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Regulatory Intelligence and Policy: Shaping the Global Landscape

By Meredith Brown-Tuttle

Welcome to the fourth edition of the 2019 Regulatory Focus Article Series. Inside you will find a collection of insightful articles covering global best practices in regulatory intelligence and policy. It is a pleasure to bring together some of the top regulatory intelligence thought leaders from around the world—all with diverse experience—to offer their perspectives on the importance of regulatory intelligence and the integral role RI professionals play in defining strategy for companies in regard to development, approval and maintenance of products, as well any changes to regulations impacting the global regulatory landscape.

Communication is Key

To stay current with the rapidly changing landscape, regulatory professionals must monitor and identify pertinent regulatory information on a continual basis. This information must be analyzed and interpreted for the application and implications to team projects, the organization and potentially other partners or clients. But generating this intelligence is just the first step. In their article, “Proactive Regulatory Intelligence Communication,” regulatory experts, Emily Huddle and Kirsten Messmer, identify communication approaches for medium to large companies and highlight the advantages and disadvantages of each.

Regulatory Intelligence (RI), in one form or another, has always been a component in a successful FDA meeting. However, in past years, as specialization of functional areas has continued to fracture and diverge, the need for quality, relevant and timely RI has increased. Regulatory manager, Matt Medlin, illustrates how to best leverage a dedicated RI function or skill set to prepare for and have the most successful regulatory interaction with FDA. “FDA Meetings: The Application of Regulatory Intelligence in Preparation and Execution” provides insight and suggestions regarding the role RI professionals can play to help assure a successful interaction during each FDA meeting phase.

Gathering Data and Analyzing Information

How do you keep track of everything, read everything and know how to get regulatory intelligence?

Regulatory and quality expert, Richard Vincins, addresses this question and more in “Managing Regulatory Intelligence for Medical Devices.” He covers how medical device guidance documents, regulations, standards and requirements are presented in increasing amounts and how regulatory professionals can access, assess, manage and ultimately report to their organizations on the potential impact of regulatory changes. He includes “tips” for making the hard work of international regulatory intelligence for medical devices easier and more efficient.
By 2018, a significant number of artificial intelligence (AI) applications had been developed for use in healthcare. For example, 2018 saw the first medical device using AI to provide a screening decision—without the need for a clinician’s opinion. Experienced regulatory professional, Pei-Ting Sarah Chou, explores the topic in “The Emerging Role of Artificial Intelligence in Healthcare,” presents current and future AI healthcare applications, examines AI’s potential for adding efficiency to pharmaceutical research and medical practice and suggests the potential for providing better healthcare and patient diagnostic and treatment outcomes. The article also examines AI applications’ ethical concerns, the potential for misuse and the case for developing ethical standards.

**Regulatory Strategy**

Regulatory intelligence professionals support the drug development process with strategic information, serve as liaisons with regulatory agencies and channel information to appropriate stakeholders. In “Regulatory Intelligence Communication for Business Impact,” regulatory experts, Kirsten Messmer and Charity-Anne Schuller, present an overview of applicable delivery methods and general considerations for communicating information via spreadsheets, text documents, slide presentations, strategy reports and competitive intelligence reports. The authors explain how to maximize regulatory intelligence when responding to specific stakeholder requests and offer recommendations for clear communication.

With the Chinese regulatory landscape constantly changing, it has become necessary to reevaluate the roles and restructure how the healthcare regulatory authorities and healthcare policy administrations are organized. In “Chinese Health Policy and Regulatory Authorities Overview,” Yingying Liu describes the recent changes to China’s healthcare regulatory authorities and healthcare policy administration. Liu outlines how the reorganization and restructuring of the former Chinese Food and Drug Administration (CFDA) and several other organizations in March 2018 affects the responsibilities and functions of the many government departments, agencies and regulatory bodies responsible for overseeing drugs, food, medical devices, testing and evaluation.

Biomedical research is advancing rapidly and a key part its advancement is in the analytical capabilities allowing comparison between a reference biological product and a biosimilar product. In “Comparison of Data Requirements for the Approval of a Biosimilar Versus the Reference Medicine,” senior regulatory affairs consultant, Olivia McBride, defines both biologics and biosimilars and explains how and why the two differ in terms of their organic natures. She also guides the reader through the biologic vs. biosimilar developmental and testing stages and through agency approval and postmarketing surveillance.

