conservative in nature and they have political masters it would be naive to think otherwise.

Regards regs then of the various agencies we've got ICH, we've got PIC/S we've got PDA in the U.S. Do you think there will be any benefit to having a global system? How can we overcome that nationalistic approach?

I think that would be great open very hard to actually justify and to organise too many people have too much vested interest in the current system is of the order of the current products and that will be very hard to overcome I'm also not sure who would actually lead that who would initiate it who would tell the FDA that they are no longer in charge of their own drugs it be another agency that would be very difficult to achieve.

Who would lead that change? Who do you think should lead that change?

In your experience, if I give you magic wand / you could change the industry and the agencies and look at pharmaceutical products worldwide and equivalents and so on, what would you change, what would be your top priority to change to improve the overall quality of medicines, of imported medicines and domestic?

That's simple 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!

Subject 14704

Do you feel that the international processes on product quality and equivalents are generally acceptable?

When you say international processes you mean regulatory?

Regulatory frameworks, so for example, you know, we don't have formal mutual recognition between lots of agencies at the moment, do you feel the general trend is that these processes that are there benefit patient safety?

Yes. I do. Umm I don't know if you want me to elaborate?

Yes, please do

I do think that the process is necessary. I think you know the process of uhh / talking about quality, so GMP type inspections and all the rest of it. I do wonder if we've perhaps gone a bit too far and I do wonder what the added value of some of the / maybe it's just because I'm getting old, but some of the things that you know inspectorates come up with now I think you know is it really going to make much difference to product quality, umm / you know the data integrity, I know, you know on paper I know it's umm / obviously we need data that's integral, that we can rely on, but we went many many years in the pharmaceutical industry without all this fuss, about data integrity, and I don't know that people were sort of dropping like flies particularly because their medicines were of poor quality. So I do think sometimes that it's gone a bit too far and it's costing a lot of money and a lot of resource without any particularly lot of added value.

Thinking about the UK then, do you feel that the products being taken now are of a better quality than the products we took 30 years ago?

Well no I don't really, particularly. In terms of you know GMP I mean they might have nicer packaging and they might be more efficacious, they might even be safer, umm, but in terms of the quality of the product, the risk to the patient that the manufacturer has been / hasn't been done correctly or that the analysis hasn't been carried out correctly, I don't think there's been a significant improvement.

Thinking about manufacturing then, Do you see a commensurate increase in quality with increased documentation or regulation?

I think / I mean I / you know / I'm trying not to sort of get myself up a dead end here, but I do think / there probably has been some improvement but I don't think there has been the improvement that you know the extra multiple-fold 10, 20 fold, increase in paperwork hasn't made the quality 20 times better, umm / I think probably there have been some improvements but I think they've been marginal improvements.

So when we look at importing medicines from overseas then should we have the same expectations we have for domestic manufacture, that quality measure, how do we assess quality ?

Well I think there is / it's / I mean I'm not saying you shouldn't have a paperwork trail and you should be able to trace all the batches and you know do inspections, on site inspections, but I just think certainly in the last 20 years or so, I just think some of the things that have come up within Europe maybe umm or you know sort of the more regulated markets, I don't know really, but I'm just not sure that there's / I don't think the increase in quality, if there is any, really justifies / necessarily justifies the massive increase in resource, effort, time, money that's spent in umm you know addressing what the expectations are.

So what do you think has been the main drivers for that change then, the extra resource required for manufacturing, and so on, if it's not a commensurate increase in quality?

Well I think it's a bit of both, I mean, I did a lecture on this years ago for when I was with the MHRA and all about sort of escalating umm standards really, or requirements, or expectations, and I did think it was a bit of both. I think it's you know GMP on paper, if you look at the GMP's, the orange guide and all the rest of it, there's not been a lot of difference over 20 or 30 years really, there's a few extra Annexes, umm, but you know Chapter 5 on Production is pretty much / I mean apart from a bit about cleaning, hasn't really changed much in 20 years and I think that its become / it's like umm / race / like an evolutionary race, you know, like gazelles get quicker and lions get to / and lions get to catch gazelles and it goes like this all the time.

Yes.

I think the industry is scared about being umm you know / having / getting deficiencies, if you like, and I think the inspectorates / or maybe individual inspectors are scared that they are going to miss something. Every few years you get one of these hot topics that comes along, probably / I'm glad you're deleting this / umm every so often you get umm like a hot topic that comes along, even going back to validation, I mean there's whole careers and businesses built on filling filing cabinets full of documents.

Yes, please expand

And umm and I do think that you know you can fill a filing cabinet drawer full of a validation document on, I don't know, just something like umm an infrared spectrometer or something like that and you think what's the point really.

It's the application of that expertise then and the understanding of / what we're using the information for and the data?

Probably yes, perhaps it is, perhaps that's what it is, perhaps people are just not really / I don't understand the risk.

And I think that 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, I mean, you know. Why?

Can you elaborate please?

See that happening and isolators are you know they are going to have to be kept in Grade C because people are saying well we're going to build our / put our isolator in a Grade C room just in case, blah blah blah, and before you know it, that will just be / that'll be it.

Looking at the regulations, in the UK the orange guide, this is my copy of 1983, 101 pages long and most of that / probably last 20 of that is an index. Whereas the 2017 guide is nearly 900 pages of the orange guide. Has this changed peoples perception of quality?

Yes, I know, yes.

So that change in emphasis you know what's the driver for that? You know if you had to put your finger on something and say that's what's forced that change, what's the driver for that?

Well I think the orange guide is not necessarily good. The orange guide has got a lot more things in it than just E.U. Its got all the legislation on GDP and guidance that wasn't previously published and umm / umm / what was I saying, sorry, I'm going to put my phone on the floor because it keeps buzzing. I won't be able to hear it now. Sorry what was the question?

So what's the driver for this change? If it's not increasing quality, you've talked about other measures and so on. What's been the driver for the change in regulation then over the past 20, 30 years?

