The Shifting Global Regulatory Landscape
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Introduction: The Shifting Global Regulatory Landscape

By Renée Matthews

Welcome to the latest Regulatory Focus Article Series on the shifting global regulatory landscape. “Series” implies continuity and thematic connection, and we deliver on that again with this collection of articles. But little did we know when deciding on the theme just how much, and how quickly, the world would change. The COVID-19 pandemic has transformed our world, and not least, the global regulatory landscape. This series captures the transition from what we used to think of as normal to the disruption and uncertainty we face today. Most of the articles were conceptualized and written before the pandemic, when the author experts were aware of, and already addressing, the inherent global shifts and realignments in their areas of specialty. Their analyses and insights remain relevant and now provide a foundation for navigating the new, COVID-era regulatory realities. In addition, other articles address the impact of COVID-19 on regulatory affairs and offer hands-on guidance on how to ensure continuity despite the massive disruptions to manufacturing and regulatory processes. On behalf of my predecessor, Gloria Hall, I would like to thank the authors for their expertise and generous contributions.

The Regulatory Environment

The changes associated with the new European Union In Vitro Diagnostic Medical Devices Regulation (EU IVDR) and Medical Devices Regulation (EU MDR) are expected to alter the regulatory landscape significantly. In EU IVDR Changes Regulatory Landscape, regulatory affairs specialist Jordana Jayne discusses the new requirements for technical documentation, periodic safety reports, notified body changes, postmarket surveillance and vigilance, labeling and product traceability under the regulation. Jayne warns that the transition to EU IVDR, and the continuous maintenance activities it will require, will place an immense strain on manufacturers, especially those that do not already have devices on the US market.

The EU IVDR’s counterpart, the EU MDR, requires manufacturers, authorized representatives, importers and distributors to function as economic operators (EOs) with distinct but broader roles and responsibilities than under previous regulations. On behalf of regulatory experts Ludger Möller and Erik Vollebregt, Randolph Fillmore emphasizes the need for clarification in certain areas of the regulation. In Economic Operators: Roles and Obligations Under EU’s MDR, Möller...
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and Vollebregt argue for the elevation of role of EOs and offer some practical solutions for EOs.

The drug and medical device regulatory environment in China has changed significantly since the introduction of regulatory reforms in 2015, according to regulatory expert Alistair Davidson, and colleagues, in China’s Evolving Regulatory Environment: Special Report. The authors provide an overview of new drug research and development, improved drug approval and review processes, and upgrades in the quality of generic drugs in China. The authors assess how the clinical trial market has responded over the past few years and analyze the future of the China market.

Since the US Food and Drug Administration’s initiation of the orphan drug concept in 1983, Singapore, Japan, Australia and the EU have followed suit. In Global Orphan Drug Regulation, regulatory affairs consultant Julie Watchorn discusses the criteria for and regulation of orphan designation in major global markets. The author outlines the application process and incentives for orphan designation globally, focusing on several major markets including the EU, US, Canada and Japan.

The insulin market has been problematic in recent years. Part of FDA’s efforts to address competition concerns and rising patient costs includes regulating insulins as biologics, rather than drugs, which was effective 23 March 2020. The move also provides a regulatory pathway for the approval of interchangeable insulin. In The Changing Regulatory Landscape for Insulin, regulatory scientists Charity Duran and Kathleen Candando, review and analyze legislative efforts to control prices and the barriers to achieving that objective. They suggest that, unless those barriers are addressed, the current approaches may not be effective at mitigating rising insulin costs.

As the regulatory landscape evolves, the pharmaceutical and medical device industry needs to develop adequate systems to ensure strategy and intelligence is embedded into the product lifecycle for new products, according to biotechnology and regulatory science specialist Darin S. Oppenheimer and colleagues. In Adopting Regulatory Intelligence and Strategy to Foster the Evolving Landscape, they discuss creating and maintaining a regulatory intelligence program to enhance regulatory strategy and suggest a regulatory framework and best practice considerations for implementing intelligence strategies in lieu of a standardized approach or framework.

Going Virtual

FDA and the European Medicines Agency announced recently that some of their regulatory meetings would be held virtually during the COVID-19 pandemic. Communications experts Jim DiBiasi and Cindy DiBiasi warn that it can be much harder to communicate effectively in the virtual meeting environment. In Preparing for Virtual Regulatory Meetings, the authors discuss how sponsors can prepare. They emphasize the importance of following best practices, such as careful planning, rehearsing the presentation, having the right technology and ensuring everyone knows how to use it.

Tammy Pelnik, an expert in quality management and assurance, provides guidelines for manufacturers who need to set up a remote internal auditing process. In Optimizing Remote Internal Quality Audits, the author describes the different audit methods and how to schedule, plan and conduct the audit. Pelnik emphasizes that remote internal auditing can support ongoing operations and improve audit effectiveness during times of disruption or the normal course of business.

The EU’s planned transition from the EU Clinical Trials Register to the
EU portal and database system for submitting clinical trial information has been delayed several times and will be further delayed because of the pandemic. In *Electronic Platforms for Submission of Clinical Trial Information*, **Fed erico Bonacci**, a specialist in clinical pharmacology and forensic medicine, and colleagues present a follow-up to their 2017 article on the impact of the revised clinical trial regulations. They provide an updated overview of some of the main international portals and analyze their specific features, including functionality and user experience.

The internet and social media have opened new opportunities for advertising, marketing and promotion of pharmaceuticals and medical devices. FDA holds companies responsible for their websites and online activities, just as it does for other promotional material. In *Applying FDA’s Rules in the new World of Online Marketing and Crowd Funding*, **Suzanne Levy Friedman** provides an overview of the agency’s policies and regulations for the promotion of medical devices through websites and social media. The author looks more closely at internet and social media marketing and online preapproval communications, crowdfunding and where FDA may focus its enforcement activity in this newer context.

While these short summaries were meant to pique your interest, I hope you spend some time reading the full articles and benefit from learning about the authors’ shared experiences. This collection was meant to give you the information for building the skills for a satisfying, successful career in regulatory affairs and providing strategies for continual professional development. Your feedback is always welcome.

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EU IVDR Changes Regulatory Landscape

This article discusses new requirements for technical documentation, periodic safety reports, notified body changes, postmarket surveillance and vigilance, labeling and product traceability under the European Union’s new In Vitro Diagnostic Regulations (EU IVDR).

Introduction

Many regulatory changes are scheduled to come into effect in May 2022 as part of the new EU IVDR (2017/746). However, it likely that EU IVDR will come into effect a year later than planned due to the COVID-19 pandemic. Regardless of any delayed deadline, the new guidelines present significant hurdles for manufacturers, particularly for those who do not already have devices on the market in the US.

Through the In Vitro Diagnostic Directive (IVDD EU 98/79/CE) currently in force, some manufacturers have taken advantage of the flexibility embedded within the self-certified directive. For example, under IVDD a human papillomavirus (HPV), an IVD is considered a “self-certified” product. However, in the US, an HPV IVD is considered a premarket approval (PMA) product. Thus, substantial additional validation data would be needed to be generated for an HPV PMA submission to FDA. The validation data generated for a PMA, or 510k, depending on the product, can be used to supplement technical files to bring them into conformance with IVDR. The flexibility that existed within the IVDD self-certification requirement is why many manufacturers typically first launched in Europe, which allowed them to generate revenue while they performed the additional studies needed for market entry in the US. Although, it is likely that not all the requirements will be met with 510(k) supporting data alone, this offers a big advantage over manufacturers who are not currently selling products on the US market.

By Jordanna Jayne, MS, PhD
Under the new guidelines, there will be a dramatic shift from 10-20% to 80-90% of all IVDs sold in the EU that will require notified body approval. With this shift also comes the additional burden of having more stringent technical documentation requirements, more postmarket surveillance, increased vigilance requirements, periodic safety reporting and labeling and product traceability.

**Notified Body Changes**

The overhaul of the classification system in EU IVDR is one of the most significant updates to the directive. A new set of instructions will guide manufacturers on how to determine the appropriate classification for their device. The classifications range from Class A (lowest risk) up to Class D (highest risk). Until now, notified body review was required only for Annex II devices. Historically, Annex II devices have comprised roughly 10-20% of IVDs marketed in the EU. The remaining 80-90% of IVDs marketed in the EU gained CE marking through self-certification which requires no notified body activities. A shift in the classification system was needed to enable the implementation of a more stringent regulatory oversight system. Under the new directive, the proportions of IVDs that would require notified body oversight increases, with an expected 80-90% of devices being classified as Class B, C or D.

**Notified Body Shortages**

This drastically changing landscape means there will be increased regulatory burden placed on manufacturers and notified bodies. As the number of devices requiring notified body oversight increases, so will the demand for notified bodies. Unfortunately, as this demand increases, the number of notified bodies is diminishing. Thus far, only three EU notified bodies have been designated under EU IVDR (2017/746). These include:

1. BSI (Netherlands)
2. BSI (UK)
3. DEKRA Certification

Currently, 12 EU notified bodies have been designated under the EU MDR (2017/745). There is growing
concern throughout the medical device industry as manufacturers do not know when, or if, their notified body will be designated. Additionally, some notified bodies are choosing to cease certifying IVDs completely. This critical shortage means manufacturers need to do the work to prepare their submissions and engage with designated notified bodies as early as possible to mitigate the risk of market access disruptions.

How is Brexit further complicating notified body changes?

Numerous political impasses prevented “Brexit” from taking place as scheduled in March 2019. Brexit finally took place on 31 January 2020 under the new conservative party leadership, three and a half years after the June 2016 referendum where the British public voted to leave the EU. IVD manufacturers have been hoping that questions surrounding the UK’s departure from the EU, and thus also from European IVD Regulations, will shortly be clarified as negotiations are worked out. Roughly 30% of CE Marks come from UK notified bodies, according to MedTech Europe. Although industry has welcomed the designations of the three aforementioned notified bodies designated under EU IVDR, this is a dramatic decrease from the previous total of 21 notified bodies. Some of the larger notified bodies, such as Lloyd’s Register Quality Assurance and UL International (UK) Ltd., have chosen to leave or at least severely limit their involvement in the market. UL decided to cease operating as a medical device notified body in the UK, but still maintains some limited IVD activities. UL struck a partnership with the Polish notified body, Polskie Centrum Badan I Certyfikacji (PCBC), to protect customers from potential market access disruptions.

While the UK was once a keystone for European notified bodies, these significant changes as a result of Brexit uncertainties over the past year, come at a time when there is already great concern over IVD notified bodies being able to meet future demands when EU IVDR is finally implemented, whether on time or at a delayed date. Unfortunately, the situation and uncertainty is more convoluted. Although the UK has officially withdrawn from the EU, they are currently in a transitional period until the end of 2020 while negotiations are finalized and new rules take effect on 1 January 2021. This means that the pre-Brexit rules of trade, regulations and business are still in place until the transition period is over. However, once the transitional period ends, notified bodies will be required to have an office in an EU member state to clear devices under EU IVDR. This could mean UK manufacturers may need to clear IVDs in EU member states to be able to sell them in Europe and also back into the UK. Industry members are hopeful that regulatory programs can be harmonized between the UK and the EU to allow the sale of diagnostics into - and out of - the UK.

Technical Documentation Requirements

The new EU IVDR risk-based classification system introduces new required technical documentation. Higher risk devices, which fall into Classes C or D, are considered to be inherently higher risk to individuals and public health and, thus, must meet the highest level of conformity. The new EU IVDR risk-based classification system introduces new required technical documentation. Higher risk devices, which fall into Classes C or D, which are considered to be inherently higher risk to individuals and public health and, thus, must meet the highest level of conformity. In addition to technical requirements, Class C and D devices must adhere to more frequent surveillance assessments and stricter vigilance requirements.

To achieve CE marking, the majority of manufacturers of Class B, C and D devices will be required to provide the information listed below to their notified body for review. Class A device manufacturers must register with a notified body and document the information listed below; however, it will not be reviewed by their notified body prior to EU market entry.
Technical documentation, as listed in Annex II, includes:
• device description and specification
• reference to previous and similar generations of the device
• design and manufacturing information
• general safety and performance requirements
• benefit-risk analysis and risk management
• product verification and validation

Clinical performance can be demonstrated through:
• clinical performance studies
• scientific peer-reviewed published literature
• published experience acquired through routine testing

**Design, Production and Quality**
Device design and manufacturing information should facilitate understanding of all design stages. This includes a description of critical ingredients, instrumentation, software and manufacturing information on production, assembly, final product testing and finished device packaging. A description of the design elements that make a device intended for self-testing or near-patient testing appropriate for an indication should be provided. Suppliers, subcontractors and sites for manufacturing should be provided.

**Conformity**
*EU IVDR* requires that for at least 10 years after the last device covered by the EU Declaration of Conformity has been placed on the market, all technical documentation, the EU Declaration of Conformity and a copy of the relevant certificate must be available for competent authorities.

**Benefit-Risk Analysis and Risk Management**
While *IVDD* did not explicitly require manufacturers to uphold a risk management procedure, *EU IVDR* does. As laid out in Article 10, *EU IVDR* will bring into play new levels of risk management expectations for manufacturers (Annex I, Chapter I). However, for manufacturers already in compliance with EN ISO 14971, many of these requirements may already be met as ISO 14971 is the foundation of the *EU IVDR* risk management system. A continuous and iterative process for risk analysis is to be applied throughout the device lifecycle. Through
risk management, manufacturers are expected to identify known and foreseeable hazards, identify “reasonably” foreseeable misuse, identify hazards through postmarket surveillance and their frequency, and amend control measures as appropriate. All risks should be eliminated as far as possible and residual risk should be sufficiently communicated to the end user. This can be accomplished through the labeling. The benefits of the device should outweigh any residual risk remaining after risk management.

**Performance Evaluation Report**

*EU IVDR* requires manufacturers to document scientific validity, analytical performance data, clinical performance data and an assessment of the clinical evidence derived from the supporting data in the performance evaluation report (PER) in accordance with Article 56 and Annex XIII. These data form the backbone of a submission. *EU IVDR* explicitly says that PERs are expected to be continuously updated throughout the lifecycle of the device. Data obtained from postmarket performance follow-up (PMPF) activities are expected to be used to update the PER as per Annex XIII Part B and Article 79.

For Class C and D devices, PERs are expected to be updated throughout the device lifecycle as needed, or at least, on an annual basis. Class A and B devices also should be updated as needed. Although the directive does not explicitly state a timeframe over which Class A and B device PERs must be updated at a minimum. During an audit, manufacturers will likely require a strong justification if their documentation has not been updated in several years.

Much of the required data needed for the PER, such as analytical sensitivity, specificity, precision, limits of detections, limits of quantitation, positive predictive values and negative predictive value have long been required by FDA. Additionally, the PER needs to support the clinical utility of the device. For example, if a device has an intended use for detecting high-risk HPV subtypes, which significantly increase the risk of a patient developing cervical cancer or dysplasia, the clinical data in the PER must support this intended use. Manufacturers must demonstrate that their device is necessary to facilitate health care professional clinical decision-making as it relates to the intended use. This process will be much easier if clinical guidelines are already established.

**Postmarket Performance Follow-up**

Postmarket performance follow-up (PMPF) requirements are detailed in Annex XIII Part B. PMPF plans are to be a continuous process facilitating updating performance evaluation documentation and addressing postmarket surveillance (PMS) plans. Manufacturers are expected to proactively collate and evaluate performance data, scientific literature or other sources of relevant data for that device and its intended use. This requirement is intended to reinforce safety, performance and validity while identifying potential emerging risks. PMPF findings must be documented in the PMPF evaluation report used to update the PER to be incorporated into the technical documentation.

**Postmarket Surveillance and Vigilance Activities**

PMS and vigilance requirements implement a method for ensuring manufacturers are gathering postmarket data to continually assess benefit-risk ratios as real-world clinical data is generated (Article 78). Once again, *EU IVDR* are setting the expectations for these requirements to be met in a pro-active, not reactive manner and in a continuous fashion. During audits, notified bodies will assess whether company efforts to proactively assess postmarket data (and thus safety) were made sufficiently. Manufacturers can no longer take a reactive stance and assume there were no safety concerns just because no incidents were reported.
safety reports (PMSR) are applicable to Class A and B IVDs. As these apply to low risk devices, they are only submitted upon request and should be updated as necessary. PMSRs should summarize PMS data and provide a rationale and details on any preventative and corrective actions implemented.

Vigilance activities feed into the quality management system and risk management requirements. Vigilance activities include reporting serious incidents and field safety corrective actions (FSCA) (Article 82), trend reporting of incidents (article 83) and analysis of serious incidents and field safety corrective actions (Article 84).

**Periodic Safety Update Reports**

Periodic safety update reports (PSUR) are effectively an extension of PMS reports for Class C and D devices. The PSUR must be updated at least annually for each device or group of devices, if appropriate. Similar to a PMSR, manufacturers must summarize PMS data providing a rationale and details on any preventative and corrective actions implemented. The PSUR should include:

- conclusions of risk-benefit determination
- summary of postmarket clinical follow up (PMCF)
- sales volume of the device and estimates of the size of other characteristics of the population utilizing the device, plus usage frequency, if practically obtainable

Manufacturers of Class D devices should submit PSUR through the online electronic system. The PSUR is reviewed by their notified body and their review of the report, and any subsequent actions to be taken also are uploaded to the online electronic system. This information is available to competent authorities through that electronic system. For manufacturers of Class C devices, PSURs should be made available to the notified body performing the conformity assessment. Competent authorities may request PSURs for Class C devices if they wish.

**Changes to Labeling**

Labeling in Europe has always been challenging. The number of languages a manufacturer’s instructions for use (IFU) could need translated is a daunting task. Some manufacturers choose to do in-house translations and maintain the IFUs as controlled documents. Others opt to have distributors take responsibility for translating IFUs into the appropriate language(s). Chapter III of the directive requires that if a manufacturer has a website they must post labels and IFU and user manuals on their website and commit to keeping them up-to-date. This means that for those manufacturers who chose to give distributors the responsibility of translating IFUs, they must now collect the IFUs and make them available online. This practice can be logistically more challenging than it may sound. Because of this challenge, it is anticipated that more manufacturers will begin processing IFU language translations themselves rather than going through distributors.

A significant change coming into effect with EU IVDR is the information requirements for labeling. It is likely that upon review many manufacturers will find they struggle for space on their labeling. All labels must indicate that they are an IVD and contain a unique device identifier (UDI) as referenced in Article 24 and Part C of Annex VI. For sterile IVDs, or those which include sterile components, sterile packaging must be indicated as sterile, sterilization method noted and instructions included pointing the end user to the IFU should the sterile packaging be damaged or accidentally opened.

To conserve space, manufacturers can use internationally recognized symbols to reduce verbiage. The use of symbols also reduces translation needs. This is permitted within EU IVDR providing that symbols used conform with harmonized standards; where no harmonized standards exist, symbols must be described within the IFU.