Regulatory experts, Suzanne Schwartz and Michelle Jump, review past and current efforts to protect medical devices and other connected healthcare infrastructure from security breaches in “Protecting the Healthcare Infrastructure: Global Cybersecurity Compliance.” The authors cover recent regulatory efforts in Australia, Canada, China, Europe, Japan and the US aimed at enhancing cybersecurity and industry’s efforts in cybersecurity regulatory compliance to protect patients as well as healthcare infrastructure.

If you thought 2017 had a lot of changes, 2018 was even busier and 2019 is shaping up to be another groundbreaking year for transformation. Global intelligence expert, Meredith Brown-Tuttle, has assembled the major changes during 2018 in “Regulatory Strategist Toolbox: 2018 FDA Regulatory Intelligence Briefing.” She provides resources for guidance documents drafted and finalized, new legislation, other areas of interest and regulatory intelligence tools to help you explore additional areas.

Léa Coulet presents an argument for the value trade associations bring to healthcare in terms of promoting best practices, policies, regulations and standards in “The Value of Engagement With Trade Associations in Policymaking, Regulation and Standardization.” The author defines trade associations and lays out their functions and the value of those functions for regulators and policy makers and also presents defining characteristics of...
good regulations and good policies. The focus is on foods for special medical purposes and the author shares examples from the work of the Medical Nutrition International Industry (MNI) in these areas.

Since the introduction of the Dietary Supplement Health and Education Act of 1994 (DSHEA), the dietary supplement market has flourished with the addition of various product streams including products containing one or more botanical/herbal ingredients. In parallel, substantial advancements in analytical methodologies have led to a better understanding of the complexity and diversity of botanical chemistry and botanical preparations. In “the Botanical Safety Consortium (BSC): The Development of a 21st Century Framework for Assessing the Safety of Botanical Dietary Supplements,” experts Daniel Marsman, Joseph Dever, Stefan Gafner, Cynthia Rider, Sibyl Swift and James Griffiths, share their insights into steps to improve the safety of botanicals in dietary supplements. These leaders explore several US legislative initiatives and efforts by several nongovernmental organizations, such as the Council for Responsible Nutrition and the American Botanical Council, to track patterns of botanical use, and the Congress of the European Societies of Toxicology’s efforts to approach safety issues, including its establishment of the Botanical Safety Consortium and its working groups.

Conclusion

While RAPS offers a complete book on Regulatory Intelligence 101, these short summaries are meant to update and provide different perspectives in RI since in regulatory there are many ways to accomplish the same thing. We hope you spend some time reading the complete articles and benefit from the shared experiences of our authors. This collection was meant to give you the information needed to enhance your knowledge and keep your company up-to-date on current regulations affecting the development, approval and maintenance of products, as well any changes to the regulations and/or regulatory landscape that may impact your efforts. Your feedback is always welcome.

Want more on regulatory intelligence?

Mark your calendar for a lively Regulatory Exchange discussion on 11 December 2019 with the expert authors of the series. More details to come.

Meredith Brown-Tuttle, RAC, FRAPS, is the principal consultant for Regulatorium a company specializing in regulatory intelligence, writing and strategy. She is the author of IND Submissions: A Primer, published by Barnett, Regulatory Intelligence 101, published by RAPS, numerous articles and currently serves as the chair of RAPS Editorial Advisory Committee. She can be reached at theregulatorium@gmail.com.

This article focuses on regulatory intelligence communication approaches for medium to large companies and highlights the advantages and disadvantages of each.

Introduction

To stay current with the rapidly changing landscape, regulatory affairs professionals must monitor and identify pertinent regulatory information on a continual basis. This information must then be analyzed and interpreted for the application and implications to team projects, the organization and potentially other partners or clients. Generating this intelligence is just the first step. Communication is an important next step to ensure intelligence is implemented, whether to facilitate efficient drug development or a successful regulatory strategy. Communication strategies might depend on the type of information, company size, industry type (e.g., pharmaceutical, biotechnology, contract research organization (CRO), consulting, etc.) and audience size.