Umm / I / hmm / I'm really glad you are deleting this. Umm / I don't but I think it a lot umm / I think that it's fear, a little bit of fear, a little bit of you know just in case, we're just going to do this, just in case.

The fear of challenge?

Sorry?

Fear of challenge or fear of failure?

Well being challenged and not meeting the challenge. Somebody / a sort of gung-ho inspector coming along and tearing them apart.

And I think there's quite / you know the FDA were famous for this years ago. You'd get some umm / you know some gung-ho inspector who wants to make a career for themselves and they start to tear big companies apart and it all gets in the papers and umm / yes, happened to <redacted> years ago, umm, and with umm / I mean it was back in the 90's and they got torn apart because of computer validation / / in the U.S. and you know they must have spent millions and millions and millions and I genuinely / alright, you know, probably wasn't perfect, but you know they were using these computers, legacy computer system for years and years and years, and I don't think many people were killed because / or died or injured because there was some lack of validation of their computer system. I've come off the point now haven't I?

No. Please continue.

Yes, no, the other thing / the showboating, I think there's a bit of showboating umm amongst some inspectors and also in the industry, you know, people like us, I don't suppose we help. We want to add / we want to be seen to add value umm / yes, this is / I shouldn't be saying this should I, my career has been built on all this!

It's all just a sham! To add value do we think well you know we think we should be doing this and we need umm / we need this extra document to cover / you know the FAT testing and we need to spend a lot of time on SAT and you know your URS needs a few more hundred pages on it and.

You are leading in to an interesting area there, something I want to explore a bit more, so considering the agencies then, our own careers notwithstanding, do you believe that the agencies are structured as meritocracies rather than autocracies?

I think / probably a bit of both, umm, you know, there is meritocracy in organisations, but / nobody wants to pop the balloon somehow, you know, the balloon's inflating and you know we're building our careers and these people are building their careers in the inspectorate and I'm sounding really cynical now, and I think it's not all bad.

Do you feel that there's a political component to this with pharma regulation or is it purely about patient safety?

Uhh I've never really thought of it being political, umm /

Do you think that very expensive drugs will always make it to market or do you think there would be a political acceptance/reluctance of paying that cost for it?

Yes. But I think that's to do with efficacy and a bit of safety. You know if you've got a really good efficacious drug, but I don't think anybody is going to be saying, oh, you know, we need to make sure that we've got / we can't have that drug because we haven't got post-use integrity testing in place. I think you know efficacy followed by safety would trump any quality. Look at the way umm you know all these things / a lot of the GMP stuff that's / I can't remember what the word was / like mitigations of out the window, QP because of Covid and uhh you know we don't have to test / I can't remember exactly what they are, there's a whole list on the MHRA website.

All of a sudden these things are allowed to happen.

You think well if it's okay now, why isn't it always okay?

If I told you that in the U.S. for the 12 months ending December last year, there was a huge increase in batch failures and product recalls for imported medicines in the U.S. as opposed to an 18% increase for domestic manufactured medicines in the U.S. And you could correlate that to an absolute decrease in overseas inspections by the FDA. Are you surprised by that?

Yes, I guess I am yes, so I mean well it depends what the recalls are for, so who is triggering these recalls? It is /

These were triggered within the U.S. because of product / detected product defects and adverse effects and adulterations.

Yes. I am surprised, yes.

So that comes back to your comment there about fear though. If companies have a fear of challenge or a fear of being caught out, you know, and if that's only being linked up to inspections, you know, oh God, we've got to be ready for the FDA in case they come knocking on our door, is there's a correlation in your experience?

Yes.

<redacted>

FDA stopped overseas inspection. is there a political component there to getting that registered and reimbursed and on the market?

Yes, I mean, you / yes, I think there is, but I think it's all about / you know if it's an efficacious medicine they will throw out GMP and quality out the window, you know, your point about them making Covid under generic / presumably to save money or to improve supply, get more units out, but nobody's worried / nobody's thinking well the generic company hasn't validated their autoclaves properly, it's all to do with you know the getting the medicine out there, never mind the quality, feel the width type /

Is it the risk benefit isn't it, analysis then, isn't it of its been to market and what the alternative could be isn't it?

Yes.

Please elaborate.

Point is that if the / if it comes down to it people will throw / will be much less worried about quality and if it's an efficacious product.

But as you say it's risk benefit, yes.

In your experience, are there certain markets that you think are very kind of gung-ho when it comes to quality and efficacy compared to what we're used to in the West?

When you say gung-ho you mean what more strict and /

No, less strict.

Casual, lackadaisical you mean?

Yes

Cavalier, more cavalier.

Cavalier, that's a good word, yes.

Yes. Umm / I don't really know to be honest. I don't know how umm overseas inspectorates work to be honest. I mean you hear stories about in India about having factories for the domestic market and factories for the regulated market umm / but I mean I've never seen one, umm / I do wonder if / I mean probably some of them are more cavalier I don't know, but I think some of them are much / I think some of them are stricter. I mean I know for a fact that WHO, in my experience, WHO apply very strict GMP and you'd think maybe WHO you

know would perhaps be operating quite a low really minimum. I know MHRA etc. are supposed to apply a minimum GMP standards but you'd think maybe that the / something lower even, dare I say, I don't want to sound prejudice about it, but you know I think WHO are probably in my experience, which is limited, I accept, they have been more strict than I would have expected from say an MHRA inspector.

Couldn't speak for / I couldn't really speak for umm most overseas inspectorates. You hear horror stories don't you about Russian inspectors going and going bonkers about / I think Russia they're interested in microbial contamination of primary packaging components and stuff like that.

So we've talked about you know politics and political influences and quality. If you had to take a drug and I gave you an option between Pantoprazole that was manufactured in the West or Pantoprazole manufactured by a company in Africa. What would your gut tell you to take based on your experience?

Well if I have a choice I'd take the uhh the Western one.

