IPAC-RS
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IPAC-RS Regulatory Roundtable Series
A Conversation with US FDA: Perspectives in the Time of COVID-19
2 November 2020

The International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS) hosted a Regulatory Roundtable with representatives of the United States Food and Drug Administration (FDA) on November 2, 2020. Panelists included IPAC-RS Chair, Ms. Carla Vozone (Vice President Pharmaceutical Development & Licensing, Hovione), Dr. Richard (Rik) Lostritto (Associate Director for Science, Office of Policy for Pharmaceutical Quality (OPPQ)/OPQ/CDER/US Food and Drug Administration), Mr. Brian Hasselbalch (Deputy Director, OPPQ/OPQ/CDER/US Food and Drug Administration) and IPAC-RS Vice-Chair, Dr. Martin Oliver (Senior Vice President, Delivery Management DPI and pMDI Platforms, Vectura Ltd.). Mary Devlin Capizzi, Esq., IPAC-RS Secretariat, moderated the discussion.

The Roundtable discussion covered a range of topics that have been top of mind for the orally inhaled and nasal drug products (OINDP) industry during the COVID-19 pandemic, including the global supply chain, inspections, guidance documents and collaboration.

Dr. Lostritto and Mr. Hasselbalch shared insights from their experience in the early days of the pandemic, including the enormous effort to address the hand sanitizer shortage. They also highlighted the intense pace of work at FDA, especially during the first several months of COVID-19 (described as "trying to jump on a moving train" and requiring "very long and hard hours" by most). IPAC-RS recognized FDA's remarkable efforts, including the proliferation of an enormous amount of FDA guidance documents over the past eight months. FDA panelists also noted that while things have now settled down relative to March - June, the Agency had also had to respond to the heightened Congressional interest over COVID-19 related issues and to provide technical assistance as Congressional committees work on legislation.

A member of the audience posed a question to FDA regarding the CARES Act provisions and if they had been extended beyond the September 23, 2020 original date in the Act. FDA noted that Congressional dates are often difficult to achieve, but this is being worked on and takes time. IPAC-RS asked if FDA had identified areas where it needs to reach out to Congress to change the existing statutes as a result of this health crisis. Mr. Hasselbalch explained that Congress wants to know what it can do proactively to help FDA. Within FDA, many contribute to developing guidance but now many are also helping on legislation beyond GDUFA and PDUFA. There is a future-looking process, which is tied to a budget making process, as described in Circular A-19 -- government agencies can propose to Congress changes in statutes, see: https://www.whitehouse.gov/wp-content/uploads/2017/11/Circular-019.pdf. Once cleared through an agency and its department and OMB, it would then appear in the next White House budget proposal.

Ms. Vozone and Dr. Oliver shared perspectives from the OINDP industry. Ms. Vozone noted that for her company, Hovione, a leading Contract Development and Manufacturing Organization, it had been

critically important to work closely with customers and suppliers to avoid disruptions and manufacturing interruptions. Both Dr. Oliver and Ms. Vozone explained that speed had been paramount during COVID-19, especially in the clinical research context. They agreed that collaboration has grown over the last few months and there is a recognition that we are all in this together and that there is a sense of urgency in all that the industry is doing.

FDA panelists described how global supply chain problems are not new to FDA and that part of FDA's job is to provide pathways to the market, including accelerated or expedited reviews. In March 2020, Congress added legislation that requires a manufacturer to notify FDA of any interruption in the supply of an API – providing alerts quickly so that other suppliers would know when to step in. This has facilitated getting a product or a replacement to the market faster. FDA has also revisited policies to explore options within its regulatory framework. For pharmaceutical producers, a risk-based approach to changes per ICH Q9 and others guidelines have been helpful to prepare for supply disruptions. IPAC-RS leaders noted that the industry has demonstrated a remarkable ability to adapt by implementing extensive and accelerated measures such as remote audits to secure supplier approvals, ramp-up production and increase capacity. The pharmaceutical supply chain is complex, interconnected and global but also resilient. Risk management plans, contingency plans, multi-source and multi-site strategies have mitigated shortages. The existing vulnerabilities derive mostly from many years of delocalization and shift of pharmaceutical manufacturing to Asia (mostly China and India). India's temporary banning of some pharmaceutical exports created serious repercussions for the supply chain. This fragility was already known before COVID-19 and the measures to correct such unbalance are accelerating.