Compliance with regulatory requirements is integral to the research, testing, approval and continued ability to market new medicinal products. As regulatory approvals are sought in new markets, the spectrum of regulatory requirements likewise will multiply. The rapid development of new scientific and technological advances has demanded an ever-increasing pace of new regulatory guidance to ensure the development of safe, effective and high quality medicinal products. Additionally, new precedents are established in the form of innovative trial designs, endpoints and statistical analysis to answer scientific and regulatory questions during the drug development process. It is an essential part of a regulatory intelligence (RI) professional’s role to follow these updates/trends, analyze the impact to the organization and disseminate the information more broadly. The RI
professional’s responsibilities are best summarized within the Drug Information Association Regulatory Intelligence Working Group definition of regulatory intelligence:

“The act of gathering and analyzing publicly available information. This includes communicating the implications of that information and monitoring the regulatory environment for opportunities to shape future regulations, guidance, policy and legislation.”

The specific responsibilities of an RI professional will depend on a variety of factors, including business needs, company size and the background and experience of the individual. Assigned RI responsibilities also will depend on whether the person is solely dedicated to the RI role or only devotes a portion of time toward RI. Regardless of whether it’s a dedicated or part-time role, it is paramount that pertinent regulatory intelligence be effectively captured and communicated via the appropriate channels in order to reach its intended audience so it can be leveraged for the greatest benefit.

The presentation of RI most likely will depend on the intended audience or customers and the type of information. The term customers can refer to individuals within the same company such as regulatory affairs colleagues or other departments, or may be outside of the company, in the case that services are provided to external clients, partners and collaborators.

The intended use of RI also determines how polished the output from the RI is required. For example, if the RI will be used as part of a larger report or contract proposal, it may be provided in a raw format since it will be shaped by the entire team to fit into the overall presentation. On the other hand, something that will be provided directly to the ultimate customer will need to be extremely polished.

The communication of RI in response to a specific request or ad hoc query is not the subject of this article, but will be addressed in a follow up article. Proactive communication as addressed in this article has to be concise, precise and with actionable RI clearly identified.

Proactive Communication of Regulatory Intelligence

Essential to the role of an RI professional is the proactive communication of changes in legislation, regulations, guidance documents and other pertinent regulatory updates. An effective communication strategy includes dissemination to key stakeholders to ensure implementation of relevant changes, with potential impacts to regulatory compliance, time and cost-effective medicinal product development and/or successful regulatory strategies. The US Food and Drug Administration (FDA) issued a suite of draft guidance documents to support efficient development of oncology products (e.g., first-in-human expansion cohorts, master protocols, adaptive clinical trials, etc.). While analyzing the guidance documents, it is essential to highlight key aspects that could provide gains in efficiency or cost-effectiveness through the use of innovative trial designs described within the guidances:

- First-in-human expansion cohorts: A single protocol allows seamless progression from dose-escalation phase to three or more expansion cohorts addressing specific research questions.
- Master protocols: Umbrella, basket and/or platform trial designs allow the assessment of multiple therapeutic products and/or multiple indications or both within one protocol.
- Adaptive clinical trials: Adaptive trial designs allow prospectively planned changes to one or more aspects of trial design based on the data accumulated from patients.

The communication strategy to disseminate RI depends on the size of the company and on the overall impact and relevance of the guidance documents to the company. This article will focus on communication approaches for medium to large companies (including but not
limited to pharmaceutical, medical device, contract manufacturing, contract research companies and consultancies). For small companies (less than 100 employees for the purpose of this article), it may be likely to inform all employees across the company at the same time. The complexity of departments and reporting lines within a larger company may necessitate more defined communication strategies.

In the case of large companies with multiple oncology products at different stages of development the suite of oncology guidance documents likely has a major impact on planning of future oncology clinical trials. Therefore, the information will need to be communicated in various ways to ensure all applicable stakeholders are informed.