Why?

Because I think I'd have a more confidence in the fact that they hadn't dropped the ball somewhere, especially if / if it was a sterile product or something, umm / I would be much more interested in taking the western one, but I mean I have bought pharmaceuticals in India, for my own use, manufactured for the domestic market and I have used them, not sterile products, but / but that's just an assessment, you know, I was / I needed some umm / oh what's it called / Loperamide, you know, the uhh Diacalm stuff.

Yes, Imodium.

Imodium, that's it, yes.

I must have run out or something, I don't / forgot.

Talking about quality and quality, we have ICH, we have PIC/S, and there's various other initiatives, if you had to pick one as the way forward, if you're looking at a single / this is very optimistic / a single quality standard what / who would be the people to push that forward, ICH, PICS, where does that sit in your mind?

Either WHO or ICH I think, I mean, I think, you know, I'm surprised ICH haven't really written one to be honest, along the lines of Q10, but for GMP, general GMP.

Do you feel that the nationalistic you know push back from that, because for example, we / if we write a file for the U.S., you know, we write a file, say Mannitol, BP, USP, JP, NF, you know, and for the most part those monographs are interchangeable, there's a few subtle differences. Do you feel there would be acceptance of a global standard, a globally acceptable material, or a globally accepted way to manufacture, or do you think each country will say, well actually, no, we've got to do it our way because it's slightly different?

Umm / I think there probably will be, but it'll probably take a very very long time and some countries will hold out, I mean, the U.S. now they will hold out for their own standards.

Things are pretty widespread. Some of the ICH stuff is quite widespread umm / you know the umm / analytical method validation type stuff.

It varies to be honest, umm / and you know these differences, yes, I mean they're political I guess aren't they? It's you know my invented here sort of thing, not invented here.

So if the industry and agency had to change what do you think would be the biggest change for the pharma industry and the agencies and how they work together?

What do I think / sorry?

What would be the biggest beneficial change between the way that industry and regulators work together?

I think that improved communication. I think / I don't think it's too bad in the UK actually, compared to some, but industry seems very concerned or worried, scared to sort of engage with the regulators. They / the regulators descend and they tell them what it is / what's what and umm it's going to be like this and the industry says yes sir and no sir and we'd better put this in place before the next inspection just in case and if there was more communication and perhaps you know sharing of / understanding of the actual risk to the patient, I think that would be a good thing to do.

Do you think that communication is different say within the UK, MHRA and industry, versus the U.S. FDA and industry?

Umm / I think there is communication in the U.S. but I think it's like a different / its got a different feel to it somehow umm because the FDA quite often have / I've been to a few factories where they an FDA person on site.

Yes.

Pretty much all the time. I went to one where it was / one where she had actual / she had an office in the / and an access card to the factory, so I'm guessing there the communication's quite good, but I'm not sure what the sort of / you know communication on paper against actual swapping of knowledge umm.

In some companies it's almost is a visceral knee-jerk reaction bot to engage an agency, "you do not talk to the agencies, unless you absolutely have to". Have you found an lack of agency/industry engagement in your experience?

When I used / yes, I mean, that's true, that is true and I think that is a problem, umm / in the UK, I mean, it was a long time ago, my boss, before I joined the MHRA, she was inspector who was <redacted>, I don't suppose you remember him, but.

He was an / he was a reasonable guy but she wouldn't / I met him, I knew him quite well, once I'd joined the agency, umm, and she was / would never have contacted to ask him anything umm because she was scared I suppose and you know she'd / he would perhaps / she was expecting a communication from him and it would perhaps be a week after she was expecting it and she'd be thinking, oh my God, what's happened, you know, why is it taking a long time to get back to us, is it because he's forgotten, or because he's in India, no, she was worried that there was some sort of ulterior motive or / so you know that's not a healthy relationship really, but /

I always think that / I think my experience, my experience obviously is with the MHRA, and I know I'm probably biased, but I do think the MHRA inspectors are quite keen to communicate. They are always quite happy to communicate, well most of them, quite happy to communicate with industry.

Do you think the option of scientific advice meetings and briefing meetings is utilised sufficiently?

Well they cost a lot of money don't they, apart from anything. You know scientific advice meeting, I don't know how much / it's several thousand / is it £10,000?

It's a hell of a lot, and I have been to a couple.

I'm not sure that / I mean / maybe it's just the ones / I went to maybe a couple, two maybe, and I was a bit horrified by the / not horrified, but disappointed I suppose by the response that the MHRA gave. It was quite clipped and you know you had to ask a specific question umm / and you got a specific answer back and that was it.

There wasn't any sort of discussion really, or not very much discussion, so I don't know / maybe it depends, because the ones I went to we were with assessors, and I suppose maybe assessors don't /

Yes, they don't know what it's like in other you know maybe Germany, France, Italy, I / don't really have a feel for it. I think / I think the position in the UK, I mean, again, I'm biased, I don't know much about other countries, but I do think it's better in the UK than a lot of other countries.

If you could change three things, if you personally could influence three things regarding pharmaceutical regulation, with respect to product quality, what would they be?

You mean actual technical facts or.

If you had the power to change, whether it's product registration process, whether it's ensuring global GMP, whether it's you know cheaper access to healthcare, what would you do?

Hmm gosh, you should have given me some time to think about this!

Your gut reaction, what would you do?

Yes, yes, sure.

What's your top priority?

Across the whole of the health provision world, provision of pharmaceuticals?

Pharmaceuticals.

Umm I think I would try to cut down / well / cut down the time and therefore expense I suppose of actually getting a product to the market. I mean how can it take you know eight or 10 years to get a product to market. I mean what's going on? I mean I know there's clinical trials and things to perform, umm, but I do think that everybody is making sure that the 'T's are crossed and the 'I's are dotted and you know again with COVID, all of a sudden, you know, we can get it done in nine months or whatever it was, instead of nine years, why can't we always do that?