IPAC-RS asked FDA to comment on the investigational-drug supply chains for clinical trials and mitigating strategies considered by the Agency. FDA speakers indicated that for INDs, stability studies could be conducted in parallel with patient recruitment. For these studies, packaging and protection against oxygen and moisture are something to consider. The type of IND, e.g., active against COVID-19 – can bring additional considerations for expediting development. FDA noted that it works closely with sponsors. Dr. Lostritto explained that packaging is very important and stability testing should be run in parallel because it is not prudent to find out half way through the clinical trials that the drug product is unstable. In addition, clinical studies will likely take longer during COVID-19, and industry should prepare for that. Dr. Oliver noted that industry is focused on more robust packaging as well as remote clinical site monitoring and direct drug distribution. CROs also are responding to the pandemic with new ways to manage those situations. Ms. Vozone described IPAC-RS members' positive experience with remote inspections, in particular, with MHRA (UK health agency) and ISO certifications although it does demand more preparation time to collect documents ahead of time and to have a suitable technical platform, but overall resources are better utilized. All recognized that industry implemented efficient ways to connect with customers and regulators such as videos to show manufacturing areas, real-time video streaming of production areas and, as a general matter, there will be many learnings from COVID-19 that will bring positive and lasting improvement. For example, a hybrid inspection system using virtual remote inspections could be part of risk assessment frameworks going forward, especially for those producers who have established credibility and trust.

Mr. Hasselbalch noted that some of what is discerned in-person is hard to discern remotely. The full sensory perspective one receives when doing an on-site inspection, for example, people to talk to and the many things that occur during an in-person inspection, including questions that are asked on the spot because of what is observed may be absent in a remote inspection. FDA has had the authority to do evaluations remotely or in advance or in lieu of in-person inspections for many years but the scope and interest have expanded during COVID-19. Regulators around the world are exploring these options, some

very positively and some with mixed results. Pre-COVID-19 international collaborations such as the Mutual Recognition Agreement (MRA) partner reports, third-country reports from MRA partners, remote record evaluations, and pre-approval or pre-licensing inspections have proven to be helpful especially during COVID-19. Agencies are also relying more on the Pharmaceutical Inspection Co-operation Scheme (PIC/S) (https://picscheme.org/en/picscheme) inspections in areas where that is legally acceptable. FDA noted that if applicants are doing something new for which a pre-approval inspection will be needed, be ready with a live-stream video**.** Dr. Lostritto added that for newer devices, there are additional complexities, including data security and data integrity. He explained his concern with malware and ransomware, especially during a time of vulnerability when bad actors take advantage.

Ms. Capizzi highlighted a question from the audience relating to how FDA determines which sites would be audited remotely as opposed to on-site visits. FDA panelists noted that FDA is still thinking through some of that but expects to consider its experience in engaging with a given company/site, the quality of the responses received for application-related requests and remote records requests, and inherent complexity and novelty.

IPAC-RS asked FDA to describe how certain FDA initiatives had been impacted by COVID-19, including KASA. Mr. Hasselbalch explained that KASA had not been impacted by COVID-19 and is going ahead unabated. He noted that structured evaluations lead to faster decisions and that IT decisions are moving along as well. Ms. Capizzi asked for feedback on collaboration among regulators globally during the pandemic. FDA panelists noted that collaboration among global regulatory agencies had absolutely increased, especially in the areas of pharmacovigilance and CMC and also in dealing with shortages. Relationships with other regulators are essential - not just for inspections but also pre-licensing assessments. These strong relationships have become stronger.

Dr. Oliver shared his perspectives on technology transfer of analytical methods during COVID-19 and noted that they had been using video technology and remote working to do that. He highlighted that training people by video is becoming more important. He explained that the learning curve had been quick. In addition to a document providing evidence that a process has happened, there is now a visual aspect to that evidence. Mr. Hasselbalch shared his perspective on technology transfers and noted that ICH guidelines on risk-based approaches are helpful. He also noted that there may be more questions from assessors, *e.g.,* how you know your video modality is useful? Dr. Lostritto noted that digital technology transfers could raise concerns, especially when there are gaps in documentation. He emphasized that industry should take care to ensure all relationships are solid, documented and traceable, and avoid situations where the right hand does not know what the left hand did.

Ms. Vozone raised the topic of clinical trials for COVID-19 related conditions. She noted that there are more than two thousand active trials registered on clinicaltrials.gov, including 368 for respiratory drugs. Many are repurposed old drugs with the safety and efficacy profile established. The standard drug development pathway takes a long time, which we do not have right now and risk-benefit analysis should reasonably allow for a pragmatic drug development accelerated pathway for COVID-19. Dr. Lostritto noted that COVID-19, as almost all infectious diseases, will likely be with us for a while, although it may wax and wane. He explained that industry and regulatory agencies need to use risk-based approaches. There will not be a "post-COVID" world. There may be a post-pandemic but not post-COVID time -- that is the nature of infectious diseases.