**Horizontal Communication**

Horizontal communication can be described as “flat” and involves disseminating information across a team, for instance a RI professional’s regulatory affairs colleagues involved in oncology clinical trials. In turn, these colleagues would engage the appropriate stakeholders in order to discuss the new guidance documents and to implement a regulatory agency’s recommendations to support their medicinal product development programs and regulatory strategies. However, this horizontal communication only would address projects already under way or are upcoming. A guidance of significant impact also should be leveraged in communication with future customers, i.e., business development. Using the example of the oncology guidance documents, multiple scenarios come to mind. Two of them are:

1. When communicating with a future potential customer at a very early stage of development, the first in-human expansion cohort guidance could be explored for applicability to that customer’s program. Highlighting the applicability of the guidance and how it could be applied to the program based on the presenting company’s experience likely would instill confidence in the potential client that the presenter is well-positioned to support the early stage program cost and time efficiently.

2. In the second scenario, the business development department is talking to a later stage client with a product that might be used in multiple indications. Here, to showcase the presenting company’s expertise, the implementation master protocol guidance and internal experience can be leveraged to demonstrate an efficient drug development program to the potential client. The necessity of communicating regulatory changes beyond a single department or team can be determined by a triage team in order to escalate the new information to a broader audience or what would be considered vertical communication.

**Vertical Communication**

Due to the broad impact of the suite of oncology guidance documents and implications outside of the regulatory affairs department, their release also should be communicated vertically, that is upward to senior leadership and across to the impacted functional areas or departments. Depending on the company size and choice of communication strategy will dictate whether the communications are initiated by a single person or a team, such as a cross-functional committee. A single person could communicate the potential impact to other department heads who then would be responsible for further dissemination of the information among their respective teams. Likewise, a cross-functional team comprised of pertinent members from various departments could determine the impact and then disseminate the information across their respective teams.

**Companywide Communication**

Information that will affect the operations of multiple departments within a large company necessitates a communication channel that will reach a wide audience in order to educate
internal stakeholders on the pertinent changes as well as overall impacts to the organization. The format used to distribute information on a company wide level depends on the content to be provided and audience expectations. Some examples of formats are email alerts or blasts, bulletins and newsletters.

Email alerts or blasts generally should contain high-level, easy-to-understand information and timely distribution is paramount. An effective email alert or blast, although an informal way to distribute RI to a large audience, should be focused and concise, concentrating on key details describing the change, the impact to the organization and any pertinent deadlines or timelines.

For less time-sensitive news, it may be more logical to compile numerous regulatory news items together in a bulletin, newsletter or digest—each of which serves a slightly different purpose. The RI professional should consider these forms of wider communication, taking into account the definitions and aims of each. From the Merriam Webster Dictionary, the definitions are as follows:

Bulletin: “A brief notice issuing usually from an authoritative source.”

Newsletter: “A small publication (such as a leaflet or newspaper) containing news of interest chiefly to a special group.”

Digest: “A summation or condensation of a body of information …,” “a product of digestion.”

Each of these publication forms serve a specific purpose and based on the definition of RI presented earlier in the article, “The act of gathering and analyzing publicly available information …” a newsletter or digest likely would be the most appropriate communication tool. Independent of how the type of format is used to communicate information at a companywide level, it is critical to include references and/or links to the original sources of information and/or further information.

A bulletin generally is a compilation of news with high-level updates. It can serve to keep a special interest group updated and/or to inform other stakeholders of updates in a certain area. A bulletin also can cover a wide array of topics, providing information in short summaries. However, within a bulletin, these summaries only convey very limited information without the provision of any type of further analysis. Often, the bulletin summaries are based on a single news release or published paper. A bulletin strictly serves to inform of events and left to the readers to draw their own conclusions or analysis.

A newsletter, according to the Merriam Webster Dictionary is a small publication conveying information to a special interest group, such as a regulatory affairs department. Newsletters and the articles within them come in all shapes and sizes. Similar to a local daily newspaper, depending on the topic and author, the analysis and depth of information will vary. The distinction between a newsletter and digest may be somewhat blurry, but a digest implies some digestion or interpretation of the information, in this case, into actionable RI. Independent of the name, a recurring RI publication should be: timely, addressing topics important to the company’s and/or client’s business needs; supported by references; informative; and concise.