You said speed and cost. So a third one?

Umm / I / I mean going back to how we kicked off, I don't know how or / how this could be done, I haven't really got / thought it through, but there must be a way of just being more reasonable about GMP, you know, you're going about with a big wodge of documents and I do think / I do sometimes think its gone a bit mad.

Subject 12663

Do you think the current regulatory process we have within the UK and in Western Europe is fit for purpose to give us safe and efficacious pharmaceuticals for every product, that includes generics and new chemical entities?

That's a very broad question. But I think on balance overall I'd probably say no, it's not fit for purpose, it's. Far too bureaucratic, it's far too complicated. Is. Extremely conservative, it is not conducive to. New developments, new technologies. Overall, this is a very complex, overly complicated system.

So would you say that's the same across all the countries in Europe, for example?

Yes, I would say that. Most of the Western European countries are all of the same ilk.

Do you see pro-active engagement from the agency or from industry?

No, I don't. The current process from the regulatory side is very reactive rather than proactive. There have been a few initiatives where they have tried to embrace new processes,

for example, and that's been very interesting. But for the most part they get bogged down in. Be overly bureaucratic. Systems that are not necessarily integrated and fit. With. The embassy agency, which is to oversee. The industry. Sometimes within industry. I have seen them reach out to. Start initiatives. Sometimes for quality, sometimes related to or something to be frank, to be given a competitive edge and I think that's something which is A bit too prevalent in large companies. The small pharmaceutical companies. They tend to be a bit more responsive and wanting to engage. Maybe I'm cynical, maybe because it's a lack of resources or lack of experienced personnel, but I suppose it could be the fact that they really want to. Develop a relationship with regulators and get the best. Possible product they can. I don't really have any direct experience in that will stop.

So do you think it's a policing model of regulation rather than an interaction and a joint striving for quality between industry and regulators?

I think that depends on the country.

Can you elaborate?

For some countries certainly North America to have that attitude of assuming fraud and illegal activity 1st until proven innocent I think well I like to think certainly been the UK and within the major European agencies that is not the case it's very much more of a Sikh evidencing a dialogue then make it determined to termination. I think the Chinese as well is very much aggressive approach to regulation, Japan less so than China and then when you my experience is dealing with India and Pakistan and other manufacturers are that they are really hit and misses to how they approach regulation.

Do you see a difference between big pharma and little pharma with their approach to regulation?

Yes as I said to nerdy question I think there is a difference I don't know what is pushing that difference forward its resources or experience but there's only difference into how they approach regulations and interactions with regulators.

From the agencies you have worked with and dealt with, do you say agencies are you know autocracies or meritocracies?

I think it's the same as any industry any business there are a mixture of people in positions that are fully justified warranted and people that are possibly in the wrong position and I don't think a regulatory agencies in exception to that rule it certainly also plans to industry!

Have you ever done an audit, a co-audit with an FDA Inspector or another non domestic agency?

I have conducted overseas inspections where inspectors from Japan and Taiwan but not with FDA or Health Canada.

How was their approach compared to yours?

It was OK I think we have to accept we have different goals really and different masters to report to and that really drives what inspector has to record has to write and justify their decisions some inspectors don't have to do any justification others have to justify every single deficiency they find and that can lead to very confrontational and quite frankly not a very good relationship with the site you are inspecting. I think what I'm trying to say is they're just all different.

Do you feel that we have sufficient control over imported pharmaceuticals?

No I don't, 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 so there is always well maybe not always but it's certainly in many cases a larger international supply chain behind the drug product that we are reviewing and approving for use within our home markets that's a complex balancing act.

If you were given the option, you had to take some a product manufactured in USA or product manufactured by a company in China, which one would you take? So domestic vs overseas.

United States every time, that's my home market so I have confidence in the products are manufactured there although sign out loud makes me sound very naive and sceptical of other manufacturers which is probably not fair on balance because I have no indication that vast George would be any lower quality than my local remanufactured product. I think as well if I'm buying and an over the counter drug price is also a component there so yeah it's been it's a bit is a bit of a mixture really more esports is not very clear I'm afraid sorry.

So what about product manufacturing in the E.U? Would you take that readily?

Generally yes however I think I think price would still be a component there I'd probably be more comfortable with Europe then say some other markets.

So do you think you know is there a political component there with regards to regulation?

Laugh always, and I don't just mean politics as in governments or political parties their internal politics within companies their Intel politics within regulators there are so many pressures on people it's hard to tease apart where the real problems stand I don't think people really go into this industry police from the science perspective about wanting to make a difference in wanting to make a quality product that helps people but I think being realistic I have to say that sometimes there are people that get through which aren't always that good in that case politics has a huge impact.

Are you surprised on that basis that the last recorded 12 months Jan to Dec last year there was a huge increase in overseas medicines imported into the U.S. that were defective and that corresponds with the lack of overseas inspections?

Not surprised at all, when the cat is away the mice will play. there are some very unscrupulous companies out there which will try and exploit opportunities like that to make a profit off the back of something which otherwise would not necessarily see the light of day.

Are you surprised it's high and appears to correlate?

I don't know not really I guess but I wouldn't really know how to expect it to be so I can't really answer that accurately.

It has been said that politics would always trump pragmatism, do you agree with that when it comes to pharmaceutical regulation?

Absolutely!!!!

Is there a moralistic component to pharmaceutical regulation?

Well I would certainly like to think so. When I started my career in prescription medicines it was said that new medicines were called ethical pharmaceuticals which always struck me as strange because should all medicine be ethical maybe its usage could be non-ethical but and if element of medicine to treat pay to see state surely must by definition being ethical process with regards to regulation however I think as I said earlier in a sense to view the politics the

money the finances they need to make a profit for the companies the need for patients have access to medicines because of two high costs this is all about us seeing act so talk it into a very grey ethical area as to how that it actually achieves and that's something which well I'm sure greater minds than mine actually played with.