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Traceability

The European database for medical devices (Eudamed) was planned to be implemented in May 2020. This implementation has since been delayed until May 2022 by the European Commission due to technical issues. The database will be simultaneously be launched for both EU IVDR and EU MDR. The Eudamed system will allow for easy traceability, improve transparency and coordinate information of products on the market in the EU. Once launched, Eudamed will contain:

- unique device identifiers (UDIs)
- notified bodies and certificates
- vigilance information
- clinical investigations
- performance studies
- postmarket surveillance

Conclusion

Changes associated with EU IVDR drastically alter the regulatory landscape in the EU. The work to be done by manufacturers to be in compliance is substantial. For manufacturers who have typically launched in Europe before launching in the US, this may no longer be a viable strategy as the burdensome requirements of EU IVDR come into effect. Notably, not only is a huge amount of effort required to transition from IVDD to EU IVDR, but manufacturers also will feel the strain of the continuous maintenance activities EU IVDR requires.

With the dramatically decreasing number of notified bodies designated under EU IVDR, manufacturers need to be prepared early. Notified bodies do not have to accept clients as they are private enterprises and, thus, some manufacturers cannot find a notified body to accept them. Additionally, due to the high demand, notified bodies are raising the price of their services. As a result, it is highly likely that a number of devices will be taken off the market, leading to shortages that may put at risk the lives of many EU nationals.
References


About the Author

Jordanna Jayne, MSc, PhD is a regulatory affairs specialist at the Hologic, Inc. diagnostic division based out of San Diego, California. She recently received her PhD in clinical and experimental therapeutics and her master's degree in regulatory science from the University of Southern California (USC) School of Pharmacy. She can be contacted at jgjayne2@gmail.com.

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Preparing for Virtual Regulatory Meetings

This article discusses how sponsors can prepare for their meetings with regulators in light of the recent FDA and EMA announcements that Advisory Committee meetings and Oral Explanations—as well as other “essential” regulatory meetings—will be conducted virtually. While this article specifies Advisory Committee meetings and Oral Explanations, the need for preparedness and tools described also applies to any virtual meetings that are held with health authorities.

Introduction

It may be hard for us to think of anything but the coronavirus right now. While many pharmaceutical, biotech and medical device companies are focused on developing COVID-19 tests, treatments and vaccines, there are thousands of teams working on non-COVID-19 products. Many of these therapies are also life-saving.

With FDA announcing they will hold virtual Advisory Committee meetings for some sponsors, as well as other virtual “essential” regulatory meetings, (EMA made a similar announcement in March), many companies are scrambling to prepare for this new reality. FDA has acknowledged the meetings would require more planning from their team. You can be sure that the same is true for companies that will be presenting virtually before these regulatory bodies.

The reality is that communicating effectively is just harder to do in this virtual meeting environment. But with PDUFA and MDUFA deadlines looming, business targets to meet and the urgency of getting their important treatments to patients—companies are preparing for virtual meetings with regulators. The challenge is how to do it effectively.
Preparing for Virtual Regulatory Meetings

Before and After COVID-19

Before COVID-19, many meetings between companies and regulatory agencies were conducted by teleconference. But there was an important difference between those virtual meetings and the ones taking place today. Before COVID-19 most, if not all, of the company team was taking the call in the same room. That meant team members could immediately put the telephone on mute during the meeting to quickly confer on strategy or project a slide or data. Now, they must find a way to do this with team members in different locations. Not surprisingly, the key to succeeding at this in a virtual environment is the right planning, the right technology and the right practice.

And virtual meetings are even more difficult for FDA Advisory Committee meetings and CHMP Oral Explanations, where there are many more stakeholders and participants involved.

Private Communication Among Team Members is Critical

Starting with planning: companies should have clear roles for each team member and decide in advance who on their team will speak and when. During the meeting, they need a system to signal when a team member wants to say something, and identify in real time what, if any, slides to show in answer to regulators’ questions.

Next, it is essential to run full rehearsals to make sure everyone knows how to execute on the day of the meeting. Rehearsing is critical because it’s often the little things that unravel a virtual meeting.

A key to success in virtual meetings is having the right technology system. And it’s not just Zoom. The best systems are a combination of proprietary tools and proven third-party virtual meeting software. These systems enable the moderator to instantly get a slide with data when answering a regulator’s question and importantly, be able to privately preview it before projecting it to regulators. This requires having multiple lines of communication during the meeting—one to project slides or data—a parallel system allowing teams to privately and quickly communicate with the speaker and with each other—and the direct line with the agency.

Just having the right technology isn’t enough. Virtual meetings bring with them an extra layer of complexity. Given all the other things company teams must accomplish during a regulatory meeting, they should take tech concerns out of the picture. That means a technology professional should run all tech during the practice and the day of the meeting. A professional can advance the slides and control the display of backup slides and enable the multiple technology threads simultaneously to accommodate the split-second private communications the team might need in order to be responsive to questions.

Preparing for “The Big Show”

FDA Advisory Committee Meetings and CHMP Oral Explanations

FDA Advisory Committee meetings and CHMP Oral Explanations are considered “The Big Show” in regulatory parlance. These meetings have always been held face-to-face—with Advisory Committee meetings also being open to the public.

Last month, CHMP started to hold virtual Oral Explanations. FDA is already notifying companies privately that they may have the option of going to a virtual Advisory Committee meeting. Where does that leave company teams? They must conduct their preparations virtually and they must prepare for a virtual meeting.

In this case, all the above guidelines apply—but preparation and execution are much more complex.

The biggest difference is the stakes. Advisory Committee meetings and Oral Explanations are usually convened because the product or issues around
Preparation for these meetings hinge on rigorous preparation and practice for the team. They must replicate the same realistic mock meetings they may have been used to doing in a face-to-face, but now on a virtual platform.

Preparation for these meetings hinge on rigorous preparation and practice for the team. They must replicate the same realistic mock meetings they may have been used to doing in a face-to-face, but now on a virtual platform. That means both the company team and the mock participants (external experts who mimic the regulators teams will be facing) need to be proficient in a virtual world. Companies should conduct a complete process and technology rehearsal with all the mock participants the day before the rehearsal so each external expert can make sure their internet connections, computers and technology are working, and that they know how to use them. It’s also important to have a clear and orderly process for the participants to ask questions of the company presenters—just as FDA Advisory Committee and CHMP members will—and when the rehearsal is over, to be able to provide immediate feedback.

Communications “Basics” Still Apply

Along with the new procedures to excel at virtual meetings, companies need to remember the same communications “best practices” they carried out for face-to-face meetings. If the meeting requires a formal presentation, presenters should script their presentation, test their content and delivery, identify the most likely challenging questions and develop credible, convincing answers.

Providing regulators with the right answer, the right data and the right slide under pressure in a virtual setting may be more complicated—but with focused training and appropriate technology, they can be successful. At the end of the day, that is a win for the companies, for public health and for the patients waiting to get these important therapies.
About the Authors

Jim DiBiasi, co-founder of 3D Communications, has guided more than 100 companies through high-stakes regulatory interactions—providing strategic and tactical communications counseling. He also coaches top executives, scientists and doctors in the pharmaceutical, biotech and medical device industries. DiBiasi is known for his ability to lead diverse teams and help them achieve their goals at decisive communications opportunities. As a co-founder of 3D Communications, he has been instrumental in developing the company’s proprietary processes, practical tools and innovative technology—all which have been built specifically to drive clear communications in both face-to-face and virtual FDA and EMA regulatory meetings. He can be reached at jdbiasi@3dcommunications.us.

Cindy DiBiasi, co-founder of 3D Communications, has built a reputation as a leading healthcare communications consultant, working with top executives at some of the world’s largest companies. Her strength is helping companies translate complex scientific and health economics information into interesting and relevant messages—and then coaching executives to clearly and confidently deliver that information in the face of objections. DiBiasi is a board member of the Consumer Healthcare Products Association (CHPA.) She has a Master’s degree from Boston University, Paris. She can be reached at cdibiasi@3dcommunications.us.

3D has authored two chapters on preparing for EMA meetings in the upcoming 9th edition of RAPS Fundamentals of EU Regulatory Affairs, scheduled for publication in June 2020.

This article provides tips and techniques for effective, risk-based remote internal quality auditing methods in a good manufacturing process (GMP) quality management system. The author covers the circumstance in which a “virtual” audit may be necessary or desirable as opposed to an on-site audit and discusses potential challenges when auditing off-site and how to overcome them. She emphasizes good communication skills, discusses the characteristics of various internal audit methods, how to prepare for remote internal audits and concludes remote internal auditing can support ongoing operations and improve audit effectiveness during unusual times or in the normal course of business.

Introduction

Internal quality audits are an essential aspect of the checks and balances in a medical device or pharmaceutical quality management system (QMS). Whether by design or by happenstance, manufacturers may need to start planning a remote internal auditing process. Fortunately, there are methods and techniques for bolstering the effectiveness of remote internal audit program and embracing the nature of remote audits can help a company not only maintain GMP compliance, but also discover hidden issues in the QMS. While remote internal audits are somewhat different in terms of logistics and planning, they can be equally insightful as on-site internal audits.

Internal quality audits allow a manufacturer’s executive management to determine if its established QMS is effectively supporting the organization’s overall quality objectives. Evaluating consistency of high-quality product and service delivery to customers depends...
on access to data and objective assessments of compliance. Medical device and pharmaceutical GMP compliance relies on internal quality audits as a means of objective self-assessment. Internal quality audits, also known as “first party audits,” entail independent evaluation of both compliance of established procedures to baseline GMP requirements and also effective implementation of the QMS.¹ For manufacturers with mature QMSs, internal audits reveal exceptional performance in instances where the baseline is surpassed.

Internal quality auditing is a regulatory requirement established in regulations, standards and guidance by FDA (Quality System Regulation, Guidance on Quality Systems Approach to Pharmaceutical CGMP Regulations), ISO 13485:2016 and ICH Q10, among others.²⁻⁵ Good practices in internal audits include planning for comprehensive QMS audits, independent evaluation of objective evidence, use of qualified, independent auditors, clear communication and assignment of audit follow-up/improvements to management of audited areas and formal reporting of audit results.⁶

While basic principles of internal quality auditing are universal, auditing practice varies widely across organizations. The auditing program in small, single-site companies is typically simple in comparison to large, geographically dispersed firms. Factors contributing to the design of the auditing program include scope and maturity of the QMS, product risk and variety of product lines, numbers of facilities, amount of outsourcing in development and in product realization and quantities and capabilities of staff. Risk-based QMSs account for these factors to define comprehensive, appropriate internal auditing processes.

Approaching auditing can be a matter of preference or necessity. When faced with the challenges of remote work for all but essential employees, a manufacturer’s quality management team has the option of incorporating remote internal audits, or delaying planned audits, unless remote auditing has already been implemented. Maintaining the planned audit schedule during a period of changing work practices may be the best choice. Internal audit results can offer objective proof that work is proceeding within the QMS and can highlight areas needing immediate improvement. Sometimes a rapid change in work practices, such as a quick decision to revert to most employees working from home, can lead to creative approaches to “make do” with less than ideal circumstances. In the moment of “making do,” performance may suffer. How will a management team have assurance that work is proceeding under the intended QMS controls? Internal audits offer a solution.

Opportunities to exploit remote internal auditing abound and the approach could prove to be both a benefit, from an audit effectiveness perspective, and a cost-saving approach for the company. However, a company’s QMS may need adjustments to adopt remote internal auditing, depending on how the audit program is defined and the capability of available resources.

**Basis for Remote Internal Quality Audits**

Various tools for working remotely, including teleconferencing, provide an opportunity for implementing remote auditing as a part of the internal quality auditing program. Remote auditing depends on availability of technology to support live, interactive conversation/ interviews and being able to review documents and data. Technology can facilitate eye contact between the auditor and auditee and support simultaneous viewing of static documents and dynamic data management systems. Current international auditing guidelines address remote audits, in contrast to historical auditing guidelines that preceded commonly-available telecon-
These developments illustrate an emerging change in the presumption that every audit necessitates an in-person, on-site experience. In a risk-based internal quality audit program, remote audits can play a substantial role.

A remote internal audit, sometimes called a “virtual” audit, is not the same as a “desktop audit.” Table A illustrates the differences between these audit methods. Throughout the remote audit, the auditor(s) is guiding the process, using risk-based criteria to direct the auditees to produce and display data and documents according to sound sampling principles. If operational area “walk-throughs” are a part of the audit scope, the auditor describes what to display and where. A remote audit will include dynamic adjustments to the auditor’s interview questions and subsequent records requests based on the information gleaned. Remote auditors are “following an audit trail” once the information presents a trail to follow. A desktop audit is most

Table A. Characteristics of Various Internal Audit Methods

<table>
<thead>
<tr>
<th>Remote Audit</th>
<th>Desktop Audit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contemporaneous, guided interview with auditee(s), using teleconferencing</td>
<td>Review of a documents versus a set of regulatory requirements conducted</td>
</tr>
<tr>
<td>Guided review of documents and data conducted with screen or file sharing</td>
<td>without Subject Matter Expert interaction</td>
</tr>
<tr>
<td>Records and data selected by the auditor using a risk-based approach and</td>
<td></td>
</tr>
<tr>
<td>sound sampling techniques</td>
<td></td>
</tr>
<tr>
<td>Guided walk through of operational work areas using appropriate live, mobile</td>
<td></td>
</tr>
<tr>
<td>technology (where appropriate to audit scope)</td>
<td></td>
</tr>
<tr>
<td>May incorporate aspects of desktop auditing (i.e., review some documents or</td>
<td></td>
</tr>
<tr>
<td>data in isolation to prepare for or refine interviews and records requests)</td>
<td></td>
</tr>
</tbody>
</table>

Every Internal Audit Method

- Risk-based process prescribed by procedure
- Approach is based on shared objectives of auditor(s) and auditee(s) to evaluate their own QMS according to the audit scope
- Scope and schedule pre-defined
- Conducted by independent, qualified auditor(s) in a professional, ethical manner
- Findings based on objective evidence
- Produce written reports
- May lead to corrections, corrective actions, preventive actions, or other follow-up (e.g., re-audit or changes to audit intervals)
often driven by a pre-existing checklist focused on procedural compliance, not on effective implementation of those procedures. A desktop audit can happen in isolation, whereas a remote audit cannot.

**Is the organization ready for remote internal quality audits?**

If the company has not previously employed remote internal quality audits, several aspects of organizational readiness should be considered. They include audit process definition, infrastructure and auditor competence. Each plays a role in supporting the ongoing effectiveness of an internal audit program.

Depending on the specificity of internal audit procedures, the QMS may need updating to address the company’s choices in adopting remote internal auditing. **Figure 1** illustrates some of the questions to consider related to QMS readiness. If any of the questions have a “yes” answer, the QMS needs to be updated to remove stipulations presuming a physical presence of auditors, auditees, documents and records.

If the company has a significant work-from-home culture, its infrastructure may be fully suited to remote auditing. A mature “tele-work” infrastructure might exist in companies with a geographically dispersed workforce, those that are virtual and rely on suppliers to perform most GMP activities, and those producing software as a medical device products and where the development and production processes are electronic and often cloud-based.

If virtual meetings are routine, or when a company has a fully electronic document management system, the infrastructure may be capable of supporting remote auditing. In other cases, the existing support for remote work, and thus for remote auditing, may be rudimentary. Infrastructure adjustments to support remote auditing could include:

- providing secure teleconferencing tools for staff
- ensuring staff have sufficiently robust internet services for remote access
- evaluating security for remote intranet access
- establishing a secure document sharing location for auditors
- updating policies and procedures related to document and data access, sharing, and related controls

If substantial infrastructure improvements are necessary, this may lead the organization to pursue a specific resource planning activity and prepare a quality plan for the infrastructure im-

**Figure 1: Considerations for QMS Readiness**

1. Are SOPs/forms written with verbage specific to “in person” auditing, “audit room selection”, “audit room preparation” or other descriptions of physical locations and activities that may not apply to remote auditing?
2. Are any required auditing tasks specific to a physical presence (e.g., clearing off whiteboards in an audit room)?
3. Are there any restrictions to document or record access in the SOPs that will be violated by a remote audit using teleconferencing technology?
4. Do audit schedules state or imply any requirements for in-person auditors?
5. For any quality records within audit scope: do SOPs stipulate paper records as the “official record” when operations have shifted to full reliance on electronic record keeping systems?
Optimizing Remote Internal Quality Audits

From afar, the auditor needs the ability to direct the auditee in a manner that results in a meaningful evaluation of the auditor’s selected information. Strong communication skills are an essential capability for remote internal auditors.

Audit Scheduling and Planning

Internal quality auditing is a risk-based process. As such, an audit schedule is typically based on several factors, such as product risk and complexity, maturity of the QMS, structure of the organization and previous audit results. Higher risk areas may have more frequent audits or larger audit teams assigned. Considering the remote audit method as another risk factor may result in more robust audit schedules. For example, if an organization is initiating use of remote audits for the first time, the schedule might start with several audits that do not include an area walk-through component, reducing the auditor and auditee’s technology start-up burden. In every QMS there are some processes where the audit entails interviewing staff who perform and manage the process, and evaluating the documents, records and data related to the process. Processes such as supplier management, corrective and preventive action, or management review are easily audited without observing a review board or executive management review meeting. These types of processes are good candidates for initial remote audits, as the primary difference with an on-site audit is the experience of the audit interactions through a screen. As long as the records and data are accessible remotely, either audit method applies in the case of a purchasing controls audit.

Similarly, an audit schedule could separate audit scopes in such a way that records-based activities take place separately from work area-based activities (i.e., sequentially). Alternatively, schedules might reflect a hybrid of remote and on-site audits or might establish audit teams which include both a remote and an on-site presence to reduce the on-site facility impact. Sequential or hybrid scheduling schemes may be necessary when auditing certain
product realization processes, such as production or product testing. When close observation of the work being carried out is an important aspect of the audit, but environmental controls prohibit introduction of additional technology to maintain environmental conditions, sequential or hybrid scheduling is an option. When an organization’s scope makes a fully remote internal auditing program impractical, a combination of methods is possible and, perhaps, even desirable.

Once the audit schedule is established, each audit needs a clear plan, including the purpose, scope, basis of requirements, timing, method and auditor role(s). Table B illustrates some additional considerations for remote audit planning when the auditor is a part of the site under audit, versus when the auditor normally works elsewhere and is unfamiliar with the corporate office or sister company staff.

Recognizing any additional logistical support needed to adopt remote internal audits is important for ensuring audits continue to be effective and objective assessments of the QMS.

### Audit Conduct

Remote audits introduce a few practical but atypical issues for an on-site audit. The first issue is in defining the “audit day.” Consider a two-person audit team with a very full one-day audit scheduled. Auditor A is on Eastern Standard Time, Auditor B is on Mountain Standard Time and the Auditee is on Central Standard Time. If the audit were happening on-site, the auditors would convene at the audit location at the designated time in the Central Time zone. Being spread out across the nation, how do the auditors now address their very full audit day? In this scenario, the concept of a “standard” workday will not apply for two of the three people involved. Clearly, coordination and flexibility are needed from the start of planning through audit conduct.