The issue of timeliness can be subjective and can vary from company to company. The pertinent question to consider is: “When does news become old news for the company?” The topic selection to be covered by each issue of the newsletter/digest will be guided by the importance to the company’s business, e.g., a device company will be less interested in updates to guidance and legislation addressing pharmaceuticals unless some its products are combination products. Similarly, if the company or clients are operating in a very specific market, news outside of that market will be less important unless the market may be a future target market.
In the example of the suite of FDA oncology draft guidance documents, it would be outside the scope of a newsletter/digest to go into significant detail for each of the guidance. Providing high-level summaries, relevance for ongoing and future projects, providing links and/or reference to the guidance document or any other source of information provided would be an appropriate amount of detail to include within a newsletter or digest article. As a general rule, any news article should be well written, free of grammatical and spelling mistakes and easy to understand. Summaries, bullet points and call-out boxes could effectively highlight the main points of a longer article. This article will not address issues of confidentiality since it assumes information would be drawn from publicly available sources.

The composition of the newsletter/digest and length of individual articles depends on various factors that may include:

- Is the topic being addressed very focused (e.g., specific guidance – short article) or has a long history or complex ramifications (e.g., larger ethical issue – longer article)
- Number of updates or guidance documents released within the time period covered (e.g., the suite of oncology guidance documents, gene therapy guidance documents)
- Number of countries covered within the newsletter/digest (in the case of cross-country collaboration)

As noted earlier, it’s critically important to include references to information obtained from other sources so as to avoid the act of plagiarism, which is, by definition, passing off someone else’s work as one’s own. Plagiarism is a significant issue and sometimes copying as few as five consecutive words in the same order can be considered plagiarism and carries the charge of literal fraud. However, there is no fast and safe rule. Citing sources of information appropriately will clearly indicate where the information came from and how conclusions were drawn.

Copyright infringement, which is the unauthorized use of a work protected by copyright law, is also an important potential issue to avoid. The RI professional responsible for issuing any information that contains copyrighted works must first ensure that proper authorization has been secured from the copyright holder for the intended use, republication, etc., of such a protected work. If the RI professional is uncertain about compliance with copyright law, advice of legal counsel should be sought, particularly as copyright law varies between jurisdictions. Further, the use rights authorized by individual copyright holders varies widely as well.

For example, looking at FDA and the European Medicines Agency (EMA) only, the authorizations granted and conditions required by each entity for use of content made available on their respective websites are handled very differently:

FDA: FDA’s website cites that "unless otherwise noted, the contents of the FDA website (www.fda.gov)—both text and graphics—are not copyrighted. They are in the public domain and may be republished, reprinted and otherwise used freely by anyone without the need to obtain permission from FDA. Credit to the US Food and Drug Administration as the source is appreciated but not required.”

EMA: EMA’s website states that “in particular, unless otherwise stated, the Agency, according to current European Union and international legislation, is the owner of copyright and other intellectual property rights for documents and other content published on this website.”

“Information and documents made available on the Agency’s webpages are public and may be reproduced and/or distributed, totally or in part, irrespective of the means and/or the formats used, for non-commercial and commercial purposes, provided that the Agency is
always acknowledged as the source of the material. Such acknowledgement must be included in each copy of the material.”

“Citations may be made from such material without prior permission, provided the source is always acknowledged.”

“The above-mentioned permissions do not apply to content supplied by third parties. Therefore, for documents where the copyright vests in a third party, permission for reproduction must be obtained from this copyright holder.”

Another consideration is the layout of the finished publication. Newsletters/digests usually contain multiple pages of text with imagery and other features to enhance readability. Can a busy executive grasp the main updates from quickly looking over the article? Choosing appropriate vehicles to highlight pertinent information and conclusions is paramount to inform the busy reader with little time. The full article text always will be available for further information.

Summary

New regulations, guidance documents and other regulatory information are issued from multiple agencies on a daily basis. The RI professional is responsible for identifying information relevant to their company and/or client and also evaluating its impact. A communication strategy for identified regulatory intelligence is a critical next step. Either a horizontal, vertical and/or companywide communication flow could be considered, depending on the essential stakeholders that need to be notified. There are a variety of formats that can be employed to communicate RI, such as email blasts or alerts, bulletins, newsletters or digests. Depending on factors such as time sensitivity, topic complexity and number of updates to be communicated, one format may be more advantageous over another. Utilization of features such as call-out boxes, bullet points, pictures and graphical representations of data may help with the readability and comprehension of the information. While making sure RI summaries are well-written, consideration also must be paid to appropriately referencing sources and legal restrictions regarding copyrighted information.