Do you think it's purely politics and risk-based that are the main drivers?

No this costs, says profits, that is how patients can access medicines managed healthcare systems private healthcare systems governmental funding it's a minefield.

We've got ICH, we've got PIC/S we've got PDA. Do you think there will be any benefit to having a global system, how can we overcome any nationalistic approach?

A single global quality system or a quality standard would be beneficial too industry and regulators and ultimately patients and that's coming from my experience working within the industry and working within agencies I think politically though however it should be very hard to achieve I think also politically there will be the home would run who will administer it who has the final say and these are all aspects that would need to be overcome. The initiatives we currently have such as you mentioned ICH it's really good but even that's not globally adopted. There has to be a substantive demonstrable benefit to having the system to overcome the natural conservatism within industry and regulation.

Who would lead that change? Who do you think should lead that change?

I think that would be very tricky in my opinion ICH probably a good place to put that because people are becoming more familiar with working with ICH and working within the framework of ICH and for the most part ICH monographs are actually quite pragmatic so I think that would be a good starting point.

On that basis then, from what you've just said, you're effectively saying that politics has a greater weighting than patient safety?

From that basis then from a nationalistic approach yes definitely!

In your experience, if you could change the industry and the agencies and look at pharmaceutical products worldwide and equivalents and so on, what would you change, what would be your top priority to change to improve the overall quality of medicines, of imported medicines and domestic?

Equality! 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.

Subject 10383

Considering the current regulatory framework we work within, in Europe and in the UK, do you think the current system is fit-for-purpose?

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.

So when you say risk-based do you mean people aren't applying a satisfactory risk management approach or is it the approach of how they assess risk in the industry?

A combination of the two really. You see very little in the way of umm science-based proactive 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.

Umm 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. So if you have the profit, customer service and compliance kind of elements that you want to try and keep in balance, the compliance part of that falls to the bottom in many companies, when under pressure, and the QP's aren't strong enough and a lot of the senior management just want the profit.

You mentioned it's used to justify inappropriate behaviour, so you think people are using risk management more, or risk assessment more, as a reactive tool rather than a proactive tool?

Yes, I mean, in many companies, you'd use / you don't see that / if you look at HACCP you should have a full risk assessment of your operation, really understand what your risks are, properly, and then you're meant to put in your control strategies to deal with those. If you look at many companies / obviously I've seen a huge range of companies, really great big ones, really not good big ones and then very very tiny ones, but I've rarely seen risk management used in that proactive way, like an HACCP, to actually really understand the potential weaknesses and then deal with them and what you see is people do a risk assessment, really to justify the situation they are in and perhaps to minimise the amount of effort they need to undertake, so when people understand that you should do a risk assessment for a qualification, they are really trying to use it to minimise the amount of work that they have to do, rather than appropriately targeted necessarily.

And so you get people who / I mean there's a company we've worked with and they've put in a completely new computer system, something that's absolutely critical, and they've done a risk assessment, it wasn't worth the paper it was written on, and they lost traceability of product, they / and it was critical product that should have been vein to vein kind of traceability and they had no concept of the risks in that system. They also then lost control of all the material that had been created in the old system and had to be moved to the new system. They went from having three people who controlled the computer system to giving 70 people super-user access. It was totally insane. And everything that went wrong, subsequent to that, was predictable.

And too many people, particularly from an I.T. point of view, come into pharma and apply kind of perhaps finance I.T. rules or something like that, without really thinking about it, in my opinion.

Okay you could argue we've made it too difficult for industry and you can definitely argue that and that the risk-based stuff was brought in to kind of improve umm flexibility and that sort of thing and you like to think that companies will be responsible and will do the best thing for patients, but it's all lip service, in my rather cynical 11 years of (05:32) perspective. And I know / hmm?

Do you feel there's a partnership there?

Sorry?

Is there a partnership between industry and regulators or is it more of policing industry umm to maintain that minimum quality?

In my experience, unless you've got a police somewhere, then the minimums are not adhered to.

People are moving jobs too quickly so when you go back / you go back after sort of two to three years, some of the companies we went to you didn't see any of the people you'd met before and the people who were there were just relearning the problems from 10 years ago. And you're like this is a nonsense. Obviously they were cheaper. They were easier. They were less fussy than the people who'd been in there before.

Because they hadn't understood that they were going to have problems as a result of it. But now we're looking at risk-based inspections and you're talking quite significant periods of time between inspections. Some sites haven't been inspected for a really long time and a desk-based assessment, quite frankly, isn't worth the paper it's written on.

Would you be surprised then in the U.S. last year, there was a huge increase in recalls of medicines?

It doesn't surprise me. I'm / I / I used to umm inspect after an inspector who I thought was very superficial, okay, so I would pick up his inspection sort of two years after he had been, and perhaps he'd been their inspector for a period of time and a lot of those sites were just dreadful because nobody had ever really said, your quality standard is wrong. One of the sites, they hadn't qualified any of their manufacturing equipment. Now I'm sorry but that's really routine inspections, what was he doing? How on earth had you got to the point where we'd got an approved site in the UK routinely releasing products and the equipment's not qualified.

Yes, I mean, even allowing for the fact that an audit is a snapshot in time, you would still at some point have picked that up wouldn't you?

Well one would have thought so, you know, just by asking basic questions, but for me, that is quite a superficial person and then towards the end /

Is that a lack of experience?

No.

A general approach, lackadaisical?

He's what I call an old boy.

Really kind of wielded power over an inspector but didn't really look properly.

So was it more the case of they'd always been there, they've always done it, they're absolutely fine, don't need to look very closely?

Yes, yes. If you've been allocated two days he'd be off site by 10 o'clock on day two.

