Cross-industry organizations

IPAC-RS Regulatory Roundtable Series: A conversation with the US FDA: Perspectives in the time of COVID-19

Mary Devlin Capizzi, JD, MBA
Faegre Drinker Biddle & Reath LLP
On behalf of the International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)

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. The roundtable discussion, which is summarized in this article, 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.

The four panelists included:

- Ms. Carla Vozone, IPAC-RS Chair, (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
- Dr. Martin Oliver, IPAC-RS Vice-Chair, (Senior Vice President, Delivery Management DPI and pMDI Platforms, Vectura Ltd.)

The discussion was moderated by Mary Devlin Capizzi, Esq., IPAC-RS Secretariat.

Early stages of the pandemic

Dr. Lostritto and Mr. Hasselbalch shared insights from their experiences in the early days of the pandemic, including the enormous effort to address the shortage of hand sanitizer. They also highlighted the intense pace of work at the 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 the FDA's remarkable efforts, including the enormous proliferation of FDA guidance documents since March 2020. The FDA panelists also indicated that while things had settled down compared to conditions in March to June, 2020, the Agency also had responded to heightened Congressional interest in COVID-19-related issues and provided technical assistance while Congressional committees continued work on legislation.

US Congress

A member of the audience posed a question to the FDA panelists regarding the Coronavirus Aid, Relief, and Economic Security (CARES) Act provisions and whether they had been extended beyond the original date of September 23, 2020 in the Act. The FDA panelists explained that Congressional dates are often difficult to meet and take time to achieve but were being addressed. IPAC-RS asked if the FDA had identified areas where the Agency needs to reach out to Congress to change the existing statutes as a result of this health crisis. Mr. Hasselbalch noted that Congress wants to know what it can do proactively to help the FDA. Within the FDA, many contribute to developing guidance but now are also working on legislation beyond the Generic Drug User Fee Amendments (GDUFA) and the Prescription Drug User Fee Act (PDUFA). There is a future-looking process, which is tied to a budget-making process, (as described in Circular A-19) with which 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 the Office of Management and Budget (OMB), it would then appear in the next White House budget proposal.

OINDP industry perspectives

Ms. Vozone and Dr. Oliver shared perspectives from the OINDP industry. Ms. Vozone said 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 stated that speed has been paramount during COVID-19, especially in the clinical research context. They agreed

that collaboration had grown over the last few months and that there is recognition that we are all in this together and that there is a sense of urgency in all that the industry is doing.

Supply chain

The FDA panelists described how global supply chain problems are not new to the FDA and that part of the 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 the FDA of any interruption in the supply of an active pharmaceutical ingredient (API)—providing alerts quickly so that other suppliers would know when to take action. This has facilitated getting a product or a replacement to the market faster.

The FDA has also revisited policies to explore options within its regulatory framework. For pharmaceutical producers, a risk-based approach to changes per the International Conference on Harmonisation guideline Q9 (ICH Q9) and other guidelines have been helpful to prepare for supply disruptions. IPAC-RS leaders commented that the industry has demonstrated a remarkable ability to adapt by implementing extensive and accelerated measures such as remote audits to secure supplier approvals, and increasing production and capacity. The pharmaceutical supply chain is complex, interconnected and global, but also resilient. Risk management plans, contingency plans, and 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.

IND Studies

IPAC-RS asked the FDA panelists to comment on the investigational new drug (IND) supply chains for clinical trials and mitigating strategies being considered by the Agency. The panelists 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. The panelists noted that the FDA 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 halfway 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 observed that industry is focused on more robust packaging as well as remote clinical site monitoring and direct drug distribution. Contract research organizations (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 the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom and International Organization for Standardization (ISO) certifications. Although it does demand more preparation time to collect documents ahead of time and to have a suitable technical platform, resources are better utilized overall.

All of the panelists recognized that industry has implemented efficient ways to connect with customers and regulators, such as videos to show manufacturing areas and real-time video streaming of production areas. In general, 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.

Inspections

Mr. Hasselbalch explained that some of what is discerned during an in-person inspection is hard to discern remotely. Examples include the full sensory perspective one receives when doing an on-site inspection, talking with people and the many things that occur during an in-person inspection. In addition, questions that are asked on the spot because of what is observed may be absent in a remote inspection.

The 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.

The FDA panelists indicated that if applicants are doing something new, for which a pre-approval inspection will be needed, applications should be ready to do a live-stream video. Dr. Lostritto added that for newer devices, there are additional complexities, including data security and data integrity. He also discussed his concerns

about malware and ransomware, especially during a time of vulnerability when bad actors can take advantage. Ms. Capizzi highlighted a question from the audience relating to the way the FDA determines which sites would be audited remotely as opposed to visited on-site. The FDA panelists noted that the FDA is still making those determinations 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.