Ms. Capizzi asked the FDA panelists if they wanted to highlight any specific guidances among the many issued in the past 7 months. Mr. Hasselbalch noted the FDA COVID-19 guidance on pre-approval and

surveillance activities and mentioned that FDA is working on another COVID-19 guidance, on the use of interactive tools and techniques. He called out Section 704(a)(4) of the statute, about how FDA expects to engage and how to use that information in its decision-making. A risk management plan guidance is also forthcoming and will impact many products, including OINDPs. Dr. Lostritto further described his work on a number of new guidances on shortages (*e.g.,* hand sanitizers, corticosteroids).

Ms. Vozone highlighted that many OINDPs, including inhalers and nebulization drugs, have saved the lives of many patients during this time. She noted that IPAC-RS members have collaborated regularly during COVID-19 and despite all the pressures of this time, the IPAC-RS Board and all Working Groups are engaged and making good progress on their initiatives. Dr. Oliver described examples of learning and sharing knowledge, and the importance of getting that knowledge out to clinicians and other stakeholders. IPAC-RS continues to lead in this area, and has done a lot of proactive work to keep the industry connected and to keep everything moving. Dr. Lostritto, who has worked at FDA for 25 years and has substantial experience in OINDPs, noted his background in industry. He acknowledged and appreciates that there is a pressure to get to clinical trials (from IND). He emphasized the importance of CMC efforts upfront so that even at the trial stage products would have a sufficiently long shelf life, because clinical trials are taking longer. It is important to make sure that the product performs well even while it is being developed and studied.

Ms. Capizzi conveyed a question from the audience, focused on whether remote audits performed by the FDA allow for conversation through a WebEx with the Agency after they have had time to review records. Mr. Hasselbalch explained that this is absolutely a possibility. It is possible that FDA would use a mixed approach of records requests and then ask to meet remotely to discuss findings (if any) and to evaluate a facility's operations using interactive technology. Different programs and applications could be evaluated on their own merits. Also, in the past, on-site inspections had to be limited to a small number of persons to manage travel and related expenses. With remote inspections, travel is not a barrier so more experts can be involved. It will not be surprising to see more expertise brought to a remote inspection compared to in-person.

The panelists pivoted to discuss how other countries may be relying on FDA to help them out with US inspections. All agreed that the MRA is working. As an example, Ms. Vozone explained that Hovione was involved with several NDA approvals that would require FDA pre-approval inspections (PAIs), which did not have to happen because of the MRA.

Dr. Lostritto provided an update on the CMC MDI DPI guidance, noting that the 1998 version was the first iteration. That guidance was not finalized and its development waxed and waned over the years. FDA issued a new version about 20 years later in 2018 and received several hundred pages of comments that has now been triaged. He explained that FDA is currently in the process of doing what is required - addressing every single comment and deciding whether the draft guidance needs to be changed or not, with an explanation of why. At the end of the day, FDA will have to decide whether the guidance has been revised enough to be published as final or to be re-issued as another draft. Many of the comments are cogent and a good number are similar, which is great. FDA has dedicated a number of personnel to working on the guidance, including writers and project managers. He noted that there is no timeline for the decision point yet as COVID-19 had put everything on hold, but he described the process to be moving ahead now. IPAC-RS confirmed that it is standing by and ready to help as needed.

On Behalf of IPAC-RS, Ms. Capizzi thanked Dr. Lostritto, Dr. Oliver, Ms. Vozone and Mr. Hasselbalch for their time and insights. She asked if each panelist could offer closing comments on what they see as a "silver lining" from this challenging time.

> Dr. Oliver: "The fact that we are having this session, putting faces to names, having a conversation, has been very helpful and we should carry this on. "
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> Mr. Hasselbalch: "We are in this together. Industry, regulators, healthcare professionals. We all have the same goal."
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> Ms. Vozone: "What we are experiencing underscores that we are moving towards positive improvement and acceleration of trends that will bring us to a better state sooner and also highlights the shared commitment by FDA and industry for high science and ethical standards."
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> Dr. Lostritto: "There is new interest and new life in risk-based assessments. We have discovered more expeditious, communicative and collaborative ways while letting the science lead us."

IPAC-RS will continue to host a wide-range of Regulatory Roundtables and welcomes feedback on each session as well as suggestions for topics top of mind for the OINDP industry.

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