Second, enabling remote access to

<table>
<thead>
<tr>
<th>Internal Auditor With Site Familiarity</th>
<th>Internal Auditor Without Site Familiarity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auditor knows staff and can identify relevant managers and subject matter experts (SMEs), is likely to know where records are stored and how data is accessed.</td>
<td>Auditor needs support to identify relevant staff for the audit.</td>
</tr>
<tr>
<td>Auditor has access to calendar system and can schedule audit time blocks based on availability of all parties.</td>
<td>Auditor needs access to SME while planning to identify relevant record-keeping systems in advance of audit.</td>
</tr>
<tr>
<td>Auditees are familiar with auditor and can address subsequent scheduling issues directly.</td>
<td>Auditor needs support to coordinate between auditees and to schedule audit time blocks.</td>
</tr>
<tr>
<td>When auditor is remote and auditee is “on site,” auditor’s familiarity enhances any work area walk-through activities. Auditor familiar with on-site infrastructure and can help trouble-shoot if needed during audit.</td>
<td>Auditees need an intermediary or additional contact information to coordinate rescheduling.</td>
</tr>
<tr>
<td>When auditor is remote and auditee is “on site,” auditor may need additional information such as floor plans to support any work area walk-through activities. Auditees have all responsibility for on-site infrastructure trouble-shooting during audit.</td>
<td></td>
</tr>
</tbody>
</table>
proprietary information is a business risk requiring careful cybersecurity consideration. This includes determining how auditors will address technology issues during the audit. On-site auditors may have options available that are not prudent remotely (e.g., “I’ll just email this file to you instead” bears a different risk from a remote location). During an audit, the auditors need to be aware of inherent risks in their work, based on the audit method and tools.

Third, it is especially important to consider the practical nature of communicating across technology for hours a day. Scheduled, regular breaks become even more important when computer-mounted cameras have a smaller field of view and non-stop sitting is a requirement.

Impact of Remote Auditing

Depending on the structure and maturity of a manufacturer’s QMS, there could be a near-term remote internal audit “start-up cost.” Figure 2 illustrates the activities previously described that may be necessary to prepare for remote auditing where addressing any necessary changes requires resources.

Remote audits, versus the traditional on-site audit method, also present additional opportunities. For example:

- When faced with unplanned contingencies that render on-site internal audits impossible, remote methods support continued objective evaluation of QMS effectiveness.

- When operational contingencies result in rapid, unanticipated changes in key QMS areas (e.g., qualifying new sources of raw materials to localize the supply base), remote internal audits can provide agile, near-term assurances of adequate controls regardless of work-site restrictions and potentially reducing business and personnel risks in a rapidly changing situation.

- For manufacturers with geographically dispersed or substantially outsourced GMP activities, audits of product realization can be more easily scheduled based on a product’s lifecycle (i.e., from raw material through finished product distribution), regardless of the entity or location accomplishing each step in the lifecycle. Planning for an audit scope that spans product realization activities provides a broader evaluation of the interrelationships of QMS processes, departmental functions, suppliers and the information exchanged between them. This approach is often impractical and not considered when auditing in person.

- Similarly, manufacturers of software as a medical device (SaMD) products and providers of services that are delivered virtually (e.g., complaint handling, production and delivery of electronic products and product labeling) often rely solely on electronic tools to complete and record activities. Their QMSs are
Remote auditing can mitigate increased compliance risks of ongoing delays in planned internal audits.

good candidates for remote internal quality audits and present opportunities to reduce audit overhead.

• For corporate-level QMSs, a traditional internal audit focuses one site at a time. When remote auditing is adopted, internal audits might be scheduled to focus on a single QMS topic (e.g., design and development) but across multiple sites simultaneously. This approach may reveal systemic QMS deficiencies not evident when focusing on one site at a time.

• Larger companies with physically dispersed audit teams can realize significant reduction in travel time and expenses by incorporating remote internal audit into their program.

• With dispersed audit teams, including a technical expert or translator, whose contribution may be helpful for a few hours during an audit, is less costly for the company when travel is eliminated, and more efficient for the expert.

Conclusion
Sporadic geologic events, such as volcanic eruptions have grounded air travel in the recent past. At the time of this writing, the COVID-19 pandemic is causing extensive changes in work practices, with employees deemed non-essential required to work from home in many companies. These types of events can render typical in-person, on-site internal quality auditing impractical or impossible. Nonetheless, for a company that is continuing critical operations, internal audits are an invaluable tool in maintaining assurances of consistent QMS compliance. Remote auditing can mitigate increased compliance risks of on-going delays in planned internal audits. Further, additional benefits from innovative audit scheduling approaches, expanded options for involving experts to augment auditor teams, and reduced overhead are possible with remote auditing methods regardless of periodic crises or world events. Adopting remote internal auditing can support ongoing operations and improve audit effectiveness both during unusual times and in the normal course of business.
Optimizing Remote Internal Quality Audits

References


About the Author

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This article provides guidance for use of the European electronic platforms for retrieving and submitting information about clinical trials and compares them with other similar regional electronic databases, such as the US Food and Drug Administration’s MyStudies mobile app and Switzerland’s national platform, swissethics. The authors present an overview of some of the main international portals, available and under development, and provide an analysis of their specific aspects, including functionality and user experience, and a comparison of them, where feasible.

Introduction

As communication with regulatory agencies via electronic portals becomes more mainstream, regulatory professionals with varying backgrounds need to understand not only how portals differ from agency to agency, but that they serve a variety of purposes.

The European regulation for clinical trials on medicinal products for human use (Regulation EU No. 536/2014) has been updated and revised to assure trials are being conducted in the best interests of the patients. In the past, most transmission and submission of information was paper-based, but that method is no longer deemed adequate or appropriate. To facilitate electronic transmission of the relevant information and records, the European Medicines Agency (EMA) working on the development of an electronic portal for communicating relevant regulations. This was not a simple feat. The agency had vastly underestimated the complexity of such a tool, as evidenced by the multiyear delay in getting the portal operational (the latest estimate for its launch is the second half of 2021). Although this might seem a mere technicality, it is not, because the EMA, along with the European Commission, has stipulated
that the regulations can come into force only once the portal is operational. In general, a portal is a website that collates specific information from various sources and facilitates access to that information.

This article, a follow-up to our 2017 article,2 addresses the functionality and usability of the EU portal and database system, now known as the Clinical Trials Information System (CTIS), from the perspectives of various stakeholders, including ethics committees, principal investigators, and clinical research organizations, and aims to demonstrate the extent to which the portal meets user expectations and requirements. As a comparison, we have included a preview of the US Food and Drug Administration’s (FDA’s) MyStudies app.

From the EU Clinical Trials Register to the EU Portal and Database

The EU Clinical Trials Register is a publicly available database of information from the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT).3 Since its launch in 2011, the register has been consistently been improved to allow for greater public access to information on clinical trials in the European Union (EU).

The EU Clinical Trials Register allows searches for information on protocol and trial results for:

- interventional clinical trials for therapies conducted in the EU and the European Economic Area (EEA)
- clinical trials conducted outside of the EU/EEA that are linked to European pediatric-medicine development.

The register contains information on clinical trials started in the EU/EEA after 1 May 2004. In addition, it provides information on older pediatric trials covered by an EU marketing authorization.

Clinical trials conducted outside of the two regions are included if they form part of a pediatric investigation plan (PIP), or if they are sponsored by a marketing authorization holder and involve the use of a medicine in the pediatric population as part of an EU marketing authorization.

Data resulting from these trials are entered into the database by the sponsors and, once sponsors have validated the data, they are published through the register. EMA regulators use the register to obtain data on clinical trial protocols.

In 2015, the EMA management board created a new system architecture for an EU portal and the existing EU clinical trials register database, under the new clinical trial regulation, EU No. 536/2014.4 This provides opportunities for widening the usability and functionality of the database (Figure 1).6

The IT architecture for the EU portal uses the International Organization for Standardization for the identification of medicinal products (ISO IDMP) standard for all underlying databases or data warehouses. The ISO IDMP standard is based on the four domains of master data in the pharmaceutical regulatory processes: substance, product, organization and referential master data (SPOR).7

The portal system consists of three databases and one underlying data warehouse. The first database is used as a workspace where the sponsors and member states can work on draft versions of submitted documents. The results are then transmitted via the EU portal to the EU Clinical Trials Register database, where they can be viewed. The third database is used exclusively for reporting trial safety information.9 Still, the repository is synchronized with the data warehouse (Figure 2).

The data warehouse is used for combined reporting purposes for the EMA, EU member states and the European Commission. Sponsors and the public can only view predefined reports.
Since June 2019, the project has been using a new agile, iterative delivery model, whereby users work on a planned and predefined number of items within fixed, four-week periods of time known as “sprints.” Goals are set for each sprint cycle, and once the goals have been met, the information can be released. Sometimes, several sprint cycles are needed to refine the information before the goals are met.

The latest release within the agile delivery model was successfully validated in December 2019. The release, which was originally nominated by member states, sponsor organizations and European Commission product owners, enhances functionality within the portal—or Clinical Trial Information System (CTIS)—relating to submission of and access to data, data transparency, assessment of the process, management of user access and user oversight.1

The CTIS will contain information on clinical trials in the EU for which applications have been submitted under the framework of Regulation No. 536/2014 or that have been transitioned, at the end of transition period, from current legal framework (Directive 2001/20/EC). There has been some progress with the implementation and the validation of the IT infrastructure and framework in recent years. However, it has become clear that there will not be a direct link between the EU portal and the FDA’s MyStudies app.10

The intention instead is to create a link with the World Health Organization’s (WHO’s) International Clinical Trials Registry Platform (ICTRP) and to populate CTIS data onto ICTRP, as is currently done with the public version of the EudraCT database.11

In December 2019, EMA management board agreed to commence an audit of the system in December 2020, following an audit readiness assessment by the nominated product owners, the EMA, and the IT supplier.

The aim of the audit readiness assessment was to identify critical business blockers, and it resulted in
Electronic Platforms for Submission of Clinical Trial Information

Figure 2. EU Portal and Database Scheme

MyStudies is an open-sourced platform that can be downloaded on the GitHub software development platform. (It currently cannot be downloaded from the Apple's App Store or the Google Play Store.) After downloading the app, an organization can customize it to meet the needs of the organization. FDA is currently engaged in two demonstration projects using the MyStudies app with the LimitJIA trial and the CARRA registry. Both organizations will be releasing their rebranded app in the future.

There are no demonstrations available for download, but it is recommended that users watch the FDA MyStudies webinar on the app.

FDA contracted with Harvard Pilgrim Health Care Institute to develop the app, and Harvard Pilgrim, in turn, subcontracted with Boston Technology Corporation and LabKey to codeveloped the app. There are no FDA guidelines on using MyStudies, but the agency recognizes that, because the software is open source, organizations may use the software if they so wish.

The MyStudies system has an interface that could allow an external

an updated plan outlining the items that still need to be developed, or fixed, for audit. The product owners will work with the EMA and the supplier to analyze and design the items in the first few months of 2020 to ensure efficient delivery.

The FDA MyStudies App

The MyStudies mobile app is available for free. It is designed to facilitate the direct input of “real-world data” by patients, and can then be linked to electronic health data supporting traditional clinical trials, pragmatic trials, observational studies and registries.

Various types of research trials can be supported on MyStudies, including, but not limited to, clinical research trials, observational studies and registries. Private and public organizations can use the app, which can be uniquely customized. The codes in MyStudies are open and comply with the US Health Insurance Portability and Accountability Act of 1996 (HIPAA). Furthermore, informed consent and qualitative data, such as questionnaires, can be obtained from the trial participants more efficiently than is the case with paper records.
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For those interested in using or further developing the MyStudies app, it is recommended they:

- Test the new release for FDA MyStudies GitHub with the agency’s IT support department.16
- Read the instructions on the Google cloud about expanding the MyStudies platform.18
- Note that the FDA is developing a four-part series of guidance documents for patient-focused drug development “to better inform medicinal product development and regulatory decision making.”19

The MyStudies app will facilitate the collection of real-world evidence through mobile devices and expand the diversity of information for clinical trials.20

Unlike the EU portal, which is a mandatory interface for the submission of clinical trial data and documentation, FDA’s MyStudies app is, in general, a voluntary-use technical tool aimed at enhancing the collation of real-life, evidence-based data in clinical trials.14,18,19,21-23

Research Ethics Committees: EUREC and the Local Network in Italy

The European Network of Research Ethics Committees (EUREC) is comprised of the national research ethics committees (RECs), associations or groupings in European countries.
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We mentioned in our 2017 article that the network published the new Regulation No. 536/2014 on clinical trials on medicinal products for human use, which repealed Directive 2001/20/EC.

Concerning the European portal and database, EUREC has no official update from the EMA expert group that is following this project.22-23

All the materials for training in research ethics and regulation are available on the EUREC website.24

Each European country has a national network of local ethics committees that vary in organizational structure, competences and activities.25

While it is not possible to provide an overview of each country’s network, we will focus here on the Italian Drug Agency, as an example. Figure 5 shows the agency’s official national register of clinical centers and ethics committees.26

The Italian government passed Law No. 3 on 11 January 2018, which allowed for important changes in the procedures for the authorization of clinical trials (article 1) and the organization and operation of ethics committees (article 2).

One particularly important provision of the law is the establishment, within the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA), of the National Centre for the Coordination of Regional Ethics Committees for Clinical Trials of Medicines and Medical Devices for Human Use.

According to the law, the center:

• is responsible for the coordination, guidance and monitoring of the assessment of the ethical aspects concerning clinical trials on medicinal products for human use performed by the local ethics committees
• intervenes, as requested by individual local ethics committees, to provide support and advice
• may be involved in procedures regarding the evaluation of clinical studies that require review after adverse event reports
• monitors the activities performed by the local ethics committees and reports breaches of the terms set out in Regulation No. 536/2014
• suggests that the ministry of health suppress noncompliant local ethics committee in cases of inertia or failure to comply with the terms of the regulation
• provides general guidance in the interest of procedural uniformity and compliance with the terms for the assessment of clinical trials on medical devices and medicines for human use

To date, the ethics committees have not harmonized with the EU clinical trial portal and database or CTIS. Harmonization refers to having a single submission for authorization of a clinical trial to a national competent authority and ethics committee and for public registration in the primary register of clinical trials.27

Managing Clinical Trials Through a Variety of Clinical Platforms

In Europe, submitting information for a clinical trial has become increasingly standardized within the last 25 years. While harmonization of submission steps within the member states of the European Union was one of the major goals of Directive 2001/20/EC, and especially Regulation No. 536/2014, there are still some issues, such as patient-informed consent, that remain under the governance of locoregional authorities, conducted mainly by ethics committees.

Therefore, submitting for clinical trials using pharmacological substances or advanced therapy medicinal products (ATMP) is a two-step procedure in most of the European member states and as well as non-EU states, such as Switzerland, requiring submission to local ethics committees and medicinal agencies, such as the EMA for Europe or Swissmedic, the Swiss Agency for Therapeutic Products.28 With the
change from paper-based to electronic submission, researchers hoped to reduce their administrative workload and to be able to submit simultaneously to local and superordinate agencies through a single-entry portal. That would, however, presuppose a nearly complete harmonization between ethics committees and medicinal agencies, as well as a crossover between ethics committees and medicinal agencies of member states.

As we have already discussed, at least for the ethics committees, harmonization has not yet been attained in Europe. Because Switzerland is not an EU member state, its relationship with the EU is regulated by bilateral treaties that explicitly do not subordinate the country under the governance of the EMA. Switzerland has subsequently come up with a national platform, called swissethics, that serves as a gatekeeper for all clinical protocols that will be evaluated by one of the seven ethics committees, depending on the region of interest. According to Switzerland’s federal administration, there are several ethics committees representing different cultural and linguistic regions within Switzerland. The platform also serves as database for national and international legislation, provides information about training in good clinical research practice, and provides templates for different types of documents, such as patient-informed consents, recruitment of study participants, or insurance. Completed trial documentation can easily be uploaded to the platform for consultation with the leading ethics committee and correspondence with the principal investigator or the national coordinating center. In the case of multicenter trials, it is possible to submit to one or more of the Swiss ethics committees.

Although swissethics’s harmonization with the various ethics committees is working fairly well, documentation for clinical trials is not posted directly and simultaneously to Swissmedic, the national competent authority.

Articles 80 and 81 of the Regulation No. 536/2014 have assigned the EMA to create an EU portal and database that is “technically advanced and user-friendly so as to avoid unnecessary
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one of the challenges for the EU portal will be to build up a common, harmonized frame that accommodates the differences between classic pharmacological products and ATMPs, which include gene therapy, cell-based therapy (which may be completely “cell-free”) and tissue-engineered structures (e.g., patches or other tissue).

work.” That goal is easily achievable when submitting for a monocentric, national trial. However, the process is considerably more complex for submission of a multicenter or international clinical trial carried out in several countries, some of which are EU member states and others, not. This may be especially challenging for public sponsors if they are not supported by professionals trained in facilitating the submission of multicenter trials globally.

The BAMI trial30 is an excellent example for demonstrating the complexity of the submission process to be by public sponsor of ATMP.

Especially in complex situations, as was the case for the BAMI trial, the voluntary harmonization process was quite time- and resource-consuming and was possibly responsible for delays in patient recruitment, as has been documented by Christine Hauskeller.27 In such situations, even electronic platforms for submission of protocols for clinical trials may not help in overcoming administrative hurdles. In the case of the BAMI trial, the difficulties were likely due to the lack of common, harmonized standards for the submission of ATMP-based trials.

One of the challenges for the EU portal will be to build up a common, harmonized frame that accommodates the differences between classic pharmacological products and ATMPs, which include gene therapy, cell-based therapy (which may be completely “cell-free”) and tissue-engineered structures (e.g., patches or other tissue). In addition, all types of ATMPs may be combined with devices such as a tissue-engineered cardiac valve prosthesis. This heterogenic group of different types of ATMPs cannot readily be compared with classic pharmacological drugs, therefore, another level of harmonization needs to address clinical trials with advanced therapies for an as-yet unmet need.

Until that goal has been achieved, from the viewpoint of a public sponsor, the ideal trial portal would be a centralized platform serving as distribution tool from where all locoregional ethics committees (as well as all superordinate national or European authorities) may obtain, revise, comment and finally accept or decline clinical trials for all of Europe.

Conclusion

The EU portal and database project will merge the interests of sponsors, locoregional and national authorities with the technical and regulatory requirements of the EMA.

In an article comparing EMA and FDA decisions for new drug marketing approvals (NDAs) during 2014-2016, Kashoki and colleagues reported that the agencies had concordance in 91%-98% of NDAs.31 The authors noted that “divergence in approval decisions, type of approval, and approved indication were primarily due to differences in agencies’ conclusions about efficacy based on review of the same data or differing clinical data submitted to support the application. This high rate of concordance suggests that engagement and collaboration on regulatory science has a positive impact.”

Clinical Trials Information System (CTIS). CTIS will contain the centralised EU portal and database for clinical trials foreseen by the Regulation.