FDA initiatives

IPAC-RS asked the FDA panelists to describe how certain FDA initiatives had been impacted by COVID-19, including the Knowledge-aided Assessment & Structured Application (KASA). Mr. Hasselbalch stated that KASA had not been impacted by COVID-19 and is moving forward. He added that structured evaluations lead to faster decisions and that IT decisions are moving along as well.

Global regulatory collaborations

Ms. Capizzi asked for feedback on collaborations among regulators globally during the pandemic. The FDA panelists indicated that collaboration among global regulatory agencies had absolutely increased, especially in the areas of pharmacovigilance and chemistry, manufacturing and controls (CMC), as well as dealing with shortages. They indicated that relationships with other regulators are essential—not only for inspections but for pre-licensing assessments. These believe these already-strong relationships have become stronger.

Technology transfer

Dr. Oliver shared his perspectives on technology transfer of analytical methods during COVID-19 and indicated that video technology and remote working has been used. He emphasized that training people by video is becoming more important. He observed that the learning curve had been quick. In addition to a document providing evidence that a process has occurred, there is now a visual aspect to that evidence. Mr. Hasselbalch shared his perspective on technology transfers and observed that ICH guidelines on risk-based approaches are helpful. He also said 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.

Clinical trials

Ms. Vozone raised the topic of clinical trials in COVID-19-related times. She commented there are more than 2,000 active trials registered on www.clinicaltrials.gov, including 368 for respiratory drugs. Many are repurposed existing drugs that have established safety and efficacy profiles. The standard drug development pathway usually takes a long time. However, because conditions are different now, risk-benefit analysis should reasonably allow for a pragmatic drug development accelerated pathway. Dr. Lostritto observed 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.

Guidances

Ms. Capizzi asked the FDA panelists if they wanted to highlight any specific guidances among the many issued in the past seven months. Mr. Hasselbalch noted the FDA COVID-19 guidance on pre-approval and surveillance activities and mentioned that the 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, regarding how the 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 related to shortages (e.g., hand sanitizers and corticosteroids).

Role of IPAC-RS

Ms. Vozone highlighted that many OINDPs, including inhalers and nebulization drugs, have saved the lives of numerous patients during this time. She indicated 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 considerable proactive work to keep the industry connected and moving forward. Dr. Lostritto, who has worked at the FDA for 25 years and has substantial experience in OINDPs, mentioned his background in industry. He acknowledged and appreciates that there is pressure to get to clinical trials (from the IND stage). 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 a product performs well even while it is being developed and studied.

Audits

Ms. Capizzi relayed a question from the audience, focused on whether remote audits performed by the FDA allow for conversation through a web-meeting with the Agency after they have had time to review records. Mr. Hasselbalch remarked this is absolutely a possibility. The FDA may use a mixed approach, using records requests then asking 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. In the past, on-site inspections had to be limited to a small number of people in order to manage travel and related expenses. However, 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 the in-person process.

Other countries

The panelists also discussed ways other countries may be relying on the FDA to assist them with US inspections. All agreed that the Mutual Recognition Agreement process is working. As an example, Ms. Vozone noted that Hovione was involved with several New Drug Application (NDA) approvals that would have required FDA pre-approval inspections (PAIs), however those inspections do not have to take place due to the MRA process.

The CMC MDI DPI guidance

Dr. Lostritto provided an update on the FDA's CMC metered dose inhaler (MDI) dry powder inhaler (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. The FDA issued a new version about 20 years later, in 2018, and received several hundred pages of comments. Many of the comments are cogent and a good number are similar, which is beneficial. These have now been triaged. He explained that the 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, with an explanation of why. Ultimately, the FDA will have to decide whether the guidance has been revised enough to be published as final or reissued as another draft. The FDA has dedicated a number of personnel to working on the guidance, including writers and project managers. He indicated 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. IPAC-RS confirmed that it is standing by and ready to help as needed.

Closing comments

On behalf of IPAC-RS, Ms. Capizzi thanked Dr. Lostritto, Mr. Hasselbalch, Ms. Vozone and Dr. Oliver for their time and insights. She asked each panelist to offer closing comments about what they see as a "silver lining" from this challenging time. Their responses were:

- **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."
- **Mr. Hasselbalch:** "We are in this together. Industry, regulators, healthcare professionals. We all have the same goal."
- **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."
- **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 that are top-of-mind for the OINDP industry.

For more information, please contact the IPAC-RS Secretariat, The International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS), 1500 K Street NW, Washington, DC, 20005, US, Tel.: +1 202 230-5607, Fax: +1 202 842-8465, Email: info@ipacrs.org, Website: www.ipacrs.org.