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Podcast: How the EU's new revised Annex 1, EudraLex Volume 4 (GMP), will affect the manufacturing of sterile medicinal products in the EU and U.S.

Presented by: Raj Pai, Josefine Sommer and Jay Jariwala

Podcast transcript	
Introduction	"The EU has revised its rules on Good Manufacturing Practice for sterile medicinal products." - *Raj Pai* "Sterile product manufacturing is probably one of the most complex types of manufacturing." - *Josefine Sommer* "There's no need to panic. This is not the first guidance that was updated and this will not be the last guidance that is updated." - *Jay Jariwala* From the international law firm, Sidley Austin, this is an exclusive podcast for readers of our new industry blog: GoodLifeSci, perspectives for the life sciences community. Keep listening for an in-depth discussion about how FDA's (the U.S. Food and Drug Administration's) new foreign inspections guidance matches up with the EU framework. Check out this interview and other important blogs on key industry topics at GoodLifeSci.com.
Raj Pai	Hello, everyone, this is Raj Pai. I'm a partner at Sidley Austin and the global leader of the Food, Drug and Medical Devices Compliance and Enforcement group at Sidley Austin LLP. Our team focuses on representing life sciences companies in connection with government investigations, enforcement proceedings, and litigation, particularly in connection with current Good Manufacturing Practice (GMP). It's my pleasure today to serve as the moderator for our podcast discussion on a brand new issue: the EU has revised its rules on Good Manufacturing Practice for sterile medicinal products. We're going to look at how this will impact all pharma companies, including those based in the U.S. Sterile injectables have been a key enforcement focus for FDA for years because of the risks of patient harm if they are solid. The publication of the revised EU Annex 1 (the Annex) has been in the works for a substantial period of time. This new standard reflects a significant update that, for the reasons we're going to discuss, will have a far-reaching impact. To discuss that impact, I'd like to introduce two of my colleagues who will walk us through answers to key questions about the Annex. I'll start with one of my newest colleagues, Jay Jariwala, who just joined Sidley in August.
Jay Jariwala	Thanks, Raj. Prior to joining Sidley, I spent about 14 years in the Agency [FDA] in various capacities, all in the GMP compliance and enforcement area. While doing so, I had the opportunity to work in different technologies, and one of them was aseptic processing. I was heavily involved in very complex situations, whether that be devices or drugs and, at the same time, I had an opportunity to serve internationally for two years, leading inspections. So I have seen this topic from the point of view of policy development and actual inspection and firms' operations.
Raj Pai	Thanks Jay. I'll now turn to my colleague Josefine Sommer who will help introduce the EU perspective. Josefine, why don't you tell us a little bit about yourself?
Josefine Sommer	Thanks so much, Raj and Jay for having me on this podcast. So I'm a European drug and device lawyer. I'm based in Brussels, just a few stones' throws away from the Parliament. And I counsel our clients on EU regulatory compliance, with a particular focus on GMP, which we'll discuss today, but also clinical trials and medical devices. In addition, I'm also an ISO 13485 (medical devices – quality management system) Medical Devices Lead Auditor.
Raj Pai	Thanks Josefine. We're going to talk about how GMP for sterile product manufacturing will be impacted by the new version of what we, in the compliance inspection world in the U.S., are calling Annex 1. I know in the EU, it's called EudraLex Volume 4. So let me start with the most simple question. What exactly is Annex 1?
Jay Jariwala	Annex 1: basically it updates the EU guidance on the manufacturing of sterile medicinal products within the EU. The new Annex was published on August 25 and the EU is giving about one year for its implementation. It basically reflects the changes in the regulatory and manufacturing environment, with an emphasis more on a holistic approach to the product quality, which is important for everybody because a holistic approach will ultimately reduce the quality issues that may result in significant actions, whether it's a