The EMA is in the process of developing a database system, the CTIS, that will incorporate the centralized EU portal and database for clinical trials overseen by Regulation No. 536/2014. The database is tailored for specific European regulatory compliance components, which are not necessarily the same regulatory requirements as those of the FDA. Despite the differences in local regulations, storage components of the FDA MyStudies system API layer conveniently allow external systems, such as the CTIS, to retrieve data from MyStudies, allowing the information technology integration with the CTIS. Additional layers of regulatory components can be added per EMA regula-
Electronic Platforms for Submission of Clinical Trial Information

This is a crucial component that could aid pharmaceutical companies warranting approvals from different agencies, such as the EMA and FDA. Despite best efforts from the EMA and service providers, there is to date no guaranteed date for the correct working of CTIS. Consequently, the clinical trial regulation cannot come into effect as the mandated portal is unavailable. However, the FDA’s smart and easy-to-use MyStudies app is already available and subject to continuous improvements and updates.

The complexity of these electronic platforms is a challenge for regulatory affairs experts and will require demanding investments for pharmaceutical companies and public sponsors, such as the hospital research centers. This article has provided a preview on the possible scenarios in coming years and has attempted, as much as possible, to simplify the technical and information technology language. It is undeniable that the existing nonhomogeneities in the organization, structure, competencies and activities of the ethics committees in several EU countries, and more generally, differences in the matter of health legislation, limit the implementation of the EU portal and database for clinical trials.

The authorization and oversight of clinical trials remains the responsibility of member states, with the EMA managing the CTIS and supervising content publication on the public website. The EU regulation introduces a new procedure, new timelines, and revised application content, and although it may increase or decrease the overall timelines in some submissions, it will bring with it increased predictability for clinical trial start-up in the EU (Figure 6).

Figure 6. Approval Application Process
Significant changes are coming for competent authorities, ethics committees, and sponsors:

- At the member state level, ethics committees and competent authorities will need to agree on how to work together to achieve the review outcome within the required timelines.
- At the EU level, member states will need to agree how to work together to achieve what is required to complete the application review.
- Industry clinical trial sponsors will need to prepare to confirm country selections without negatively affecting planned study start-ups (i.e., avoiding multiple applications to add member states), respond to application review queries within shorter timelines, and manage changes so they can be submitted when needed, rather than waiting for an ongoing application to be completed.32

Acronyms

- Clinical Trial Information System (CTIS)
- European Economic Area (EEA)
- European Medicines Agency (EMA)
- European Union (EU)
- Food and Drug Administration (FDA)
- International Organization for Standardization for the identification of medicinal products (ISO IDMP)
- Pediatric Investigation Plan (PIP)
- Substance, Product, Organisations and References (SPOR)

References


Electronic Platforms for Submission of Clinical Trial Information

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Global Orphan Drug Regulation

By Julie Watchorn, RAC

This article discusses the criteria for and regulation of orphan designation in major global markets. The author outlines the application process and incentives for orphan designation globally with a focus on several major markets including the European Union, the US, Canada and Japan. She explains variations on the criteria for orphan drug designation in each region as well as application requirements.

Introduction

Orphan Medicinal Products (OMPs) are medicinal products indicated for treatment of rare or life-threatening conditions affecting a very small proportion of the population. The rationale for the concept of orphan designation was to encourage development of medicinal products for rare diseases which may not always generate a high enough commercial value for a sponsor to develop and market without support or monetary incentives.

The US Food and Drug Administration (FDA) initiated the orphan drug concept with the 1983 Orphan Drug Act, after which Singapore, Japan and Australia followed suit, with the European Parliament adopting the European Union (EU) Regulation on Orphan Medicinal Products (Regulation EC No. 141/2000) in December 1999. Since its introduction, a large number of medicinal products have received orphan designation worldwide, with 1668 current orphan designations for various products and indications in EU with 133 having received marketing authorization at the time of writing. In the US, 4461 currently active orphan designations have been granted by FDA at the time of writing with 839 having received marketing authorization.

The Application Process

A sponsor can apply for orphan designation at any stage during drug development prior to submitting the marketing authorization application. A valid submission containing all speci-
fied requirements will then be reviewed by relevant agencies and an outcome provided to the applicant.

As seen by the first two arrows in Figure 1, a sponsor applying for orphan designation in EU will submit a request for orphan designation to the European Medicines Agency (EMA) and to be assessed by EMA’s Committee for Orphan Medicinal Products (COMP). If successful, the sponsor may be able to benefit from protocol assistance and other incentives, such as fee reductions in the EU, to assist the sponsor in getting to the stage of submitting their marketing authorization for approval. The orphan designation submission in EU should contain the application form with details on the active substance, proposed indication, product related details, sponsor information and relevant manufacturer information. The applicant also should provide the information required for section A to E, which consists of a description and prevalence of the condition, potential for return on investment, other methods for diagnosis, prevention or treatment of the condition and a description of the stage of development. The orphan designation submission must be made by defined monthly deadlines, which are aligned with planned COMP meetings in which the orphan designation requests are discussed. An opinion will be reached by COMP within 90 days of the start of the procedure. However, the opinion could be provided to the applicant earlier if there are no questions from COMP.

In the US, the sponsor must submit an orphan drug designation application to FDA. The application should include the sponsor contact and drug name, description of the rare disease or condition for which the designation is being requested, a description of the drug and scientific rationale for the indication, a summary of the drug’s regulatory status and marketing history, as well as documentation showing the disease or condition affects less than 200,000 people in the US or a rationale to demonstrate a lack of expectation for recovery of Research and Development (R&D) costs through US sales to 200,000 or more patients per year. The application will be reviewed by the Office of Orphan Products and Development (OOPD) within FDA.

Criteria for Orphan Designation

The criteria for orphan diseases differ by region, as do incentives offered to sponsors that successfully obtain orphan drug designations. The prevalence threshold, as outlined in Table 1, varies by market, which may impact the eligibility of a product for orphan

Figure 1. Orphan Designation and Drug Development Pathway in the EU

![Diagram of Orphan Designation and Drug Development Pathway in the EU](image-url)
### Table 1. Overview of Global Orphan Drug Framework

<table>
<thead>
<tr>
<th></th>
<th>US</th>
<th>EU</th>
<th>Japan</th>
<th>Australia</th>
<th>Singapore</th>
<th>South Korea</th>
<th>Taiwan</th>
<th>Brazil</th>
<th>China</th>
<th>Switzerland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Competent Authority</td>
<td>FDA/OOPD</td>
<td>EC, EMA (COMP)</td>
<td>MHLW, PMDA, NIBIO</td>
<td>TGA</td>
<td>HSA</td>
<td>KFDA, CPAC, MFDS</td>
<td>TFDA</td>
<td>ANVISA</td>
<td>NMPA (SFDA)</td>
<td>Swissmedic</td>
</tr>
<tr>
<td>Prevalence Threshold</td>
<td>200K (approx. 7.5/10K)</td>
<td>5/10K (approx. 246K people in EU)</td>
<td>50K (4/10K or 0.05% of population)</td>
<td>5/10K or lack of financial viability (unless all fees in paragraph 45(12) (c) are waived)</td>
<td>20K</td>
<td>20K</td>
<td>-</td>
<td>65/1K</td>
<td>1/500K or neonatal morbidity &lt; 1/10K</td>
<td>5/10K</td>
</tr>
<tr>
<td>Research Grants</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Tax Exemptions/Tax Credit</td>
<td>Yes</td>
<td>Possibly at national level</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Scientific Advice and Protocol Assistance</td>
<td>Yes</td>
<td>Yes Obligatory CP for MAA</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Smaller Trial Sizes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Pre-Licensing Access</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Fee Reductions</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Accelerated Review Procedures</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes***</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Market Exclusivity</td>
<td>7 years*</td>
<td>10 years**</td>
<td>10 years</td>
<td>5 years</td>
<td>10 years</td>
<td>10 + 2 years</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*No reduction even if prevalence changes. Clinical superiority clause for second applicant.
**6 years if criteria no longer met, 2 additional years if paediatric development completed in compliance with an approved PIP).  
***Priority review can be discussed with FDA if the product is eligible.
Global Orphan Drug Regulation

designation across regions, as could the practical application of orphan regulation. For example, in the EU, an orphan disease is the entire “spectrum” of the disease while the US FDA allows orphan designations that are subsets of, rather than, the entire disease. Major markets are discussed below and a summary of criteria and requirements for 10 regions is provided in Table 1.

**European Union**

In the EU, according to Regulation (EC) No. 141/2000, to be considered for orphan status a medicinal product must be “intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made.”

Alternately, the medicinal product can be “intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and, that without incentives, it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment and that no satisfactory method of diagnosis, prevention or treatment of the condition in question exists that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.”

The eligibility criteria for EU are outlined in Table 1. The flowchart is Figure 2 can be used to help sponsors determine whether their product is eligible for orphan designation.

COMP was established to examine applications submitted for orphan medicinal product designation to develop relevant policies and guidelines and liaise internationally and with patient support groups on relevant matters.

To obtain orphan status for a medicinal product in the EU, the sponsor should submit an application to the agency at any stage of development before the marketing authorization application is made. The submission should be made via the EMA’s secure online IRIS platform. The application should contain the required information specified in Regulation (EC) 141/2000. Within 90 days of receipt of a valid application, the agency will provide the sponsor with an opinion. An appeal may be submitted by the sponsor within 90 days of receipt of opinion. The Commission will adopt a decision within 30 days of receipt of the opinion. Once granted, the designated medicinal product will be entered in the Community Register of Orphan Medicinal Products (Register) and each year the sponsor is required to submit a report outlining the state of development of the designated medicinal product to the agency.

A product will be removed from the Register upon request of the sponsor if the criteria in Article 3 are no longer met before market authorization is granted and at the end of the period of market exclusivity per Article 8 of Regulation (EC) 141/2000.

Orphan drug incentives in the EU include protocol assistance, access to the centralised authorization procedure, 10 years of market exclusivity and protection from market competition with similar medicines with similar indications once approved and reduced fees for regulatory activities. The market exclusivity, which can be extended by two years in the EU should the medicine comply with an agreed Paediatric Investigation Plan (PIP). However, this differs from the US orphan designation status where no pediatric investigation plan is required for such products. Other incentives also may be available in individual EU member states.

Fee Incentives available from EMA are included in Tables 2 and 3.
United States

To be eligible for orphan drug designation in the US, the number of people affected by the disease or condition for which the drug is to be developed must be fewer than 200,000 persons. A sponsor can request an orphan drug designation at any time during the drug development process before submitting a marketing application for the drug for the same rare disease or condition. A sponsor can also request orphan-drug designation for an already approved drug for an unapproved use without regard to whether the prior marketing approval was for a rare disease or condition.16

Further guidance is available on FDAs website.17 The list of drugs currently assigned orphan status also can be found here.

Financial incentives provided by orphan drug designation in the US include tax credits to defray the cost of conducting clinical trials and eligibility for seven years of market exclusivity. Additionally, no user fee is required for orphan drug product New Drug Applications (NDAs) except when an application also includes an indication for a non-rare disease or condition. Sponsors may also seek waivers of annual post-approval fees.18

Drugs awarded orphan status in US are exempt from the requirements

* Contact the EMA orphan medicines office for more guidance.
** Article 3(1)(a) of Regulation (EC) No. 141/2000 provides an alternative criterion to the prevalence number, based on evidence of insufficient return to justify the necessary investment.
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of the Pediatric Research Equity Act (PREA), which requires marketing authorization holders to conduct clinical trials in pediatric populations. However, in the case of an orphan drug intended for treatment for cancer or determined by FDA to be relevant to pediatric cancer, such drugs would not be exempt from the requirements of PREA.19

Japan

In Japan, to be eligible for orphan designation, the number of patients in which the drug would be indicated should be less than 50,000, approximately less than 3.9 per 10,000 individuals.

Eligible drugs should be indicated for the treatment of serious diseases, including difficult-to-treat diseases. In addition, they must be drugs for which there are high medical needs satisfying one of several criteria. There should be no appropriate alternative drug or treatment in Japan. High efficacy or safety should be expected compared with existing medical products. There also should be a theoretical rationale for the use of the product for the target disease, including an appropriate development plan.

In relation to regulation and review of and support for development of orphan drugs, there is close collaboration between the following three main groups:
1. Ministry of Health, Labour and Welfare (MHLW)
2. Pharmaceuticals and Medical Devices Agency (PMDA)
3. National Institute of Biomedical Innovation (NIBIO)

Table 2. EMA Fee Incentives for Applicants Other Than Micro, Small and Medium Sized Enterprises14

<table>
<thead>
<tr>
<th>Service Description</th>
<th>Incentive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol assistance (non-paediatric-related*)</td>
<td>75% reduction to the total applicable fee</td>
</tr>
<tr>
<td>Protocol assistance (paediatric-related*)</td>
<td>100% reduction to the total applicable fee</td>
</tr>
<tr>
<td>Inspection (pre-authorisation)</td>
<td>100% reduction to the total applicable fee</td>
</tr>
<tr>
<td>Application for a marketing authorisation</td>
<td>10% reduction to the total applicable fee</td>
</tr>
</tbody>
</table>

* Paediatric-related protocol assistance is restricted to the development of an orphan medicinal product for the paediatric population, where the advice requested does not include the adult population.

Table 3. Fee Incentives for Micro, Small and Medium Sized Enterprises15

<table>
<thead>
<tr>
<th>Service Description</th>
<th>Incentive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol assistance</td>
<td>100% reduction to the total applicable fee</td>
</tr>
<tr>
<td>Scientific services**</td>
<td>100% reduction to the total applicable fee</td>
</tr>
<tr>
<td>Inspection (preauthorisation)</td>
<td>100% reduction to the total applicable fee</td>
</tr>
<tr>
<td>Application for a marketing authorisation</td>
<td>100% reduction to the total applicable fee</td>
</tr>
<tr>
<td>Postauthorisation activities, including annual fees, during the first year after marketing authorisation</td>
<td>100% reduction to the total applicable fee</td>
</tr>
<tr>
<td>Inspection (postauthorisation)**</td>
<td>90% reduction to the total applicable fee</td>
</tr>
</tbody>
</table>

** Fee reductions for scientific services and postauthorization inspections are not funded by the special contribution from the EU for designated orphan medicinal products but are provided for by Article 7 of Regulation (EC) No. 2049/2005 on SMEs.
Incentives for orphan designation in Japan include administrative and scientific advice from NIBIO, monetary support for research and development expenses through NIBIO, priority consultation and review and reduction in fees for consultation and application by PMDA and extension of the re-examination period by MHLW.20 The Orphan Drugs Working Group was initiated in Japan in 2011. The aim of this group is to review and analyse problems related to development of orphan drugs, encourage sponsors to develop medicinal products for orphan diseases, standardize the development of orphan medicinal products in terms of data requirements for approval, labelling information and timing of development, as well as strengthen collaboration with other regulatory authorities.21

As with the EU and the US, the orphan application can be submitted in Japan during the development phase before application for authorization to market. The development pathway, including orphan designation, application is outlined in Figure 3.

**Brazil**

In Brazil, the national health authority, National Health Surveillance Agency (ANVISA), classifies drugs for treatment of rare diseases as those intended to treat, diagnose or prevent a rare disease, used in a serious debilitating condition, and intended to significantly clinically change disease evolution or make disease remission possible.23 A ‘rare disease’ in Brazil is classified as a disease affecting up to 65 persons in 100,000 individuals. When applying for approval for clinical trials, a sponsor must specify whether the application refers to a rare disease. A description of the rare disease to which the drug is intended to be indicated, and the relevance of the drug for treatment, diagnosis or prevention of the disease, must be included with the application. Prevalence and incidence data of the rare disease for which the drug will be indicated, as well as supporting document of designation of the drug for rare diseases where applicable, should also be included within the application.24 Further details are included in Table 1.
Canada

Health Canada does not have a specific definition of a rare disease. In Canada, drugs such as those that treat serious, life-threatening or severely debilitating diseases or conditions, and which may have designated orphan status in other markets, such as the US or EU, may be eligible for priority review or other resources from Health Canada. When filing an application for marketing a new drug the available resources include but are not limited to:

- scientific advice on clinical trial applications and design and new drug submissions
- accelerated pathways (priority review)
- eight years of data and patent protection for a new innovative drug, including six months paediatric data extension when applicable
- Special Access Program (SAP) allowing manufacturers to sell a drug that cannot otherwise be sold in Canada such as when a conventional approved treatment has failed or is unsuitable or unavailable.
- fee mitigation or deferral options
- Guidance on the use of foreign reviews and third-party data Scientific Research and Experimental Development (SR&ED) program
- Tax Incentive program from the Canada Revenue Agency. This program includes case refunds and/or tax credits for expenditures on eligible R&D work done in Canada.
- Tax rebates from the SR&ED program represent approximately $4 billion annually to companies of all sizes in Canada. Features include refundable tax credits, R&D expenditures that can be carried forward indefinitely, salaries, material, contracts and incremental overhead, tax deductible capital equipment for R&D, tax incentives for research performed in Canada and funded by non-residents.25

Australia

In Australia, an orphan drug designation may be granted for a previously unregistered medicine or an already registered medicine with a new orphan indication, and a new dosage form medicine or a major variation application meeting all relevant criteria, including the significant benefit criterion.26

An orphan designation is specific to the sponsor, orphan indication for which the designation was granted, and the dosage form of the medicine, meaning that the orphan designation cannot be transferred from one sponsor to another. Additionally, because an application can be made for only one indication, if a sponsor wishes to obtain orphan designation for more than one indication, separate applications need to be submitted for each orphan designation.

The word ‘condition’ is used in the text of the 1990 Therapeutic Goods Regulations. This is intended to ensure the regulation also applies to treatments for conditions other than classical diseases, such as some genetic disorders.

Conclusion

Table 1 summarizes the availability of orphan programs and relevant incentives available in several markets worldwide. As evident from the table, as well as from the discussion above, there are significant differences in orphan designation requirements across global markets. When developing a new medicinal product intended to treat a rare condition, it is important that the sponsor considers the disease prevalence and severity, as well as other available methods of diagnosis, prevention or treatment of the condition. These criteria determine whether the new product demonstrates significant benefit to currently available therapies and, subsequently, if the sponsor will be eligible to obtain incentives associated with orphan designation in each market in which the medicinal product is intended to be marketed.
Global Orphan Drug Regulation

References


11. Ibid.


Global Orphan Drug Regulation


21. Ibid.

22. Ibid.


24. Ibid.


About the Author

Julie Watchorn, RAC, is a regulatory affairs consultant at Parexel. She has a master’s degree in biotechnology and is a current holder of the RAC certification. She has five years of experience in regulatory affairs with a current focus on clinical writing for regulatory submissions with previous experience in product lifecycle management. She can be contacted at Julie.Watchorn@parexel.com.

This article discusses the opportunities and challenges of creating and maintaining a regulatory intelligence program across regulated industry. The authors suggest a regulatory framework and best practice considerations to implement intelligence strategies in lieu of a standardized approach or framework.

**Introduction**

The pharmaceutical and medical device industries are faced with many challenges associated with the development lifecycle and overall sustainability of products over time. One of these underlying challenges for this highly regulated industry is the evolving regulatory landscape inherent within the global marketplace. As the regulatory landscape continues to evolve, it is essential for the pharmaceutical and medical device industry to develop adequate systems to ensure strategy and intelligence is embedded into the product lifecycle for new products, as well as to ensure legacy products already on the market continue to meet the expectations of today’s regulations.