And that wasn't uncommon. His walk through production was short. It was a walk through production. Not an actual inspection of it. So that was aggravating. But then also, towards the end of my time there, I took on a big site, and I had to do multiple visits to it and they had quite a significant change in leadership, perhaps a year before I took it on as a site, and I started / I broke up the site in to multiple short visits. Now it was quite clear that some areas of that factory had never been inspected. Now this was a site that was supposed to be sugar, okay, they / the way they talk at industry meetings they thought they were God's gift as a company and as a site and yet I did one inspection one day and I went through their dry products part and it was embarrassing, they were and should have been embarrassed. They'd moved in to engineering areas, in to void areas, I found soil, literally on the floor in a wash room which was adjacent to a packaging hall. We went in to void areas where dirty equipment had been put in to it, just to try and hide it from the inspector coming.

We went in to one room and they are like, oh no, the door must be locked, and I just touched the door and it wasn't locked so we went in and it was mortifying for everybody there and then went in to one of their production areas and years I think before they'd taken out an old

I.T. system and they hadn't replaced what it was collecting as batch records with a paper record, so part of their process had no records for it.

Now they just changed management and nobody was looking at it from a sensible point of view of what should you have in your process.

And it shouldn't be difficult. It should never have been a challenge. But without an inspection on site, somebody bothering to go in to those areas, I don't believe that site would ever have sorted it out.

So given this sort of variable approach within the agencies, as you know different inspectors look at different things, and pick up on different topics, do you think this was relevant?

I don't think I was the best inspector by a long way, do you know what I mean, I /

I did my best to do a good job, but you know, I'm not a sterile's person. I wouldn't be brilliant on anything numerical, umm, you know, there's big gaps in terms of what I think I am competent at, that you should have people like me at least in all those companies.

You've not got them.

So it's knowing what you don't know is the key aspect?

Yes.

And they get too busy. I think the QP role uhh the way it's assessed I think its pulled in a certain group of arrogant-type people to be fair. I don't think they want to admit they don't know everything. And that is a worry. And then they just set peoples back up in the management teams and then they / you get this sort of, oh well, that's quality's problem, type of mentality. Well I don't blame the people who are focused on profit and customer service, I don't blame them actually, for trying to ring fence the responsibilities. There's a certain logic in there isn't there?

Exactly, umm, and that's what I found aggravating, because some of these places, it wouldn't have taken much to be compliant and they make it difficult, really difficult for themselves, because I think they are trying to make things too complicated. At the end of the day what do you really need to do? You really need to say what you're going to do and you need to do it and keep a record of it. It's not beyond like mega intelligence levels is it?

But in going back to the legal frameworks, I am concerned about the focus to risk-based and the weaknesses that that will engender. I was talking to an American company last week and they were saying, well, one of the questions was, bless them, umm, uhh, how did I think that the new European Annex 1 would impact upon aseptic operations, particularly in America, which is subject to the 2004 Aseptic Practices Rules. And I said look it shouldn't make any difference because America has adopted ICHQ9 through the modernisation of pharmaceutical manufacturing and therefore you're subject to doing risk assessments, minimise those risks through control strategies and ensure that you use current good manufacturing practice, which, by the way, means you should have RABS in all of your areas, you shouldn't be doing open processing and this sort of deathly silence came on the phone and you know this was to groups of like 35 people at a shot. Did five sessions and quite clearly they've got RABS-free operations and they are using the 2004 American guidance as a justification for doing that.

Doing what?

And they knew about ICHQ9. They knew about current good manufacturing practice. They knew the FDA had been raising issues. It's just madness.

Yes, so talking about the agencies then in particular, do you think the agency is set up / and obviously from your experience, is it an autocracy or a meritocracy, I mean, do they have the right people in the right roles? Are they using the right experiences to assess plants and processes?

The experience I have obviously is of the MHRA/EMA.

And I would say the inspectorate of the MHRA is really good. They have a very strong process for stopping people from joining now that are the wrong type of people and they've had that process since Lynne Byers put it in, what would it be, about 17 years ago, so the agency prefers to carry head count deficit rather than recruit the wrong people.

So personally I think now / there were a group of people when I joined that needed to retire and they have retired and I think the people that are there now are mostly sound, but of course, within the last five years, an awful lot of the people who are really good in my middle sort of five year block / so say for the first five years I was there were people who needed to retire, okay, not many of them, but one or two of them I would say, needed to just go. Then there was a five year block when I would say it was really / it was really strong. You think umm uhh / do you remember <redacted>

Yes. So when he was there was a strong group. You had / you had John <redacted>, you had umm / that group of people who were / who I think knowledgeable, but also did work hard, and took it really seriously, so that was a good period of time. And then, over the last five years, they've just / well seven years probably, they've lost huge amounts of people, and I don't know enough about the people they've recruited, but of those people I know they have recruited, they are good and they are strong, so I think they learnt a lesson of having the wrong type of person in there. They had a very umm good psychological evaluation when you joined and they've got a umm / like a targeted profile of the mentality of the people they want.

And occasionally they've gone outside of that profile and they have paid for it, so they've learnt not to do that, that you're better off not having umm / necessarily the / you know / you're better off without the wrong person quite frankly.

So as long as they stick to that, and I think they will, because the management team is still that same group, if you like, that / of the inspectorate, this is, umm, you know, I think it's probably alright, but umm, they are subject to massive change and they've got a big restructuring coming up again and they were always subject to being the inconsequential part of the agency, because within the agency, it's the assessors that matter.

So the relationship between industry and MHRA, in this country anyway, have you found that, in your experience, you know, now as an <redacted>, or previously working for have you found that to be a problematic relationship?

I'd question whether there is a relationship.

Is agency engagement sufficient?

I would say / but that's not what I'm thinking of when I say industry relationship. You're talking about specific companies that have asked for help and support and information.

Yes.

And, in those cases, it's brilliant I think.

Umm if you are building a new facility and you get the inspectors engaged to review your design, which they will do, umm, then those new site meetings, used to be Andy Hopkins did loads of them, and if you can get them to do them, umm, you know I think that's incredibly valuable.

In some big pharma, when there's almost visceral knee-jerk reaction, you do not talk to the agency, have you seen this?