References


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FDA Meetings: The Application of Regulatory Intelligence in Preparation and Execution

By Matt Medlin, PhD, RAC

This article illustrates how to best leverage a dedicated Regulatory Intelligence (RI) function or skill set to prepare for and have the most successful regulatory interaction with FDA. It provides insight and suggestions regarding the role RI professionals can play to help assure a successful interaction during each FDA meeting phase.

Introduction

Regulatory Intelligence (RI), in one form or another, has always been a component in a successful FDA meeting. However, in past years, as specialization of functional areas has continued to fracture and diverge, the need for quality, relevant and timely RI has increased. While all stakeholders within the organization are keen to see that the firm’s next meeting with FDA is successful, regulatory interactions, and in particular, during milestone FDA meetings, come with unavoidable high risks. Yet, such meetings are a potentially high reward aspect of drug development. At the center of this is the regulatory professional and his or her ability to orchestrate meeting preparation and carry it through efficiently.

Background

Agreements reflected in the 21st Century Cures Act,¹ along with commitments made during the PDUFA VI² negotiations and other initiatives/voices in industry and government alike, contributed to the issuance of two key guidances in December 2017.³,⁴ Those guidances, “Draft Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products” and “Best Practices for Communication Between IND Sponsors and FDA During Drug Development,” had a substantial impact on the role that RI plays in meeting preparation and execution. While this article is not the venue for an expansive dissection of changes or updates in guidance, several examples, including increased reliance on and the role for
non-division specific regulatory project managers and a commitment of five calendar days for receipt of meeting preliminary comments for some interactions, provide the RI professional with an opportunity to have great impact on having successful meeting outcomes.

In addition to recent legislation, market forces and other factors, there is also an increasing “avalanche” of guidance, FDA-sponsored presentations, Ad Comm and Public Meeting materials, and precedent, all of which require analysis. Along with the increase in regulatory fodder for review, personnel turnover at FDA is resulting in less institutional knowledge and fewer seasoned reviewers who can interpret intended meaning in an a drafted regulatory strategy and/or provide reliable direction to a sponsor to avoid “landmines” during future interactions. Each of these changes increase the importance of having reliable, thorough, thoughtful RI and heightens the value of RI’s contribution FDA meeting preparation and execution.

Interaction Planning Phase

An essential question to ask the company (and yourself) before submitting questions to FDA is, “Do answers to these questions already exist?” This kind of industry introspection is the realm of RI. Of course, members from any functional area of a project team will review for themselves if their question for the agency (often phrased as a proposed approach) has been addressed. However, these “needle-in-a-haystack” searches often come up empty. Here, two activities a regulatory function serves are, first, to decode the proposed questions from various functional areas and rephrase in regulatory terminology and second, to begin a targeted search of guidances, approval packages, advisory committee materials, etc., to determine if similar questions related to similar products/indications have been addressed in the past. Measured and thorough information management is critical. Establishing a centralized, curated, project-specific repository of RI documents is well worth the time required during interaction planning and will pay dividends throughout the preparation. Once established, share this resource and work diligently to provide specific guidance to various team members for information that should be reviewed.

At the end of the day, there is a limit to the amount of information the agency can review in one package. That reality is reflected in the number and quality of responses to individual questions. Filtering out and removing superfluous questions is a key activity during a regulatory interaction and planning phase. Also, it is important to produce and hone clear, unambiguous questions. To help achieve this, the RI professional’s work product should help to translate questions into regulatory language so that all parties - before, during and after the interaction - are speaking the same “language.” Finally, be sure that your project team is putting their best foot forward and timelines are correctly established. RI should be sure that the correct meeting subtypes are being applied to the planned interaction. This effort can be a “moving target” in cases of meeting re-categorization in response to updated PDUFA commitments. Keeping the team apprised of the impact this has on the eventual timelines for submission, agency response, meeting dates and final meeting minutes, will help to avoid the landmines and surprises in future internal company milestones meetings.