**Background**

With advances in technology, novel products are being developed to address unmet medical needs, such as new drug delivery systems and the incorporation of digital technology into the treatment environment. For example, drugs that were previously difficult to administer, such as IV injections, are now available in pre-filled syringes for easier self-administration as well as the incorporation of digital adherence monitoring devices. These changes require health authorities (regulatory bodies responsible for protecting public health by enforcing applicable regulations, i.e., US FDA and Health Canada) to respond with new regulations and frameworks to ensure safe and effective use of new novel products. Industry
professionals often find it challenging to stay abreast of new and emerging regulatory requirements as well as any changes to how health agencies may choose to enforce them. The resulting impact of this evolution has created the need for regulatory intelligence programs to monitor changes to regulations and international standards. These programs allow for efficient data management, better priority alignment internally and overall improvements with aligning to global strategies, resulting in a competitive advantage. Such a program also helps an organization to employ best practices and key learnings to mitigate risks which can potentially result in lost revenue and time, delay market approvals and adversely affect company reputation.

The evolving regulatory landscape is defined in this article by the constant regulatory changes and requirements which occur in response to advances in the pharmaceutical and medical device industries as a result of new technologies and scientific techniques. One way to manage the evolving regulatory landscape is by staying up to date on regulatory information, which can be gathered from several different sources ranging from health authority information, trade journals and organizational websites. This essential information provides intelligence from a regulatory, market, competition and product information perspective. Regulatory intelligence is the science of applying gathered information and being able to implement it in a way that builds a successful regulatory strategy, which mitigates noncompliance and minimizes risk to products, patients and the company. When compared to other functions in industry, the regulatory intelligence discipline is one that is not well defined, as it is still maturing, but the need for such programs continues to grow in parallel with the increase in the accessibility of this data. Best practices from other disciplines can be leveraged as a starting point, such as principles from business intelligence programs, this is still an inherently challenging program to effectively implement and gain management support for. To date, there are no industry standards or generally accepted framework in place for achieving a successful regulatory intelligence program. The absence of a precedent is largely due to the arduous task of creating a standardized program, especially when the program is heavily dependent upon unique company attributes. Each product will have its own regulatory requirements which may vary by markets, in addition to each having its own exclusive business arrangements. This article outlines a template framework for organizations to apply and develop a regulatory intelligence program. These tools can enhance an organization’s regulatory strategy to minimize risk or potentially mitigate challenges.

The Foundation
As new information is received, it is transformed into intelligence by assessing for any potential impact to an organization’s products, procedures and processes. Intelligence, strategy and execution are the foundational pillars of in business operations and have direct impact on the reputation, compliance and cost of quality. It is necessary to understand the impact of current regulations and international standards to products, and the direction which the landscape is heading is critical to plan, anticipate and understand a path forward. Guidances or regulations developed by health authorities provide organizations with insight on current best practices in industry to help assure product quality and success of the overall business. Each source of regulatory information can be pieced together to understand the broader picture. This allows for informed decision making and strategic planning to overcome various nuances and reduce time to market. Once the assessment has been completed, the outcomes can be

One way to manage the evolving regulatory landscape is by staying up to date on regulatory information, which can be gathered from several different sources ranging from health authority information, trade journals and organizational websites. This essential information provides intelligence from a regulatory, market, competition and product information perspective.
Adopting Regulatory Intelligence Strategies to Foster the Evolving Landscape

applied to develop regulatory strategies and executing on those strategies has favorable outcomes in terms of compliance, company reputation, costs associated with quality events, such as fines or recalls. This process should continue throughout a product’s lifecycle in order to ensure a robust and effective regulatory intelligence program (Figure 1). As we can see, this is often easier said than done and is often where organizations fall short due to an inadequate or complete absence of a regulatory intelligence program, which provides information for the success of keeping the product on the market.

Information that feeds a regulatory intelligence program comes in many forms such as new policies, regulations, guidance documents and standards to name a few. Regulatory information can be sourced from many available services including but not limited to Cortellis, Tarius, Association for the Advancement of Medical Instrumentation (AAMI) and British Standards Institute (BSI). Other sources may come from within an organization, such as communicating with policy and country level regulatory personnel, among other supportive functions.

A regulatory intelligence program can complement project management using support from product development and regulatory teams to address new regulatory requirements. Over-laying agency timelines onto project schedules can help to quickly identify gaps in a regulatory strategy and make teams aware of anticipated challenges and ensure the proper steps such as change controls, testing, and reporting are completed. Failure to communicate the associated risks of non-compliance with regulatory requirements can lead to consequences such as product recalls, 483s and fines. Agency timelines should be reassessed and updated as needed, as there may be changes to timelines based upon new regulations or international standards, pathways to approval, product classifications, etc. Thus, it is important to continually re-review to facilitate a robust and strategic project timeline as shown in Figure 2 and Figure 3.

Competitive information is any data about similar companies, their processes, practices or products within the industry. Outcomes from such benchmarking can be strategically applied as a framework to your own organization to drive regulatory decision making. Learning about and
understanding new techniques to optimize a process and utilizing this information can help to develop best practices. This information is located within publicly available records and through the Freedom of Information Act, which provides access to warning letters, product recalls and US Securities Exchange and Commission (SEC) filings.

Market information can provide insight into the needs of the current and future market. This can be collected from various media sources such as the news, public databases, trade organizations and observing emerging diseases to determine any unmet medical needs.

Product information comes from within an organization and includes data about the product portfolio and pipeline and provides information on where and how products are registered and marketed. This information can be found in internal databases, product filings, labeling and other documents.

There are many inherent challenges with regulatory intelligence programs as these are not one size fits all. Unique business arrangements impact these programs in many ways. For example, let’s say Company A and Company B both market a product to treat the same condition. Company A is the manufacturer for the product and distributes globally, while Company B is a small national organization which does not import or export their products. Both scenarios have different regulatory and marketing requirements. To successfully import or export the product to market, Company A must ensure that all certificates and authorizations meet all specific local country requirements. Intelligence from one market can be applied to help shape other markets with less established regulations.

Budgetary constraints are another challenge encountered. Some companies don’t have a budget to allocate or
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dedicate resources to a new function, especially one as time intensive as regulatory intelligence. Subscription services are also an expense to consider when developing such a program and can be quite expensive but help save time and resources by doing the research to collect large amounts of data. These challenges which organizations can face impact the ability to gain management support for these programs. Management may want to know if you can prove they were able to file a product earlier because of intelligence that was implemented in a regulatory strategy. Can you prove you avoided costly fees by maintaining compliance for your products or processes because of regulatory intelligence? Performing a cost-benefit analysis can demonstrate to management the value which these programs can add (i.e., save time and improve quality).

Utilizing lessons learned from previous application experiences with a product in different markets can help to develop strategy for a current program. Archiving communications with health authorities can facilitate further understanding of regulatory decisions, as well as identify precedents for regulatory requests. These communications can help organizations to anticipate how the agency would likely respond based upon review of this historical data for trends and can be a key source of product intelligence. Competitive information can be utilized to create regulatory intelligence that can be applied to develop a regulatory strategy. For example, if Company X is looking to develop Product Y, they can utilize public information from their competitor, who recently registered and started marketing a similar product in the same market. Company X is also interested in. Gaining insight into challenges or requirements that a competitor faced during health authority review can be found by various databases within health authority or government sites. These resources provide information on what additional studies a health authority may have required for product approval or for postmarketing commitments, what classification the competitor product was registered with and what regulatory approval pathway was utilized for approval. Additional information such as product labeling or recalls, warning letters and 483s are also available using these public resources. Sites like clinicaltrials.gov provide information on which company is conducting a clinical trial, the investigational product, target population for the indication, clinical endpoints studied, etc. Competitor company websites also hold information on products in their pipeline and include details on these products such as therapeutic areas, submission types, phases of development, product registration, mechanism of action or therapeutic target, product classification and company partnerships or collaborations. Researching competitor’s successes and failures and applying these lessons learned to develop and streamline internal processes can be an invaluable tool.

When assessing products currently in development, the organization should discuss how and anticipate when they plan to register the product. The type of product will determine the type of regulatory pathways available to the organization. The type of product also will aid in identifying the appropriate set of standards, policies and requirements to follow. Once the suitable regulatory documents are identified for the product type, the organization should assess if the product, as it is currently being developed, would meet all current requirements. Having a target for submission will determine the scope of forecasting (e.g., within the next year) needed to adequately anticipate regulatory changes for the approval pathway being sought.
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For products that have recently been introduced to the market, understand that the requirements which had been met throughout the development stage may have changed by this time. Assess whether there are additional standards or policies which were not previously required for the product to meet.

It is important to acknowledge the pace of change and respect that it is inevitable as regulations are constantly evolving to meet needs. The organization should assess and plan how it will manage regulatory requirement changes for products. Identifying the changes needed early on is advantageous, as it provides ample time to prepare by the enforcement date. Anticipating plausible scenarios which could require modifications to the product provides an organization with a competitive advantage; the organization remains agile, proactive and compliant.

The impact assessment considerations stated above for new products, also should be applied to products in the sustaining phase of their lifecycle (mature products). In addition, the organization needs to plan how they will accomplish bridging the gap between policies and standards applicable during its original registration to the current requirements for the mature product in order to stay on the market.

Steps to executing a successful regulatory intelligence program:

Figure 4 outlines the framework for regulatory intelligence. Gathering the information that feeds a regulatory intelligence program is the key to building a robust regulatory intelligence program. However, there are many challenges to overcome during this stage. There is a lot of information available but much of it may not be applicable and it is a time-consuming process to sort through and review extensive amounts of information to determine relevancy. Additionally, this information will not just come from one source. Many of the subscription services that are available are great at providing information, but it is impossible to receive everything from one source, especially if working on a global scale. Therefore, much of the information may be duplicated and additional sorting will have to be completed before the information can be assessed for relevancy and then again for impact. Another challenge one may encounter is language barriers. Information can come from most any country and may need to be translated in order to utilize it.

Once relevant regulatory information is gathered, an assessment will need to be completed in order to determine the impact on an organization. For global companies, this would ideally be completed by a Subject Matter Expert (SME) in the country where a new or revised policy has been issued.
It is crucial to consider all products in the pipeline and portfolio when assessing new regulatory information. When completing an assessment, some useful considerations include: determining the type of product or process that the policy addresses, what functional areas might be affected by the policy (e.g., CMC, Clinical, Labeling, Manufacturing, Pharmacovigilance), relevant stakeholders and what products may be affected. Products that are registered, but not actively marketed also can be affected, therefore these products also must be assessed. If an initial assessment determines there is a potential for impact, additional reviews should be completed by cross-functional teams and this process should be standardized throughout the organization. This confirms all aspects have been considered and ensures compliance with new requirements. It is also helpful to maintain records of these assessments for future reference, such as in the case of an audit, if the policy is revised or a process changes. This provides a baseline to compare these changes against and identify any gaps without having to do a complete reassessment.

After the assessments have been completed, the next step is to share all relevant findings to the identified internal stakeholders. It is crucial to provide any regulatory requirement changes as soon as possible to facilitate timely planning of changes to the developing strategy, as enforcement dates depend upon the intended purpose and criticality of implementing such mandates. There will always be some level of residual risk in all scenarios, further highlighting the need for an efficient and effective communication approach within the regulatory intelligence program. Different methods for alerting colleagues should be considered and tailored to the specific needs and culture of the organization. Keeping in mind common issues such as email fatigue, other platforms for disseminating alerts may be more effective and include internal social media sites, databases, and newsletters.

In order to implement a successful regulatory intelligence program, key takeaways from the assessment of gathered information should be utilized to build the strategic framework. Devising a strategy without having considered or applied regulatory intelligence can result in non-compliance, which has associated risks and can create a domino effect, leading to product hazards, recalls and fines. These risks can have legal implications, negatively impacting the business, the company’s reputation, and most of all, the patients. Thus, maintaining compliance is vital to the success of a product.

Once a plan has been established, it is time to execute upon the regulatory strategy, completing the regulatory intelligence process. A successful program will have clear lines of communication within cross-functional teams, each having well-defined roles and responsibilities for maintaining the program and will track both milestones and metrics to measure its success. Understanding how a product is viewed by each regulatory authority in potential markets of interest is vital to gaining market approval. Looking across the global market and knowing those countries with similarities in their regulatory requirements can help to streamline the submission process for multiple markets. Additionally, it is beneficial to identify any alternative regulatory pathways across the globe, which may provide a competitive edge such as an expedited approval or grant market exclusivity.

Metrics can be challenging to collect but are extremely important for demonstrating the importance of a regulatory intelligence program and is a continuous activity. One method is to highlight the near misses that were avoided because of the utilization of regulatory intelligence. Such near misses can be represented, for example by the cost associated with a potential

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A successful program will have clear lines of communication within cross-functional teams, each having well-defined roles and responsibilities for maintaining the program and will track both milestones and metrics to measure its success.
recall. Reviewing warning letters for competitor’s products can provide insight on issues which are introduced once the product enters the market. Understanding the root cause of such issues encountered by the competitor’s marketed product can facilitate implementation of additional controls or other mitigations for your own product; possibly avoiding fines or recalls.

A study was conducted to assess the advantage of being first-to-market, specifically looking at products which generated more than $100 million in sales per year, with at least one competitor product during the patent life. The outcome of this research demonstrated that first-in-class products achieve a greater-than-fair market share ten years after launch, equating to a 6% market share advantage over later entries as shown in Figure 5.5

A well-designed regulatory intelligence program can add value in reducing submission time; understanding and identifying all requirements set forth by regulations prior to submission of the application to the agency will ameliorate the time to market, rather than the application being on hold for missing requirements. Premarket application decisions for medical devices can take an average 320 days. Agency’s review of the premarket application takes a substantial amount of time, thus any delays to timelines can have significant financial consequences, especially when competing to be first to market. The requirements for medical device manufacturers are quite complex and challenging to navigate, thus if a manufacturer fails to meet FDA requirements, it will delay time to market. In Figure 5 the average market share is dependent upon order of entry into the market. The impact of not being first to market can have significant financial consequences, which can span over decades.

The following is an example of the impact to organizations if regulations are not appropriately assessed and implemented. In 2019, the US Food and Drug Administration (FDA) Class I device recall category, which represents serious health hazards and even death due to device defects, accounted for nine out of the 10 largest device recalls globally. The top 10 medical devices recalled totaled more than 52 million units. The cost associated with a recall is not only the profit loss for the units, but time and reputation. Each year, warranties and recalls cost the medical device industry $2.5-$5 billion; a significant loss in revenue which can be prevented. FDA estimates that roughly 400 recalls could be prevented each year if manufacturers had implemented more stringent design control practices. A
single medical device product recall can cost a company nearly $600 million in revenue, in addition to damaging the company’s reputation and consequently a decrease in shares of up to 10%. The impact to reputation does not only impact the individual company, but the medical device industry as a whole. Historically, one major quality event each year results in an average of a 13% stock price drop across the industry.

Organizations can manage costs over time by building quality into each step of design and manufacturing, through approval to market, and by maintaining post-marketing commitments to ensure product successfully stays on the market. The total cost of quality for the medical device industry has been estimated at $17 to $26 billion annually (12-18% of industry’s revenue). This estimate includes the daily quality and revenue loss costs from non-routine events. In addition to lowering costs, quality best practices also reduce risk, produce better products, and help improve patient safety. Major observations, recalls, warning letters, consent decrees, and lawsuits (non-routine costs) account for $1.5-3 billion per year, in addition to $1-2 billion in lost sales for new and existing products. Top performing organizations are successful with incorporating best practices into every aspect of the business. For an average quality performing company, adopting these best practices can increase profits by 3-4%, and the preventable non-routine costs can be reduced by 50%. A second study was conducted by McKinsey and Company, which focused on emerging best practices being utilized by organizations to increase quality. The cost of quality was described by three categories: direct cost of ensuring good quality, direct cost of poor quality and indirect quality costs.

Practices consistent with good quality outcomes are robust product and process controls, stronger operational maturity regarding people and assets, effective quality systems, and robust quality culture and practices across the organization. Implementing these best practices can mediate these costs, saving up to 1.6-3.0% of industry sales.

**Conclusion**

Overall a strong business case can be made to support the addition of a regulatory intelligence program to enhance regulatory strategy, mitigate risks and develop a competitive advantage. Advances in technology and communication allow for greater accessibility of information and have created the need for such a program. The extensive accessibility of information can be overwhelming; thus, it is important to identify what is relevant to an organization’s requirements. The application of a regulatory intelligence program allows companies to anticipate changes to agency requirements, thus becoming proactive instead of reactive and avoiding risks and quality events. This article provides a framework to follow to develop a program; however, each program must be adapted to fit each organization’s unique requirements and needs.
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References


5. Ibid.


7. Ibid.


9. Ibid.


11. Ibid.


13. Ibid.

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Economic Operators: Roles and Obligations Under EU’s MDR

By Randolph Fillmore

Regulatory and legal experts share their views on the European Union’s revised Medical Device Regulation (MDR) and the EU’s requirements for Economic Operators (EOs) to play major roles in medical device authorizations and postauthorization monitoring. The article also highlights roles and responsibilities for Manufacturers, Authorized Representatives, Importers and Distributors (MAID) for assuring compliance with new EU MDR in addition to public health/patient safety goals. The article was developed in cooperation with Ludger Möller and Erik Vollebregt who will be presenting this topic at RAPS Euro Convergence, 26–28 October 2020 in Brussels, Belgium.

Introduction

The EU Medical Devices Regulation (MDR)\(^1\) and In Vitro Diagnostic Medical Devices Regulation (IVDR)\(^2\) introduced a complete economic operator regime for medical devices. After being approved by the European Council and the European Parliament, in May 2017, the European Medical Devices Regulation (MDR) came into force. MDR implementation is set for May 2020.\(^3\) While the new regulations aim at enhancing medical device safety and effectiveness, their genesis is the result of several years of new developments, both scientific and technical, in addition to the perceived need to redesign the EU regulatory landscape to improve quality and safety and alignment of medical devices regulation with EU goods regulation for other CE marked goods set out in the 2008 template New Legislative Framework for the Marketing of Products (see recitals 25–27 MDR). Since 2008, the EU has gradually implemented the economic
Through MDR, new roles and responsibilities have appeared up and down the medical device supply line with the requirement that Manufacturers, Authorized Representatives, Importers and Distributors (MAID) function as Economic Operators (EOs) with distinct and sometimes overlapping roles and responsibilities.

operator requirements in every CE marking directive and regulation that was renewed. Through MDR, new roles and responsibilities have appeared up and down the medical device supply line with the requirement that Manufacturers, Authorized Representatives, Importers and Distributors (MAID) function as Economic Operators (EOs) with distinct and sometimes overlapping roles and responsibilities. In short, under the EO mandate, quality and regulatory compliance responsibilities have risen to new heights and are much broader than with the older regulations.

Which MAID EO is responsible for what?