Exactly, unless you absolutely have to.

And you have to go through God in America in order to give you the approval to talk to them.

And so?

So you know there is / there's two / when you said the relationship between industry and the regulators, I was thinking more in the context of the umm the committees.

And I used to attend the Blood Regulators Oversight type of meetings, where they tried to get all of the blood umm industry in uhh for those meetings and you just found it was always information push from the agency, very rarely anything from the blood industry, other than, you're being too harsh really and so I think for the pharma industry, umm, I never really attended those sorts of / there is a / you know umm / what do they call it / a umm / it's not an interested parties is it, it's uhh / umm / stakeholder.

Stakeholder meetings and I really struggle to see how industry would join in in those stakeholder-type meetings with the MHRA. I never attended the real medicines ones. But I think if you can get them to you know help you on an individual company basis for a new site or a new design or major changes that you want to make, umm, then good, but I think it is difficult to get those meetings. If you're looking at new products and product licences then you can pay for those technical meetings I believe.

Yes, you can.

And that's much easier umm but I think on the inspectorate side that's more of a challenge.

Why?

Because there aren't many inspectors at the end of the day.

Are there sufficient experts?

To get them to help you, from a technical point of view, it's really you know / it's not easy for them to give you that resource.

No, exactly. And if it's a fairly standard dry product site, they'd just say why aren't you using a consultant.

Which I think is a reasonable question.

So impact of limited resources?

Yes.

Talking wider field here, We have lots of imported medicines that come in to the UK, in to the E.U. Are there some areas of the world that give you more concern than others? So, for example, if I gave you / if you went to the chemist and were offered two types of naproxen, we've got one which comes from a factory in Bangladesh or we've got one that came from say Northern, which one would you pick and why?

I don't think I'd answer that question for a start, but what I would say. is I believe, if you went through the last 20 years worth of critical findings, I think you'd find more in America than anywhere else and we have deemed them to be equivalent.

Can you expand?

Aseptic processing in America in the 2004 Standard <redacted> owned a really big generics company in America and it was just a disaster and that site got closed. I can't remember the name of it now. Ben Venue maybe? Was it <redacted>?

<redacted>?

Might be <redacted>. Well you know / I think in terms of possibly umm historic compliance / and some sites I've been to in umm India they have just been great. Now how many of them umm were great, kind of because they were inspected so often and they just got really good at being inspected, I'm not really sure, how much of it was really like truthful and fair and / all the rest of it, was debatable. Equally I went to some which were terrible.

How many companies did you inspect where you felt you were having a full disclosure audit? Did you ever feel you had a full disclosure audit?

I think if you think that I think you're being very very naïve.

Can you expand?

I would say that there is a company in the UK that I thought / just relatively early on, I thought they dealt with me as a fellow professional, that they were open and honest and transparent with me, and on my third visit it became apparent they were withholding three quite significant compliance projects. Now they were a company that routinely phoned me between inspections and asked for help and advice and told me they were being you know really open and honest and all that kind of stuff and on the third visit I realised they'd got these three big compliance activities going on and I think from that moment on it changes how you view everywhere that you go to.

Please elaborate?

You know, but everywhere has to manage inspections. We used to go to a big international type company and they had a lovely guy in their warehouse who just burst in to tears when he couldn't find a sample in the retained samples. He was under such pressure from his management team and he was a nice guy, you know, and it made you realise how ghastly their management had been before you turned up on site.

How they also held you at the gatehouse, they would play silly games in the inspection, and they were one of the so-called sort of you know most ethical companies in the UK.

Have you seen in previous employers that there was a policy on managing inspections?

Yes.

And that included running the clock down?

Yes.

Such as prolonging meetings. Document retrieval. And if an agency spoke to any more junior members of staff, they were / afterwards they are interrogated?

Oh yes.

So I think umm you know that particular company that behaved particularly badly I'd asked for a document covering a particular topic and they bought me the single page from the procedure that had it. I was really cross with them and uhh / uhh / about three years later, <redacted> gave them a critical in their steriles facility. There was a party at the agency practically because they'd been so ghastly to the inspectors, everyone was just delighted that they'd got a critical, well, how dreadful is that for UK pharma that we are celebrating when one of the biggest companies in the world, a UK success story, is given a critical finding.

That's appalling.

You aren't going to quote me directly on that are you?

No, I'm not quoting anything directly, not at all.

You can't work together / you can't work together. I can't give / when I was in the inspectorate, I couldn't give them the answer.

(redacted)

What's really aggravating though. is you think you're dealing with a company in an open and honest way, right, that company that got the critical, at one point, we had to go as an agency inspectorate and spend the day with them, because the relationship had fallen down significantly, and they spent and this and that and the other and they were the big I am kind of thing and it became apparent that at one of their sites they were doing things that they'd not told us about and their inspector was furious and when you think about the cost of the inspectorate being at that site for the day, to have this sales pitch from a company we're meant to be regulating, I thought it was disgraceful.

The amount of value of the inspectorate in that room on that day was disgusting. It was a massive massive inappropriate use of the inspectorate.

Has the review process become warped?

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.

And at the same time told everybody how bloody marvellous they were and how good they were. They weren't good. They were like every other company umm / and I didn't trust them at all. And the sad thing is you'd be a fool if you did.

But that's not clear when you join the agency and when people try and explain it to you / I mean I came from what I understood to be an ethical company, largely, and I found it very difficult to believe that the companies I thought were the big boys in the UK, were going to be like that, I was so disappointed after I was given one page of a procedure (31:11) I took it personally for a really really long time.

Do you believe people become institutionalised in industry/agency and you end up believing your own publicity in the end?

Yes, yes.

That's very much the mentality you know.

Do industry try managing the inspectorate because they know the key areas, the key buttons to press and that's wrong, that's fundamentally wrong.