	recall, regulatory actions of those nature. And it integrates very well with the regulatory framework that has been put out and adopted across the world, such as quality risk management, pharmaceutical quality systems. And this harmonization is really good because now it brings this Annex 1 into the fold of the international regulatory harmonization environment and I'm excited about that.
Raj Pai	Thanks, Jay. We know that the publication of the Annex has been, as you noted, awaited for some period of time. Why is that?
Josefine Sommer	So, that's a good question. I think, as manufacturers will know, sterile product manufacturing is probably one of the most complex types of manufacturing. The work to revise this new Annex 1 started about five years ago, it's been in the works for a very long time. I think what we've ended up with here today is much more modern guidance, as Jay also mentioned, which takes into account some of the modernization which is also happening at ICH (International Council for Harmonisation) level over the past couple of years, in particular with respect to risk management.
Raj Pai	Makes sense. So let's get to a question a number of our listeners will be asking: how do pharma companies need to prepare now, with a year to go?
Jay Jariwala	Well, there's no need to panic. This is not the first guidance that was updated and this will not be the last guidance that is updated. In this particular case, I think the EU has provided until August 2023. Now that does not mean that we need to wait until August 2023. The work must begin now, so that we are ready when EU will expect those guidelines to be implemented. So, what I will do? First thing, you know, go through the Annex carefully. Look at and identify the gaps that are within your quality system that will present either change in the requirements, or new requirements, and identify those areas. Draw up a plan. Sterile product manufacturing in itself, as Josephine mentioned, is a complex process. Every change would have to be carefully evaluated, and sometimes it may also have an impact on the regulatory filings. With the ongoing production, things may take time to plan. Some of the changes, as I said, may need regulatory filing. So, the first step gap assessment: draw up a plan, see where gaps are and how we can close those gaps in a meaningful way by August 2023.
Raj Pai	That's really helpful, Jay. I think that gives us an idea of the long term way to approach this. I'm wondering if each of you can give us a specific example of one thing that companies need to do right now. Josephine, I'll let you go first.
Josefine Sommer	Yes, thanks. I guess the first example I can give relates to a new requirement about a Contamination Control Strategy, or CCS. I think many facilities will already in one way or another have such a CCS in place but it's, as Jay also mentioned, it's now a codified requirement. So, under Annex 1, facilities are now required to have a CCS or Contamination Control Strategy, which should define and identify all the critical control points of the facility and then assess the effectiveness of these controls. It should be done both at design, procedural, technical and organizational level. To Jay's point, you know, it could actually have an impact on the product filing as well. So, once these critical controls have been identified, the expectation in Annex 1 is that the facility will implement a monitoring plan or measures to manage these risks. And I think there is also some expectation that their effectiveness should form part of the periodic management review. I think many facilities already have this as an integral part but, again, now it's codified also in the EU. Perhaps what's particularly new about the CCS is that it's meant to be a singular document, basically serving as a point of reference for the critical control points and a way to demonstrate control within the facility. What you're going to ask is what should companies then do? Well, I guess they ought to start with what Jay already mentioned: start with current control plans, collect these, put them into one document and then start identifying and addressing the gaps per the Annex 1 requirements, as any risk assessment or gap controls with this will require input from many parts of the organization. And, of course, also as in any strategy, the CCS is a living document and should be updated based on data that's collected and trended and used by the facility.
Jay Jariwala	And if I could add a couple of more things that I found extremely interesting, there is new content on the barrier technology that is designed to prevent contamination, such as wraps or the isolator. Annex 1 doesn't go as far as mandating what to use but where, by the way of robust risk assessment, they are asking the manufacturer to look carefully at whether the barrier technology they are implementing is suitable for their existing needs and controls. And some of the other things: I think there is a major focus, as we already talked about, on the barrier technology and risk management. There's a focus on personnel controls, such as accounting and training.
Raj Pai	So I think, Jay, I think that that takes us in depth with regards to the document itself. I'll ask you and Josefine, I'll start with Josefine, what about the jurisdictions that are impacted by the revision: which jurisdictions are impacted?
Josefine Sommer	Yes, so I can speak from a European perspective. So clearly the new Annex will cover all manufacturers who manufacture products for the European market. And this is regardless of where the facility is located. So facilities, of course, located in Europe, but also in India or the U.S. If those facilities manufacture for the European market then they need to meet this standard. There may also be some impact even for manufacturing that takes place in Europe, if those products are exported, as

	there's a general requirement in Europe that products that are manufactured within Europe need to meet European GMP standards.
Jay Jariwala	Yes, and, you know, just to carry forward that thought: Josefine, the new Annex, as I was stating earlier, aligns extremely well with other regulatory authorities worldwide. FDA has its own aseptic guidance and there are facilities within U.S. that may be selling products in EU. So, as Josefine suggested, regardless of facilities location, facilities located in U.S. might also be impacted. Also FDA and EU regulators work together, I mean, there's extremely close collaboration between both regulators. They share information on the issues under their mutual recognition agreement. I believe, this particular Annex helps FDA as well. It's not only EU, I think. This Annex, in certain ways, helps FDA under the mutual recognition environment.
Raj Pai	Let's expand on that, Jay, because I think that's going to be a key point here. FDA makes a lot of decisions, they are evaluating and making decisions on sterile product manufacturing sites under MRA. How is that going to be impacted now with Annex 1?
Jay Jariwala	Yes, so let me start with a little bit on MRA. It's an agreement between EU and FDA. And what it essentially does, it allows sharing of information between the two authorities. One of the unique aspects of this agreement is FDA can consider inspections conducted by member state within their boundaries, and look at them and can take into account and consider them as an inspection for them. During the pandemic, FDA had to realize new ways, different ways, unique ways, to provide the oversight because of the lack of travel. So FDA may consider this for PII (professional indemnity insurance), PLI (public liability insurance) purposes, and now what's really interesting is with the revised Annex 1 there will be much more information available for FDA decision-making. As and when EU investigators start visiting facilities post-August 2023, they will be evaluating those sterile manufacturing facilities against the standards of the revised Annex 1 and that would provide FDA greater details about those facilities. Now sterile product manufacturing, as we know and as Josefine says, it's one of the most complex types of operation. This Annex, the alignment of the Annex, will help FDA to consider an inspection to be equivalent. To that end, it must also align with their own expectations. So, in the past, when FDA looked at those inspections by EU regulators, they might not have given them many aspects that they considered core to their evaluation of a sterile manufacturing facility. With the revised Annex 1, they may have greater details now, so this may have implications on the facilities that fall under MRA. Also, EU coverage will be much more comprehensive and will give FDA more detailed information about a sterile manufacturing facility. I also want to acknowledge that I do not anticipate FDA to change their inspectional strategy or reduce the surveillance inspections of sterile manufacturing facilities. However, I definitely believe that FDA will use this more detailed information obtained through MRA reports in a risk-based manner and prioritize the facilities for inspection.
Raj Pai	Well, that's certainly a point of impact that we'll need to be aware of and keep monitoring, and I think we'll be monitoring all of the impacts related to the MRA. So, thanks to this discussion, I think people have better awareness of what we might see going forward. Thanks to both Josefine and Jay for taking the time today to help provide that guidance. Very much appreciate it and I hope everyone was able to take that away from this.
Jay Jariwala	Thank you Raj for this topic. This is a great discussion.
Josefine Sommer	Yes, thanks a lot for moderating.
Raj Pai	Thank you all.