- **Manufacturers**: responsible for Eudamed registration, technical documentation, design, development manufacture and assembly, handing, storage and distribution, corrective actions, UDI labeling, complaints, postmarket surveillance and the PRRC.
- **Authorized Representatives**: responsible for Eudamed registration, technical documentation, corrective actions, UDI labeling, postmarket surveillance and PRRC.
- **Importers**: responsible for Eudamed registration, handling, storage and distribution, corrective actions, UDI labeling, postmarket surveillance.
- **Distributors**: responsible for handling, storage and distribution, corrective actions, UDI labeling, complaints and postmarket surveillance.

**Learning to Play by the Rules**

While the EO emphasis in MDR means that there many and varied new rules, how can supply chain players adhere to the rules and determine their obligatory roles for doing so? According to Erik Vollebregt:

“They can determine this by understanding their role in the supply chain and by understanding the rules, which requires understanding of the concept of ‘placing on the market for the importer and ‘making available for the distributor.’”

For Vollebregt, ‘placing on the market’ means the first making available of a device other than an investigational device. He emphasizes the operation of ‘placing on the market’ is reserved for, and can only be done by, a manufacturer or an importer. He adds that the placing on the market is “the most decisive point in time” in the new legislative framework and that “there is a widespread misunderstanding that companies can ‘appoint’ economic operators like importers and distributors, but this is not how the MDR works. The MDR uses a definition for each economic operator, which means that the facts of the economic operator’s situation either fit the definition or not. So companies should not rely on contracts to appoint an economic operator, but rather analyze if the relationship agreed under the contract fits the MDR’s definitions or not.”

Ludger Möller clarifies further that the placing on the market refers to the placing on the market of each individual single product. Sometimes it is mistaken that this refers to a group of products and once a product is placed on the market “for the first time” that then subsequent products can be further placed on the market. This is a misconception since there is no first placing on the market! Should a requirement change the very next product may then have to be updated before it is being placed on the market.

**Eudamed Registration, PRRCs and Their Responsibilities**

According to Vollebregt, MDR requires manufacturers, authorized representatives and importers to register in Eudamed, the EU’s electronic database. “The idea was that Eudamed would allow complete transparency of the supply chain, but now that Eudamed has been delayed, we will have to see how the existing national mechanisms that should be used until Eudamed is up will work for the EOs.”
Möller outlines that a recent MDCG guidance clarifies that the PRRC of the manufacturer and of authorized representative cannot be the same person. Besides the reason given in the MDCG guidance the responsibilities of the manufacturer’s PRRC for the conformity assessment procedures are specifically excluded from the mandate a manufacturer may give to the authorized representative. This would open doors for a conflict of the interest in creating its own records. How can someone verify that a technical documentation has been drawn up and at the same time being responsible for it.

Overlapping EO Obligations and Sharing Resources

According to Vollebregt, the EO function does not translate well to large companies when multiple EOs are under the same joint control. This reality, he says, makes amending supply chain contracts a good idea. Can a company pool resource between various EOS? Yes, says Vollebregt.

Vollebregt also notes that EOs among the MAID players along the chain have “overlapping” obligations; but that the number and scope of obligations reduces going down the supply chain after starting with manufacturers and authorized representatives as the most obligated and importers and distributors less so. Understanding which EO obligation is whose obligation may be key to quality control. This obligation identification requires what Vollebregt calls “awareness and awakeness” on the part of the MAID players.” They also suggest that efficiency-driven companies will strive to find the most efficient ways of achieving what regulators expect from them.

“Accordingly, there is a shared interest among EOs to cooperate more intensively, including sharing resources to avoid duplicating work,” said Vollebregt.

Some observers may be concerned about a business/regulatory model that may, inadvertently, include either EO work duplication or that the EO function and quality may be undermined by some EOs in the MAID supply chain taking for granted that “someone else has already done that or will do that.”

Regardless, spreading compliance responsibility among all MAID players appears to have been an EU objective from the start.

EO Roles

Manufacturers and ARs appear to be most directly affected in terms of EO responsibilities. According to Vollebregt, there are “big changes” in store for ARs, those both inhouse and external. Too, there are now prescriptive rules for an AR mandate and contract. “As with notified bodies, ARs are now recruited into market surveillance,” said Vollebregt in a recent presentation. “ARs must provide information, cooperate in investigations and verify that appropriate conformity assessment procedure has been carried out by the manufacturer. The AR must have a PRRC.” He added: “I expect the requirement for ARs to terminate the mandate and report the manufacturer to the authorities and notified body to lead to a lot of friction and conflict. Historically, many manufacturers see the AR as a communication channel with authorities but certainly not as a party that has anything to say about the manufacturer’s compliance.”

According to Möller, the authorized representative now have been called the “little notified body” and indeed remembering the introduction of the MDD in 1998 some notified bodies indeed only verified at that time that the technical documentation was drawn up. A clear requirement of the authorized representative today. In addition, the authorized representative has the power to stop the European business quickly with terminating the mandate. This is an interesting requirement in a cooperate setting. For example, this applies as well for a
subsidiary and that subsidiary would have to terminate the mandate with the mother company.

**The PRRC**

The Person Responsible for Regulatory Compliance (PRRC) is a vital part of the EO function. Vollebregt outlines the PRRC requirements by reference to MDR Article 15,5 which says a manufacturer must employ a PRRC and that the PRRC role may be shared between several persons. He also notes the PRRC for the manufacturer and the AR cannot be the same person and that the PRRC for the AR must be located within the EU and that PRRC qualifications must be proven by demonstrated member state equivalency.

Who can be a PRRC? According to Vollebregt a PRRC:

- is qualified through education or experience
- has a university degree or study recognized equivalent by a member state
- has a degree in law, medicine, pharmacy, engineering or other relevant discipline
- has more than one year of experience in medical devices in regulatory affairs or quality management systems
- has four years of experience in medical devices (for MDR) or IVDs

Vollebregt lays out the responsibilities of the PRRC as follows:
- assuring the conformity of the devices is appropriately checked in accordance with the Quality Management System (QMS) under which the devices are manufactured before a device is released onto the market
- assuring the technical documentation and the EU declaration of conformity are drawn up and kept up to date.
- assuring the postmarket surveillance obligations are complied with in accordance with Article 10 (10) MDR/10 (9) IVDR
- assuring the reporting obligations referred to in Articles 87 to 91 MDR/82 to 86 IVDR are fulfilled
- assuring in the case of investigational devices the statement referred to in Section 4.1 of Chapter II of Annex XV MDR/XIV IVDR is issued

**Authorized Representative and Non-EU Manufacturer Liabilities**

Regarding manufacturers who are not established in the EU:

(35) For manufacturers who are not established in the Union, the authorised representative plays a pivotal role in ensuring the compliance of the devices produced by those manufacturers and in serving as their contact person established in the Union. Given that pivotal role, for the purposes of enforcement it is appropriate to make the authorised representative legally liable for defective devices in the event that a manufacturer established outside the Union has not complied with its general obligations. The liability of the authorised representative provided for in this regulation is without prejudice to the provisions of Directive 85/374/EEC, and accordingly the authorised representative should be jointly and severally liable with the importer and the manufacturer.8

Möller outlines that he was surprised of the lack of understanding among importers in terms of their existing liability obligations even though the directive on liability is quite clear on this aspect. The above paragraph indeed mentions the importer but it does not so under the respective article 13. The MDR indeed adds confusion to the liability regime since the requirements are clearly outlined in the Directive 85/374/EEC. This is also most likely the reason that importers are obligated to add their name and information where they can be contacted with the product. It is interesting to observe that the liability concern is now a concern of the regulatory department with the
focus on the patient. It was previously only in the financial department and the task was to protect the company. It does not matter, the result is the same.

Manufacturers

Regarding manufacturers’ liabilities:

(74) Manufacturers should play an active role during the postmarket phase by systematically and actively gathering information from postmarket experience with their devices in order to update their technical documentation and cooperate with the national competent authorities in charge of vigilance and market surveillance activities. To this end, manufacturers should establish a comprehensive postmarket surveillance system, set up under their quality management system and based on a postmarket surveillance plan. Relevant data and information gathered through postmarket surveillance, as well as lessons learned from any implemented preventive and/or corrective actions, should be used to update any relevant part of technical documentation, such as those relating to risk assessment and clinical evaluation, and should also serve the purpose of transparency.9

According to Möller, president of the Medical Device Safety Service, the new rules under MDR will render the medical device business to be “business NOT as usual.” He suggests that the overlapping EO roles and obligations among MAID players may work against “business as usual” because importers and distributors have, historically, not been in the verification “business.”

Among those questions are:
1. Can I consider myself a distributor?
2. As a manufacturer, do I need to control my importer?
3. As an importer, do I like to be controlled by my supplier?
4. Can I have my subsidiary act as an importer?
5. Do I want to take on the role of the AR?

The question will be addressed during the RAPS Euro Convergence, 26–28 October 2020 in Brussels, Belgium and proposals for solutions are going to be provided.

To many of these unanswered questions, the “gray answers” may be both “yes” and “no.” For example, regarding question number 2 above, Möller says this question touches on a “fundamental shift in regulatory thinking. The regulatory department of the manufacturer likes to control that requirements are indeed implemented and some indeed start to believe that the importer should be controlled with their supplier evaluation program. This may be possible if the manufacturer has a strong product, but it should not be forgotten that the importer in the first place is the customer for most of the manufacturer. The sales and marketing department may not agree with the activities of the regulatory department. Möller has more questions:

• How (exactly) does a distributor check on the importer and manufacturer?
• How (exactly) does the importer check on the manufacturer and the authorized representative?
• How (exactly) does the authorized representative check on the manufacturer and importer?

Vollebregt offers that these “how” questions reflect the need for relationships among MAID players that are “mutual and reciprocal” and points to the need to apply a “certain degree of quality control over each other.”
Conclusion

The experts each emphasize the need for clarification in certain areas of MDR’s elevation of the roles of EOs and offer some practical solutions for EOs to consider during the RAPS Euro Convergence. The CAMD and later the MDCG indicate that guidance is forthcoming. The experts also emphasize the need for all MAID players to hasten their efforts to comply with the looming May 2020 implementation.

“The Economic Operator (EO) regime under the MDR and IVDR is not new, it is based on the goods package as set out in Regulation 765/2008, which provided a template for regulation for CE-marked goods and established the ‘New Legislative Framework.’ MDR and IVDR strengthen and make more explicit the obligations of economic operators with substantial overlap and repetition.”11,12 Furthermore, the MDR has already been in force since May 2017.

These requirements have now found their way into the MDR with a focus on compliance via the extension of EO responsibilities and obligations to all MAID players—up and down the supply line—coupled with the parallel responsibilities of the PRRC.

References


9. Ibid.


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Introduction

China’s drug and medical device regulatory environment has changed dramatically in the last four years, with various reforms initiated since August 2015 when China’s central government issued its notification, “Opinions on Reforming the Review and Approval System for Drugs and Medical Devices.” The notification aims to eliminate the backlog of drug applications, upgrade the quality of generic drugs, encourage new drug R&D in line with global development and improve the quality and transparency of the review and approval process.1

Following the notification’s issue, the authors have observed several policy improvements over the last four years, including:

• The new drug review timeline has been shortened significantly. The clinical trial IND timeline, which had taken one to two years prior to 2015, has been reduced to about three months (60-working-day silent approval).
• The National Medical Product Administration (NMPA, previously CFDA or SFDA) joined ICH as a full regulatory member in July 2017. Some International Council
The CDE issued its 2018 annual report on 1 July 2019, demonstrating how the clinical trials and new drug development market has grown in China with many new drug clinical trials have been approved in China.²

New Drug R&D Has Grown Significantly

In China, the Center of Drug Evaluation (CDE) is the key drug reviewing entity under the NMPA. The CDE issued its 2018 annual report on 1 July 2019, demonstrating how the clinical trials and new drug development market has grown in China with many new drug clinical trials have been approved in China.² Figure 1 shows the number of new chemical drug IND approvals nearly doubled from 2014 (87) to 2018 (172).

In addition, the new drug classification was changed in 2016. Previously, a “new drug” meant new chemical or biological entities not approved in China; now “new drug” means entities not approved anywhere else in the world. This explains why the 2014 and 2015 data are as high as they are as they include approvals for the “new drugs” or those already approved in foreign countries, but not in China.

New biological product IND approvals increased even more substantially from 2014 to 2018. Figure 2 shows the number of new biological product clinical trials approved more than tripled (from 110 to 349) during that time.

Figure 3 shows the fast pace at which the number of new chemical drugs approved in China has grown from 2016 (23) to 2018 (132).

Meanwhile, Figure 4 shows the number of new biological products approved in China also grew very quickly from 2016 (17) to 2018 (41).

Assessing the Trends

In reviewing the CDE annual report and the information on clinical trial approvals and new drug registrations noted previously, a number of changes emerged. For example, with the hiring of new drug technical reviewers by the CDE, the reviewer team has grown and strengthened. As a result, the application backlog has reduced significantly, from a high of 22,000 in September 2015 to less than 3,500 by the end of 2018.

Because of the influx of staff, the CDE now has sufficient resources to keep close communication with applicants via a variety of pre-submission consultation meetings and ensure reviewers are dedicated for priority review and complete project review within the promised dates. To strengthen the quality of clinical trials performed in China, in July 2015 CFDA began requiring all trial sponsors to conduct trial data self-inspections, which
would then be audited by CFDA. This requirement had a significant impact on the local China pharmaceutical industry as it requires companies to ensure their data and trials meet global standards in an environment where, up until this time, such standards were sometimes ignored. As a result, the number of total drug applications declined dramatically in 2016. At the same time, CFDA encouraged local and foreign new drug innovations by offering a variety of incentives, such as priority review treatment, shortening the review timeline and process, new Marketing Authorization Holder (MAH) policy and joining ICH. These initiatives caused drug applications to grow quickly in 2017 and 2018 (Figure 5), with many global trials initiated by foreign sponsors and emerging local new drug and new biotechnology innovators.

Priority review and pre-submission consultation meetings are important practices for encouraging new drug innovation and have been well-established by leading regulatory authorities in the US, EU, Japan and elsewhere for many years. However, due to resource shortages before 2016, even though a similar practice did exist, CDE routinely rejected requests or was not able to meet expectations. Since then, there have been major improvement due to the increase in reviewer resources.

In 2018, 313 applications were granted priority review. The CDE has specific criteria on how to grant priority review to the projects. These include such factors as a new drug developed in parallel with the US or EU, whether the drug has significant clinical value, whether the drug is indicated for pediatric use and rare diseases. Among the 106 new drugs approved in 2018, 83 of these have benefited from this process with much shorter IND and NDA review timelines.

CDE also has become more open to drug applicants. Formal consultation meetings are important for drug sponsors to communicate directly to the drug reviewers. In 2018, there were 1,982 meeting requests from different applicants, including 824 (42%) for pre-IND and 555 (28%) for pre-NDA. Applicants have other options to make requests during the IND evaluation, post-Phase I or post-Phase II. Among the 1,982 meeting requests, 322 (16%) resulted in final face-to-face meetings, a significant increase in meeting requests compared to 2017 when there were 840 meeting requests and 321 (38%) final meetings. Based on experience with pre-IND requests, CDE reviewers

Figure 5. Acceptance of Various Applications From 2015 to 2018
will clearly answer the questions from applicants, although it is not necessary to hold face-to-face meetings.

Thanks to a more favorable clinical trials and drug registration environment, coupled with much shorter IND and NDA review timelines, there were 106 new drugs approved in 2018, including six locally developed Class I (i.e., first in world) new chemical entities and three new biologicals (the most in China's history), as well as 67 innovator drugs from foreign countries. China's local new drug innovators are now playing a significantly more important role in the market. As Figure
Due to regulatory reform and policy changes, many new drug and biotech innovators are significantly stepping up activities, venture capital is being injected, and talented Chinese R&D professionals are coming back to China, all of which is contributing to a boom in China.

As noted in Figures 6 and 7, local new drug innovation in the China market has caught up with and surpassed global players. Due to regulatory reform and policy changes, many new drug and biotech innovators are significantly stepping up activities, venture capital is being injected, and talented Chinese R&D professionals are coming back to China, all of which is contributing to a boom in China.

Many local companies have moved from the manufacture and supply of quality generic products into innovative R&D, including full-blown clinical development in China and elsewhere. These companies have a range of new drugs in development and, in the next five to 10 years, these will start to be approved and launched in China and the rest of the world. Investment in these companies is significant and increasing as their future potential grows.

There are also a host of recent examples of licensing deals between new Chinese innovators and overseas companies as the stability and potential of these companies can afford an efficient and effective route to development, approval and commercialization of their partners’ drugs in China.

Projecting the New Drug Development Market in China

Today, China has caught up with and surpassed Japan to become the second largest pharmaceutical market in the world. More importantly, China is growing faster than both the US and Japan, making it attractive for local and global pharmaceutical and biotech companies.

Furthermore, the Chinese government’s main purpose with this regulatory reform is to encourage local and global new drug innovation to meet the needs of Chinese patients, while discouraging the development of high-competitive, low-quality generic drugs.

This initiative has led to the boom of new local China drugs, especially new biotech research. These include:

- In China, there are some CAR-T projects reaching the point of application for clinical trials.
- Some foreign and local PD-1/PD-L1 projects at clinical trial stage, NDA and even marketing authorization.
- The first biosimilar product approval in China in February 2019, and many biosimilar products are at clinical trial and NDA stage.

Expectations are that after the US, EU and Japan, China will become the next “hot” area for new drug development. Expect also there will be more foreign sponsors undertaking global trials in China. Meanwhile, local China pharmaceutical and biotech companies will go outside their country for clinical development in the US, Europe and Australia. Foreign-developed new drugs will be approved in China in a much shorter time, while locally developed new drugs could be developed and approved in China and the US in parallel.

All the previous developments are contributing to the evolution across a wide group of stakeholders in China and present opportunities such as:

- New drug and biotech innovation and the development of new drugs and new biological products for China and the global market
- Contract research industry, such as CRO, CMO and central labs, etc.
- Clinical trial sites are currently all government-owned big hospitals mostly in large cities, all of which are GCP accredited by NMPA. Based on the new policy, GCP accreditation will no longer exist and the government is encourag-
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There is strong encouragement for projects under priority review and special treatment with much shortened review timelines, while discouraged products may take much longer time and may be challenged or rejected by authorities.

Even under this open, harmonized environment and growing market, not all new drug innovations are welcomed or encouraged by NMPA and CDE. On the other hand, not all generic drugs are discouraged. There is strong encouragement for projects under priority review and special treatment with much shortened review timelines, while discouraged products may take much longer time and may be challenged or rejected by authorities. As the following section further describes, key criteria will be therapies for treating urgent and/or unmet medical needs.

NMPA and CDE’s Main Consideration: Urgent and Unmet Medical Needs

NMPA and CDE’s main consideration for new drug approvals is to meet unmet medical needs. On 20 December 2017, NMPA issued “The Guideline on Conditional Approvals for Urgently Needed Drugs.” This guideline is clear on defining on unmet medical needs.