It is wrong, it is, but actually if you were in that same position and you had to get that product in, I mean, I don't think I would do it, because I couldn't bring myself to do it, but I can think of myself 20 years ago and I might have done it.

I had a boss who I was scared of quite frankly. If they told me to do something I probably would have done it.

Is there a political element within companies.

Absolutely. Well like I say this previous boss she scared me and uhh / I look back and uhh I don't know why I didn't leave earlier. She was evil, quite frankly.

And you know that there's many other people like that in many many companies.

Yes, exactly.

What about joint FDA inspections?

The ones I met I only did a few joint inspections and they were a waste of time because they were umm / they could have done them in an office in America, so that kind of threw me.

Umm in terms of uhh like <redacted>, who is the guy who did a lot of the data integrity stuff, he's as mad as they come, umm, and you know [laughs] he's like / okay, I mean / but he's right, but he is as mad as they come, and in being so he kind of lost the argument really and we're drifting back in to kind of a sort of high level oversight type of thing, but I mean he was very good, but obviously he had a bit of a nervous breakdown really and uhh you know you only need to write / read umm / where is it the book / right, Bottle of Lies.

Yes. It describes his nervous breakdown in that book and I've met him once and yes I see it <redacted>. I think he's <redacted>. He can only do labs and data integrity type stuff, if that makes sense.

That forensic interrogation?

Yes, and he does it brilliantly, and he's in to his computer systems, but you know, would he actually do a normal quality systems type inspection, probably not.

Umm but equally / at least he'd get out of the deviation system which you know these two people that I watched them for a week, at a company in the UK, they spent half an hour on site in the whole time they were there.

Come on [laughs] And that was the site where I found all the voids and the umm / and the / you remember I said there was a site where there was soil in it.

It was that site. And they spent half an hour on site. It was a huge site. So you know there's no point doing a risk based inspection on a site like that, you need to get in to the site.

Do joint inspections work?

I think from an American point of view we've accepted them for the joint inspection type of thing but a lot of sites we used to go to I don't think they were particularly inspected by the FDA, but their products are a medicine in the UK.

Can you expand?

Umm / so there were things like umm after-bite, which is a umm / if you've been bitten it's like a hydrogen peroxide liquid that you put on your skin after where you've been bitten, umm, it's an over-the-counter product in most of America, uhh, they had the main production site which was quite old, don't think they'd really qualified their water system properly, but frankly you are making a sodium hydrochloride but I / no it wasn't hydrochloride, it was umm / anyway, the liquid that you were making was quite extreme peroxide is it, peroxide, maybe.

Could be peroxide. And umm / but it was you know I don't think they'd really qualified the water system. The facility itself was a non-sterile site, had open drains underneath tiles, and when you / because no one was lifting the tiles because they'd been told to seal them, God forbid, umm, when we did lift them there was soil in there, so that was like in the filling room, so you know, uhh / so umm it was a site I don't think ever really got inspected by anybody meaningful from the FDA because for them it's an over-the-counter product and they didn't need to, so when you then applied European GMP, it's no good, but was it a critical site, no, because I can't really believe that that sort of product is ever going to cause umm more of a reaction than just what the chemical is in it.

Yes.

<redacted>

So without that knowledge and experience I think you'd struggle to be honest to be completely effective.

It was never going to be good enough?

No. And then I think another site I think of in America, it was a new application, and it was for an acne cream and the particular type of acne cream it was, it had in it, and in UK it was a medicine and in America it was a cosmetic, so I went to effectively a cosmetics factory in America. I cannot believe anyone had ever inspected it, I just / I don't believe, to this day, anybody could have done, because it was essentially a warehouse and the warehouse doors opened straight in to their filling area and so you were you know outside air. There was no clean filtered air anywhere. And so because of the European requirements they'd put a tent over a filling line as a clean room tent, an isolator over a line, and underneath this line was a huge open trench drain. I mean literally this sort of broad, this sort of deep, which went all the way around the warehouse, through their wash area, through all the fill tanks, and then underneath all of the filling lines, so it was black with mould.

But they'd got their tent on top of it so it was obviously providing clean filtered air there.

And I spoke to the guy who owned the company and I said why are you doing this? And they're like, well, you know, we've done work for this company, I said, but they are the marketing authorisation holders, they're not the ones that are going to get the negative press as a result of this application and the critical findings and the umm you know the statement of

non-compliance, that will come to your site, and at the time, nobody had said you couldn't withdraw applications during an inspection, and so they withdrew the application during the inspection because the end of day two I'd already got like a side / perhaps three sides of critical findings.

And I hadn't even started on validation which was / well I quite liked, as I told him, I mean I found cockroaches this big in their storage areas you know and umm / so uhh / you know talking to him I'm like why would you do this? You've clearly not really understood your whole site would be inspected. You thought I'd just go into your tent and say nice tent, thank you, and he was like yes, really. Why would you end up in that position?

Good preparation?

No.

Were they aware of what's required.

No.

Can you expand?

And it's that political / it's a different structure isn't it because of the cosmetic side of things and the fact that borderline products are different in different countries, I would say that was unhelpful from an industry point of view.

Yes, so if I could give you a magic wand to change how pharma is regulated and manufacturing to make it better, make it safer, and equivalent, what would you do?

I'd make the Head of Production responsible for compliance.

What's your thinking behind that?

It / if they were the ones who were ultimately responsible they wouldn't push things out just for profit or for customer service.

If I had one wish?

Yes.

One wish.

Yes

I believe in the independence of QA, don't get me wrong, but most companies they are writing the investigations as they are supposedly reviewing and approving them, but they are not, they are really driving what people have to do. I stood and watched a production man and a quality lady in America argue for about an hour and a half over classification of a deviation. They'd got a massive backlog of deviations. They did not have the time for that kind of conversation and the man from production had no idea what a mess they were in. I mean how could he not know?

It was terrible.

Umm but if he'd been responsible for it, I think you'd have had a different conversation. There would have been no conversation like that.