Unmet medical needs usually include:

- conditions without any approved therapy
- conditions where there is available therapy, but new drugs have an advantage over current therapies for the following reasons:
  - obvious improvement on the disease’s serious consequences
  - significant efficacy compared to current therapy
  - can be effectively combined with other key drugs, while current therapy cannot be the same efficacy as current therapy, but with a better safety profile (lower toxicity) or better or more compliance for patients
  - resolves newly emerging or expected public health needs

Experience working with NMPA and CDE has shown a new drug’s value can be assessed using the following criteria:

- Is there an available therapy? Is there any advantage over current therapies?
- Is it indicated for a life-threatening disease, a rare disease or pediatrics?
- Is it for the treatment of an infectious disease, such as HIV or HBV?
- Is it for the prevention of an infectious disease, such as a vaccine for public health?
- Is it less expensive, even if it has the same safety and efficacy as current therapies?

To address these issues and questions, several procedures have been implemented.

Procedures for the Evaluation and Approval of Foreign-Approved New Drugs With Urgent Medical Needs

On 23 October 2018, NMPA and the National Health Commission (NHC) issued this procedure with the central consideration that, due to long review timelines and drug lag, there are some innovative new drugs that have already been marketed in the US, EU or Japan for many years. However, they are not yet approved in China. Subsequently, CDE is responsible for arranging local experts to select some potential drugs approved in the US, EU or Japan, but not yet approved in China. These
For selected drugs, NMPA encourages drug holders to discuss drug registration as they will have specific channels for these applications. Applicants will have pre-submission consultation meetings with CDE reviewers showing the assessment on ethnic sensitivity or, if the drug is already marketed in Japan, Hong Kong, Taiwan or Macao, provide an evaluation report on the clinical and postmarket usage in these areas. Applicants have significant opportunities to submit an NDA directly to NMPA without any local trial requirement. Based on this specific regulatory pathway, NDA evaluation should be completed within three months for orphan drugs, or six months, as compared to one to two years for the normal prior process. Administration approval by NMPA should be completed within 10 working days, as compared to two months for the former process.

Based on the previous procedure, in November 2018 and May 2019, CDE released two lists of urgently needed new drugs. A total of 74 new drugs were listed. All of them are already marketed in the US, EU or Japan, but not in China. Additionally, most of them are for rare diseases, such as Eliglustat, Velaglucerase Alfa and Taliglucerase Alfa (indicated for Gaucher disease) and Fingolimod, Dalfampridine and Lemtrada (Alemtuzumab) (indicated for multiple sclerosis). Apart from orphan drugs, some drugs that have a clear advantage over current therapies, such as Maviret (Glecaprevir/Pibrentasvir) for HCV because it is for public health, a serious life-threatening illness and has clear advantages.

CDE announced in its 2018 annual report that 10 of the listed drugs have been approved.

**Conditional Approvals for Urgently Needed Drugs**

On 20 December 2017, NMPA issued "The Guideline on Conditional Approvals for Urgently Needed Drugs." This guideline is for the new drugs (TCM, chemical drugs and biological products not approved in China) with indications for serious life-threatening diseases and those without available therapy. The purpose is to shorten clinical trial timelines and provide earlier use for patients. Conditional approval could be granted based on:

- clinical trial results using surrogate endpoints or middle endpoints, which can predict efficacy and benefit
- early or mid-term clinical trial result, which can predict benefit and advantage over current therapy
- orphan drugs already approved in foreign countries

**Acceptance of Clinical Trial Data Performed in Foreign Countries**

On 6 July 2018, NMPA issued "The Guideline of Accepting Clinical Trial Data Performed in Foreign Countries." The principle of acceptance of foreign clinical data is summarized in Table 1.

Although this guideline is suitable for all drugs, NMPA and CDE have their own criteria as they view generic drugs as a lower priority although an applicant may have BE study data from foreign countries. Priority is given to new drugs with the potential to address unmet medical needs. The guideline clearly states “as for drugs indicated for serious life-threatening disease, or rare disease or for pediatrics, and without any currently available therapy, if the foreign clinical data is treated as ‘partially accepted’ after assessment, ap-
Generic Drugs

Encouraging innovation does not mean discouraging all generics, as some may have benefits for lowering the price of innovator drugs. However, if there is only one player in the market, the result could be higher cost. If a drug is too expensive to be accepted by patients or accepted by social medical insurance, this represents another kind of unmet medical need and another reason why NMPA encourages first-launched generic drugs so long as the patent has expired and no other intellectual property issues exist.

In January and December 2018, CDE issued two lists of drugs to the local pharma industry, one listing drugs with their patents expired, terminated or invalid and another citing drugs without any local generic in the China market.10,11

In total, 16 drugs are listed with clear statement that all 16 have specific medical value and are without patent protection. Clearly, CDE’s intent is to encourage local pharmaceutical firms to produce these drugs, all of which still have potential market value and, thus, increase access to these drugs for the public.

Meanwhile, CDE offers priority review treatment on these patent-expired (or first-launched) generic drug applications. Based on CDE’s 2018 annual report, among the 313 priority-reviewed applications, 25 (8%) fall in this category. Among 83 drug approvals via priority review process, 10 (12%) are patent-expired or first-launched generic drugs. This is compared to 2017 when among 50 drug approvals via priority review process 10 (20%) were patent-expired or first-launched generic drugs.

Finally, the most important development for the China pharmaceutical industry in 2019 was the August announcement regarding the passage of the new version of Drug Administration Law (DAL) previously approved and issued by the National Congress Committees.12 This took effect 1 December 2019.

The current effective law dates to 1985. There have been many significant changes in this new version, which can be considered the over-arching law for the China pharmaceutical government and industry and the basis for policy and regulation by NMPA. It is clearly oriented toward unmet

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application can be treated as conditional acceptance of foreign clinical data, and result in a request for post-marketing collection of safety and efficacy data for further assessment.”
medical needs, as noted particularly by the following three clauses:

- Clause 16: encourages clinical-value-oriented new drug innovation, supports new therapeutic mechanism, multitarget research or new drugs with clear or specific efficacy, and encourages (including priority review) new drugs specific to pediatrics.

- Clause 26: for drugs indicating serious life-threatening disease without effective therapy or for urgent needs for public health issues. If its mid-term clinical trial result can show benefit and efficacy and predictable clinical values, conditional approval can be granted.

- Clause 96: encourages research and manufacture of drugs in short supply. Will have priority review on urgent short-supplied drugs, and new drugs for preventing serious infectious diseases or rare diseases.

Apart from encouraging new drug innovation to meet unmet medical needs, there are other new policies or systems that were not covered in the previous version. These include:

- Drug Marketing Authorization Holder (MAH) system, which refers to enterprises or R&D institutions that hold a drug approval license. The legal representative and the principal responsible person of the MAH shall take full responsibility for the quality of the drug products.

- The drug traceability system, in which NMPA should formulate unified drug traceability standards and regulations, drive mutual communication and sharing of drug traceability information.

- The pharmacovigilance (PV) system, in which NMPA should establish a system to monitor, identify, evaluate and control adverse reactions or other responses related to drug usage.

These new policies and systems are important for strengthening drug administration, ensuring drug quality, protecting the public’s medication safety and legitimate rights and interests, all while protecting and promoting public health.

One common question for global regulatory agencies is how to use Real-World Evidence (RWE) to complement randomized clinical trials in evaluating the efficacy and safety of drugs. China is also considering how to respond to this question. For example, CDE issued its “Key Considerations in Using Real-World Evidence to Support Drug Development” in May 2019 to “provide clarity on the definition of real-world research, outline the use and scope of real-world evidence in drug R&D, explore the basic principles for the evaluation of real-world evidence, and consequently provide scientific and practical guidance for the industry to consider when utilizing real-world evidence to support drug development.”

The draft defines RWE and provides scenarios where RWE supports drug development and regulatory decisions.

DAL also incorporated some recent improvements and achievements into regulations, such as a new management system for clinical trials, priority review and conditional approval, management of drug standards, postmarketing management system and a strong sanctions system. These new regulatory topics are also important in consolidating the results of the regulatory reforms instituted since August 2015.

**Conclusion**

Since China’s regulatory reform started in 2015 there have been many policy introductions and improvements. These have markedly stimulated enthusiasm for new drug innovation and venture capital, with many enterprises committing to new drug and biological product research in China. This reform also has attracted foreign pharmaceutical and biotech companies to conduct clinical trials and have their drugs registered in China. From CDE’s
2018 drug review annual report, this growing trend is clear and is having a significant impact on China and the global pharmaceutical, clinical trial and CRO industries. Many companies not previously considering including China in their clinical development ventures or as a market for new drugs are now actively pursuing such activities. This is a trend expected to continue.

The importance of addressing unmet or urgent medical needs cannot be underestimated for drug researchers and manufacturers. This does not mean all new drugs are welcomed, nor are all generics discouraged by NMPA. However, any pharmaceutical company or innovator, before commencing R&D activities in China, must conduct a careful market to ascertain the urgent or unmet pharmaceutical needs in China.

References

1. Opinions of the State Council on Reforming the System of Review and Approval of Drugs and Medical Devices. 2015. No. 44. National Medical Products Administration (NMPA) website.


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Bill Wang, former director, regulatory affairs, PPD, has 27 years of experience in the China pharmaceutical industry, including 19 years in regulatory affairs with local China pharma and CROs, with a strong working knowledge of China regulations, guidance and requirements.

This article discusses the rising price of insulin and its historical context. The authors review and analyze legislative efforts to keep prices reasonable for patients and review the various barriers to making insulin less expensive. They conclude by looking at the potential effects of regulatory changes by FDA to transition insulin from regulation under the Federal Food, Drug and Cosmetic Act (FD&C Act) to the Public Health Service Act (PHS Act), and suggest that insulin, being a relatively well-characterized molecule, deserves special regulatory consideration.

Introduction
Diabetes affects more than 30 million Americans, approximately 7.4 million of whom use one or more formulations of insulin to achieve glycemic control. Effective management of blood glucose levels is essential to reducing diabetes complications, comorbidities and mortalities. However, insulin prices have risen dramatically in recent years, in part due to a lack of competition from generic insulins. Although Congress and FDA have taken steps to promote the development of “generic” interchangeable insulin products with the aim of increasing market competition to lower prices, the price continues to rise, nearly tripling between 2002 and 2013. As a result, people suffering from diabetes are forced to choose between paying for life-saving medication and affording other necessities.1

A recent study, published in the Journal of the American Medical Association (JAMA), found that roughly one-quarter of patients with Type 1 or 2 diabetes are using less insulin than they are prescribed to manage high costs.2 Insulin rationing exposes patients to serious short and long-term health consequences and contributes to the $327 billion annual cost for
diabetes in the US. In 2017, healthcare expenditures on insulin alone were almost $15 billion.3

On 23 March 2020, insulin products will transition from being regulated as drugs to being regulated as biologics. This change is part of an effort to promote competition to reduce pricing and provide - for the first time - a regulatory pathway for the approval of interchangeable insulin, which could be freely substituted at the neighborhood pharmacy without the intervention of a healthcare provider.4

**Insulin Development History**

Insulin was not always as costly as it is now. It is an unfortunate irony that the Canadian researchers responsible for the isolation of insulin in 1921 sold the patent to the University of Toronto for three Canadian dollars with the sentiment that everyone who needed the medication should be able to afford it. By 1923, insulin was being commercially produced by Eli Lilly and, by the end of the same year, the Danish nonprofit, Nordisk Insulin Laboratory (what would later become Novo Nordisk), followed by developing its own insulin in Scandinavia. In the ensuing decades, manufacturers improved insulin formulations, first using animal derived insulin and, in 1982, producing human insulin in bacteria using recombinant DNA. Further advancements were made in the 1990s with the production of insulin analogs better able to mimic the pharmacokinetics of the body’s own insulin production.5

Since the 1990s, the rising cost of insulin has dramatically outpaced inflation. In stark contrast to the Canadian researchers’ 1921 vision of accessible and affordable insulin, insulin has instead become the “poster child” for unrestrained pharmaceutical price increases.

"Since the 1990s, the rising cost of insulin has dramatically outpaced inflation. In stark contrast to the Canadian researchers’ 1921 vision of accessible and affordable insulin, insulin has instead become the “poster child” for unrestrained pharmaceutical price increases."

then.7 Lower cost insulin alternatives for purchase over-the-counter exist for uninsured or under insured patients. For example, Novo Nordisk’s Novolin R and Novolin N (regular and neutral protamine Hagedorn [NPH] insulins) can be purchased under Walmart’s ReliOn brand for $25 per 1000-unit vial, which would translate into approximately $400-700/year for most with Type I diabetes. However, clinicians are often reluctant to recommend them and patients reluctant to take them because they are perceived as being less desirable therapies, a possible result of the newer insulins being promoted as being preferred, or superior, therapies. Thus, insured patients must play a continuous game of catch up, switching medications as insurance companies periodically change which medications they cover.8

**The Regulatory Landscape for Insulin**

A contributing factor to rising insulin costs is a lack of competition from generic insulins. In the US, just three companies—Eli Lilly, Novo Nordisk and Sanofi Aventis—dominate the insulin market. All three insulin makers have raised list prices to similar levels.9 Insulin manufacturers have been protected from generic competition by how insulin has historically been regulated. As the biotechnology industry began to develop its first biologics for human therapeutic use in the late 1970s and early 1980s, some biologic products were regulated as drugs under the Federal Food, Drug and Cosmetic Act (FD&C Act), including insulin, while others were regulated as biologics under the Public Health Service Act (PHS Act), e.g., cytokines, monoclonal antibodies and blood factors). Under this framework, drugs (and insulin) were regulated by the Center for Drug Evaluation and Research (CDER), while biologics fell under the purview of the Center for Biologics Evaluation and Research (CBER). Prior to the enactment of the
In contrast to biologics, a pathway for approval of generic drugs has existed since 1984 through the Hatch-Waxman Act. However, no generic insulins have been brought to market through the generic pathway due to the added complexity of insulin in comparison to many small molecules. Insulin aside, the Hatch-Waxman Act was successful in facilitating generic drug development and reducing the cost of small-molecule drugs by allowing generic drug makers to submit an Abbreviated New Drug Application (ANDA), rather than a full NDA, to demonstrate that the generic is the same as the brand-name drug (Reference Listed Drug (RLD)).

Generic drugs were able to reference the RLD instead of conducting the full range of costly nonclinical and clinical trials expected of a new molecular entity, provided that bioequivalence and “sameness” were demonstrated. Prior to the approval of the Hatch-Waxman Amendment, only 35% of brand-name drugs had a comparable competitor. Currently, nearly all drugs have a generic competitor and generics account for 90% of US prescriptions dispensed, but only 23% of prescription drug spending. Despite the tremendous impact of the generic drug pathway for providing affordable and competitive alternatives, this pathway is not available to insulin users. Hoping to change this, US Representative Mike Kelly (R-PA) introduced H.R. 4244, the Market Access for Generic Insulin Competition Act (MAGIC Act) in September 2019. If passed, the legislation would establish an approval pathway for generic insulin production via the ANDA process.

Although no generic insulins are currently available, follow on insulin products (those relying, in part, on safety and efficacy findings for an FDA approved product) have been approved by CDER under Section 505 of the FD&C Act. To date, two follow-on insulin products have gained approval through the 505(b)(2) pathway:

1. Basalgar (Eli Lilly), a follow on to Sanofi’s Lantus (insulin glargine)
2. Admelog (Sanofi), a follow on to Eli Lilly’s Humalog (insulin lispro)

These follow-on products have had some success in capturing market share from their reference insulin products and have lowered insulin costs for some patients. For example, Basalgar is priced 15% less than its reference product Lantus, but still remains listed at $450 for a 30-day supply. These modest savings are contingent upon the less expensive insulin product being covered by a patient’s insurance plan; if a drug is not covered, out-of-pocket expenses offset any potential savings. Generics are, in part, successful at lowering drugs costs because a pharmacist can readily identify and substitute a cheaper alternative. Although these follow-on insulins present some cost savings for patients, a truly interchangeable insulin that could be freely substituted for brand name insulin at the pharmacy level remains the goal for reducing diabetes associated treatment costs. However, it should be noted that for interchangeable insulin to have any meaningful impact on lowering prices, the introduction of multiple “generic” competitors would likely be necessary, otherwise the price reductions would be modest.

Insulin’s Transition to Section 351 of the PHS Act*

Recognizing the need to create more affordable biologics, Congress passed the BPCI Act. Similar to the Hatch-Waxman Amendment for drugs, the BPCI Act was passed to create a regulatory approval pathway for the marketing of highly similar follow-on biologics, known as biosimilars, and the generic equivalent for biologics, interchange-
The Changing Regulatory Landscape for Insulin

ables, under the PHS Act. To provide a pathway for interchangeable insulin, FDA is planning to transition insulin products (and selected other products), which are currently approved under the FD&C Act as drugs, to being deemed licensed as biologics under the PHS Act in accordance with stipulations of the BPCI Act.* In 2018, then acting FDA commissioner Scott Gottlieb announced FDA would leverage this pathway to promote competition for insulin.18 This transition, set to occur on 23 March 2020, will, for the first time, provide a regulatory pathway for the approval of clinically equivalent (interchangeable) follow-on insulins. As of December 2019, 26 biosimilars have been approved by FDA; none of these are currently designated as interchangeable, however.*

Under Section 351(k) of the PHS Act, an application for a biosimilar product must present data demonstrating the product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency (PHS Act 351(k)(6)(2)). Supporting evidence of biosimilarity should be based on data derived from analytical studies (structural and functional tests), animal studies (toxicity tests) and clinical studies (including assessment of immunogenicity and pharmacokinetics or pharmacodynamics) (PHS Act 351(k)(2)(a)). However, unlike generic drugs, biosimilars cannot be substitut-ed by a pharmacist to “stand in” for a branded biologic; it must be specifically prescribed by a healthcare provider.

Interchangeables take biosimilarity a step further by fulfilling all the requirements listed above while also being proven to produce the same clinical result as the reference product in any given patient. According to FDAs guidance on interchangeable products, this is accomplished through the use of “switching studies” to demonstrate that “the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such an alternation or switch.”19 Switching studies typically assess whether alternating a patient between the reference product and the proposed interchangeable product affects clinical safety or efficacy when compared against patients who are treated exclusively with the reference product.

FDA has recently updated its approach to insulin, as described in a draft guidance issued in November 2019, Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products.20 The guidance states that current analytical tools may provide an adequate comprehensive analytical comparison to demonstrate that a proposed interchangeable insulin product is “highly similar” to its reference product; therefore, uncertainty regarding immunogenicity is reduced, and “an applicant would not need to conduct a comparative clinical immunogenicity study...”
It remains unclear whether this new regulatory framework for insulin will have the same success at reducing costs as did the Hatch-Waxman Act. Regulatory expectations for biosimilar approval and interchangeability are nascent and still evolving, thereby contributing a degree of uncertainty to the approval process. Transitioning insulin products will be regarded as standalone products under 351(a), despite the fact that several were approved as follow-on drugs to an RLD. For example, Basaglar gained approval via the 505(b)(2) pathway and its NDA referenced the originator (the RLD), Lantus. Despite being a follow on to Lantus, Basaglar will not be regarded as a biosimilar to Lantus after the transition to the PHS Act. Therefore, transitioning insulin products originally approved as follow-on products will still need to demonstrate biosimilarity and interchangeability per the stipulations outlined under Section 351(k) of the PHS Act to achieve these designations.

If interchangeable insulin products are to be developed and marketed, there must be ample incentives for their development. The 351(k) pathway provides one year of marketing exclusivity for the first interchangeable biosimilar biological product approved for a reference product (PHS Act 351(k)(6)(a)). However, with respect to market forces and the litigation landscape, there are potential barriers. Of the 26 biosimilars approved by FDA (as of December 2019), only about one-third have been launched due to patent litigation. The complexity of manufacturing processes for biologics lends itself to the creation of “patent thickets,” whereby innovator companies create overlapping patent rights that biosimilar sponsors must navigate to reach commercialization. Lengthy patent litigation has delayed the launch of a number of biosimilars, including Erelzi, Amjevita, Cyltezo, Mvasi, Ogivri, Hyrimoz, Herzuma and Truxima.23

In addition to the regulatory hurdles affecting the development landscape for insulin, the evolving insulin marketplace for currently approved products also could diminish the attractiveness of developing interchangeable insulin. Of note is the introduction of authorized generics for insulin. Contrary to their namesake, authorized generics are not generic drugs, but brand name drugs marketed as generics at lower list prices. Eli Lilly released an authorized generic of its insulin lispro in March of this year; Novo Nordisk plans to follow suit with authorized generics of NovoLog and NovoLog Mix in January 2020. The introduction of such products, while possibly providing short-term cost savings to patients, may undercut the profitability of interchangeable insulin products during the one year exclusivity period. It is worth noting that the introduction of authorized generics is just one of several strategies innovator companies use to block competition. For example, brand-name companies frequently engage in “patent evergreening,” a practice that artificially extends patent life by making slight modifications to old drugs, thereby preventing the entry of competitors into the market.24

Finally, the current regulatory approach assumes that competition spurred from the introduction of interchangeable insulin will lower prices. The current state of the insulin market suggests that in the setting of unregulated drug pricing, competition may not be as effective. Competition for insulins, albeit with a relatively small number of competitors, does exist to some extent. While there are no interchangeable insulins in a regulatory sense, some insulin products are used interchangeably in the clinical setting. As mentioned previously, it is not uncommon for physicians to switch a patient’s prescription in response to
changes in insurance coverage. Still, prices have continued to rise. The list prices of common types of insulin have tripled over the last ten years, despite being the exact same products offered a decade ago.25

**Conclusion**

Insulin, a relatively well-characterized molecule of comparably less structural complexity than other biologics, deserves special consideration with respect to how it is regulated. FDA held a hearing in May 2019 to obtain feedback from industry, healthcare providers and patients regarding the approval process and unique scientific considerations for interchangeable insulin.26 The overwhelming sentiment was that without interchangeability, the regulatory transition allowing for approval of “generic” insulin under Section 351(k) would have no meaningful impact on rising costs. Public comments received at this meeting are reflected in the recently issued guidance for interchangeable insulin, which provides additional clarity regarding comparative clinical immunogenicity studies and other criteria for approval. Even so, the barriers to accessible and affordable interchangeable insulin extend beyond the regulatory paradigm under which they are approved. Without addressing other problematic issues, the current approach alone may not be effective at mitigating rising insulin costs.

**References**


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Applying FDA’s Rules in the New World of Online Marketing and Crowdfunding

By Suzanne Levy Friedman, JD

This article provides an overview of US Food and Drug Administration (FDA) authority, regulations and policies regarding promotion of medical devices through websites and social media. The principles discussed generally apply to promotion of pharmaceutical products also. The author discusses internet and social media marketing and online preapproval communications, specifically addressing “crowdfunding” and where FDA may focus its enforcement activity in this newer context. This article was adapted from a RAPS Convergence presentation held in Philadelphia 21–24 September 2019.

General Rules of Marketing and Promotion

What are claims?

Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), FDA has jurisdiction over medical device labeling, as well as over advertising of prescription drugs and restricted devices. Importantly, FDA and the courts have broadly interpreted "labeling" to encompass essentially any material that is used to facilitate the sale of a product; it may, but need not be, physically affixed to the product package. Examples include:

- letters/e-mails to customers
- brochures/flyers
- price lists/catalogues
- trade show exhibits
- literature
- website materials
- social media posts and interactions
- testimonials by health care professionals or patients
Advertising can include information in published journals, magazines or other periodicals, and broadcasts through media such as radio and television. Promotion refers to any activity meant to facilitate the sale of a medical device and includes all oral and written statements by a manufacturer or its representative, regardless of medium, whether in person (e.g., presenting product capabilities at public forums), in print (e.g., distributed collateral) or online.

Unless exempted by regulation, a medical device requires either 510(k) clearance, premarket approval (PMA) or de novo down-classification prior to commercial distribution. In the US, commercial distribution refers to displaying, promoting or otherwise offering for sale for a specific intended purpose, taking orders or entering into distribution agreements and discussing when the product will be available. Company labeling/advertising may promote a device only for cleared/approved intended uses. Advertising, promoting or labeling a product for a new intended use that requires premarket clearance or approval, may be deemed adulteration and/or misbranding in violation of the FD&C Act.

Medical device claims are tied to the device’s intended use and the company’s intent in selling it. These may be express or implied. As a general rule, claims must be adequately substantiated by scientifically valid data (e.g., statistically valid sample size, peer-reviewed publication) at the time the claim is disseminated in order not to be considered false or misleading (and thereby in violation of the FD&C Act). Relevant facts about underlying studies should be disclosed. For cleared devices, data to support certain claims may sometimes be kept in the sponsor’s regulatory files without requiring submission of data or a [new] 510(k) notice. However, FDA increasingly seeks to review the support for a claim prior to its being made. Significant performance claims must be submitted for review. Clinical outcome claims must generally be supported by clinical data. For PMA-approved (Class III) devices, approval of a PMA supplement is generally required to support new claims, even if there has been no change to intended use.

FDA also may find a claim false/misleading if it reflects misstatement or omission of material fact, lack of fair balance, lack of adequate directions for use or misleading representation with respect to another device. Risk information should not be minimized (e.g., tiny font at the very end) and should be presented in a manner that is balanced and consistent with the presentation of benefits. FDA considers comparative/superiority claims inherently misleading unless based on appropriate head-to-head testing. In addition, the agency is sensitive to claims about FDA regulatory status, as it does not want to impart an erroneous impression of official endorsement of a product.

Marketing, Advertising and Promotion in the Online World

The emergence of the internet and social media, such as blogs, Facebook and Twitter, have opened new channels of communication and opportunities for advertising, marking and promotion of pharmaceuticals and medical devices.
However, when compared to traditional print marketing, marketing through the internet/social media does create new challenges because of the differences in format, audience and accessibility. Many companies have internal Standard Operating Procedures (SOPs) to ensure consistent activities in this space, particularly with respect to controlling employee statements on today’s social media platforms. FDA has issued Warning Letters for misuse of the internet and social media for a number of issues which are not unique to online marketing but do manifest there somewhat differently.

A Bit of Reprieve

FDA draft guidance7,8 issued in 2014 provides some assistance in understanding the agency’s interpretation of how existing rules should be applied in the context of the newer internet promotional vehicles. This guidance also provides a bit of leeway for manufacturers to navigate limited-character settings (e.g., Twitter) by deferring complete instructions for use to another site and providing a mechanism (e.g., hyperlink) to allow direct access to a more complete discussion of risks. Nevertheless, each post or webpage is required to provide a balanced presentation of both risks and benefits, and must include at a minimum the most serious risks and the risks associated with any discussed particular use or population. Importantly, just because a platform exists does not mean it is appropriate for a particular product—if it cannot adequately convey the key information in a non-misleading manner, it should not be used.

Separately, in June 2018, FDA finalized two guidance documents which providing manufacturers some additional leeway in communications about their drugs/devices. While FDA has, through these guidance documents, defined a broader category of claims as “on label,” it stops short of permitting claims regarding unapproved uses, patient populations, doses and situations that might shift the risk/benefit balance. The types of information covered by both still constitute promotion, so corresponding requirements still apply (not false/misleading, balanced, etc.)

In its guidance “Medical Product Communications That are Consistent With the FDA-Required Labeling,”9 the agency concedes that FDA-required labeling is not meant to encompass all information about a drug/device and its approved uses. This is important, as cleared or approved indications for use range from one sentence to a few paragraphs. If a company can only use that text to promote the product, it would be challenging from a business perspective. To that end, the guidance permits manufacturer communications to include claims that are not contained in, but “consistent with,” FDA-required labeling as long as they consist of truthful, non-misleading data/information about cleared/approved use(s), and clarifies what that entails. Information/data supporting a “consistent” claim that is not misleading must be “scientifically appropriate and statistically sound.” The “consistent with labeling” framework is more notable for PMA-approved devices, as for cleared (and exempt) devices, the guidance directs manufacturers to the pre-existing framework for assessing 510(k) modifications.

FDA’s guidance, “Drug and Device Manufacturer Communications with Payors, Formulary Committees and Similar Entities,”10 defines a specific audience with appropriate knowledge/expertise (“payors”) and related entities—to whom firms may disseminate Health Care Economic Information (HCEI) that is “related to” a prescription product’s cleared or approved indication. Importantly, while this guidance also allows some claims which are not directly encompassed by the product’s clearance or approval, the audiences with whom they may be shared explicitly exclude patients and health care professional users.

Importantly, just because a platform exists does not mean it is appropriate for a particular product—if it cannot adequately convey the key information in a non-misleading manner, it should not be used.
Social media platforms using the internet and social media tools, such as blogs, YouTube, Instagram and Facebook have raised unique challenges as compared to traditional print marketing. In terms of social media marketing, a company is responsible for any site/content that it owns, controls, creates, influences or operates, content generated by an employee or agent acting on behalf of the firm, and promotion on third-party sites where it has any control or influence.

Internet and Social Media Promotion and Enforcement

FDA considers website materials as “labeling.” This includes information to which a company links on its website. Portal pages should direct visitor to sections of the site if clearance/approval is not universal. Disclaimers regarding US regulatory status are not enough. Regarding press releases, FDA permits more information than otherwise typically allowed in labeling, but restrictions still apply and the material should be in a distinct, clearly identified section of the website.

Social media platforms using the internet and social media tools, such as blogs, YouTube, Instagram and Facebook have raised unique challenges as compared to traditional print marketing. In terms of social media marketing, a company is responsible for any site/content that it owns, controls, creates, influences or operates, content generated by an employee or agent acting on behalf of the firm, and promotion on third-party sites where it has any control or influence (e.g., editorial, preview or review privilege). This includes marketing communication carried by someone else but on behalf of the firm. However, a company is not considered responsible for content that is truly independent from it (e.g., user-generated) and not prompted by the company, even if it is on a company-owned or -controlled medium, message board or chat room. It is unclear exactly where FDA draws the line on what constitutes “prompting” in this context, so many companies prefer a cautious approach to third-party marketing of their products.

More specifically, companies are responsible for the following:

- providing fair balance and required context on platforms with space restrictions and functionality limitations
- monitoring user-generated content for Adverse Event (AE) reporting requirements
- responding to “misinformation” posted by users on webpages owned, operated or influenced by the company (includes potential off-label information and false, misleading or biased materials)
- controlling employees’ comments and responses

The fundamental requirements for promoting via social media are the same as for any other forum, such as accuracy, being non-misleading, including key risk information and fair balance. The key violations cited in internet and social media marketing are the same as in other promotional platforms and center around promotion outside the scope of clearance/approval, promotion without any clearance/approval and misleading presentations (e.g., unbalanced presentation of risks/benefits). The difference is that the violations are carried out via links on company websites, search engines and meta-tagging as opposed to other, more “traditional” means. FDA is now looking to such “tech-savvy” applications as a basis for construing evidence of company intent or inappropriate promotion.

A New Type of Preapproval Communication: Crowdfunding Medical Devices

A key concern with any preapproval communication is that it may lead potential users to forgo cleared/approved therapies based on the promise of a pipeline product that has not been and may never be found safe and effective. FDA does not want a false impression to be given; its primary mission is to protect the public health.

Against this background, newer avenues for preapproval communications raise some unique questions not explicitly covered by FDA’s existing policies. One area for consideration is “crowdfunding.” Crowdfunding websites enable companies to showcase uncleared/unapproved devices and to promise or provide them to consum-
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One of the draws is that it enables capital to be raised from a larger pool of people than was historically possible through standard funding avenues; it also rapidly raises awareness of (and interest in) the product. Questions that apply to all preapproval communications including crowdfunding, but which manifest a bit differently in this context, include: when does soliciting for funding of a developmental product become preapproval commercialization or “priming the market?” Are companies “priming the market” when social media is involved? At what point does funding become a “purchase?”

Other important issues include:

- the potential inappropriate display/promotion of an investigational device for a specific intended purpose
- the perception of taking orders or [preparing for] selling an uncleared device through its delivery or promising to deliver it upon FDA clearance
- the promotion to a non-specific/layperson audience may encourage FDA to scrutinize communications more closely as “direct to consumer” (DTC) marketing, because the audience is less educated in assessing risks/benefits than health care professionals.

There is a notable lack of direct FDA guidance on what a company should or should not do in terms of crowdfunding marketing/promotion. An article in the Boston Globe a few years ago (2015) reported FDA as stating that companies must follow marketing and advertising regulations regardless of how funds are being raised and noted the agency did not respond to questions on the legality of specific crowdfunding practices, saying it will tailor its regulatory approach as appropriate. This emphasizes that the fundamental rules in this context are the same, but does not give companies any practical advice on how to move forward as the marketing mediums shift and evolve.

With a dearth of targeted FDA guidelines addressing crowdfunding, regulatory professionals are left striving to apply existing rules and guidance and hope they are doing it right. In this situation, consideration of existing legal frameworks, current agency policies where there may be parallels, and any cases of FDA enforcement action or intervention in a similar campaign provides useful insights for evaluating the likelihood of FDA attention to a particular campaign. Companies set to engage in crowdfunding should assess the proposed campaign and its website per FDA’s general framework, and provide only truthful, accurate and non-misleading information. They also should not imply a product’s safety or effectiveness where this has not yet demonstrated to FDA. A key concern (not specific to crowdfunding, but important to look out for) are videos, images or statements on the website that may violate FDA rules/policies around preapproval commercialization. Additional nuances more unique to this context include:

- stage of product development
- higher-risk devices are more likely to garner FDA concern
- content of campaign, e.g., explicit clinical outcome claims or superiority to alternatives versus “general wellness” type claims
- whether the device’s FDA regulatory status is conspicuously stated
- if product is 510(k)-pending, whether campaign is consistent with FDA’s Compliance Policy Guide (CPG)13
- consistency with FDA’s laws and policies for investigational devices14
- structure of investment

Factual statements limited to technical characteristics or statements regarding the company’s mission, are less likely to garner attention than significant claims related to a product’s safety or effectiveness. If a 510(k) is pending, all statements should be limited to and consistent with what was submitted to
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FDA. In terms of the campaign’s structure, providing or promising to provide the device might be seen as tantamount to taking orders for it or generating a list of future customers, both of which practices would be a violation of FDA requirements. Specifically, a “promise” of a device in exchange for a donation is more likely to generate FDA concern as a ‘pre-order,’ or purchase, as opposed to more limited “rewards.” Along the same lines, if there is no promise of a coming device and/or the company is only fundraising for early R&D or to support a planned regulatory filing, that is both less controversial and less likely to raise concern from an FDA regulatory standpoint. Therefore, it is important for statements to make clear exactly in what manner contributors’ money will be used.

Precedent also sheds some light on FDA’s priorities in this space. A number of recent medical device crowdfunding campaigns have been cut short without clarity as to whether this was motivated by an FDA communication. In other cases, products that appear to warrant FDA regulation as a medical device have been funded in this manner without evidence of any FDA objection to their lack of clearance or the claims being made. Based on available precedent, FDA is more likely to step in where the crowdfunding platform is used to conduct DTC marketing for a type of device it finds particularly concerning. For example, FDA has long scrutinized promotion/sale of genetic testing without FDA review or physician oversight (recall, for instance, the Warning Letter issued to 23andMe expressing concerns over clinical/analytical validity). When Tute Genomics offered to sequence the entire genome and exome of contributors to its Kickstarter campaign, and to provide them with a report containing information on actionable variants in their DNA and the risks of developing various diseases, FDA took notice. The company suspended the campaign only two days after it began, informing backers that the agency had expressed concern.

**Takeaways**

Newer avenues for internet marketing, including in the sphere of preapproval communications, raise unique questions not explicitly covered by existing regulations and FDA policies. Crowdfunding is an interesting new way to raise money for new inventions from a broader population base, and one which may be more representative of the full audience that would use a device; but it also has potential pitfalls. Similarly, social media and other internet marketing presents great opportunities but also notable risks. With very limited public instructions on how to proceed with specific types of such newer communications, companies must interpret the available guidance and precedent and determine how much risk they are willing to incur in the gray areas. Signs indicate that FDA will continue to apply its governing risk-based framework in deciding where to focus its attention; by and large, “triggers” for FDA scrutiny appear when statements or practices are inconsistent with past policy/enforcement and/or raise notable risks for consumers. Ultimately, to successfully balance business needs with regulatory compliance in selecting a path forward, companies will need to take into consideration existing regulations/policies, past actions by FDA and common sense. The “rules of the road” remain the same; how they are applied in practice in these newer contexts just takes a bit more thinking.
References


2. 21 CFR § 1.3(b), Kordel v. US, U.S. Supreme Court, 1948.

3. “Material facts” refer to relevant warnings and risk information, qualifying requirements for use, potential consequences from use of a product as suggested in the piece and adequate directions for use (prescription and over-the-counter devices have slightly different requirements in this last respect, but the fundamental categories of information that must be included are the same).


5. 21 CFR Part 801: Labeling. Subpart A: General Labeling Provisions. Sec. 801.6 Medical Devices; Misleading Statements. “Among representations in the labeling of a device which render such device misbranded is a false or misleading representation with respect to another device or a drug or food or cosmetic.” Even where a company is comparing to a prior version of its own device, head-to-head supportive testing should be provided. Typically, such testing must be reviewed by FDA prior to serving as a basis for claims. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=801.6. Accessed 7 January 2020.


11. There are two types of crowdfunding. The first, on which this article focuses, is rewards-based: individuals donate to a cause or pre-purchase products without getting shares or a stake in the recipient of the funds. The second is equity/investment, where funding is tied to an equity interest granted to the payor.

15. “Cur is Crowdfunding a Medical Device That Isn’t Cleared by the FDA and That’s a Problem.” *The Verge.* 14 May 2015.
17. For instance, Upright Technologies promoted its wearable biofeedback device intended to correct posture by vibrating to remind the user to sit straighter. The website had offers of sale comparable to other crowdfunding campaigns and explicit efficacy/clinical outcome claims. The company appeared to have data supporting its assertions, but the device was not, and still is not, FDA-cleared. [https://www.kickstarter.com/projects/upright-go/upright-go-fix-your-screen-slouch-correct-your-pos](https://www.kickstarter.com/projects/upright-go/upright-go-fix-your-screen-slouch-correct-your-pos). Accessed 6 January 2020.

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