Authoring Phase

The more work done to familiarize team members with regulatory requirements, guidance, precedent and terminology during the preparation phase, means less work is required during authoring. Regardless, RI reminders and ongoing surveillance of the evolving regulatory landscape is required throughout authoring of documents to be submitted. In addition to these ongoing activities, the authoring phase is an appropriate time to begin looking closely at key players within the agency related to your program/technology/indication. If that previous precedent or established expertise of a resource within the agency, even if not within the review division is important to conducting a successful interaction, then RI should identify this individual(s), discuss their participation with the team and invite them to the interaction.
Also, increased turnover within the agency should be accounted for at this time. Prior to submission, make certain the team is informed and documents are updated to account for a change in the appropriate Office of Division due to restructuring, Division or Deputy Directors, and other invitees named within documents to be submitted. Requesting reviewers with previous experience in the indication/technology, those who have had provided past helpful guidance to other sponsors, or to your company, is also advisable. RI also should find the best selected reviewers for specific invites and confirm that they are still employed with the agency before making such a request. As mentioned previously, personnel turnover at FDA has increased in recent years, increasing the likelihood that assembling the same review team for each milestone interaction is not a realistic assumption.

With increased turnover also comes less familiarity with even long-established regulations or guidance, particularly if the guidance under consideration is related to an aspect of development with which your particular review division may not be familiar. Be sure the team considers including additional detail regarding regulations and guidance in submitted documents. Do not take for granted that those within the agency are familiar with all FDA guidance and regulation. Additional RI work to identify selected reviewers with specialized expertise from outside the Division also should be considered. Finally, do not overlook the submissions work at the end of this Phase. Technical submission requirements, as with all other regulatory matters, are constantly evolving and increasing at a substantial pace. However, your company chooses to manage regulatory operations, be sure that those on the team involved in final submission via the Electronic Submissions Gateway (ESG) is aware of any changes in these requirements.

**Meeting Execution Phase**

Under new guidance, in some kinds of meetings your ability to access, review and provide curated information will be put to the test. In some instances, the agency will provide Meeting Preliminary Comments (MPCs) five calendar days ahead of the interaction. This affords an opportunity for a much more thorough response and discussion with the agency when the face-to-face or teleconference occurs. Also, it allows a review of any newly released guidance, precedent or other information to be conducted to further support the rationale contained within the meeting package.

Also note the MPCs will contain a finalized list of meeting attendees. This will bring more certainty to who will be “running lead” for the agency from various functional areas. Finding summary review documents authored by/signed off on from reviewers with whom you will be interacting can be helpful for the team to level-set and understand the expectations and point-of-view of a reviewer before the interaction. In addition to review documents, unofficial or non-FDA based publications, PowerPoint presentations and white papers can also be very helpful in understanding the rationale, rebuttals or suggestions provided by a particular reviewer.

RI and logistics also should be accounted for at this stage. It is not uncommon for project teams to be nervous or have “angst” about the interaction itself, particularly if they have limited experience interacting with the agency. There is, after all, a lot on the line and, if face-to-face, you are going to the agency’s “turf.” Taking the time to review and determine if there have been any changes in security procedures (lobby guard badges, parking restrictions, attendee screening, foreign visitor forms, passport/visa requirements, etc.) is worth the effort. Along with these preparations comes the work to inform the project team of these procedures ahead of time to relieve any anxieties that may come with the “safety precautions” taken as part of any trip to FDA’s campus.

Lastly, RI in response to Meeting Minutes adds value. If clarification is needed in meeting minutes in the form of an addendum to the minutes there is value in reviewing other meeting minute addendums - either from that division or from similar disagreements - that resulted from development of other products. Providing the team with relevant examples of...
final language adopted for other minute resolution processes will allow the group to formulate the best language from the start.

Conclusion

As with so many other aspects of drug development, RI has an increasingly valuable role to play in FDA meeting preparation and execution. Thorough exploration and knowledge of management principals from the outset, and for the duration of the interaction, followed by targeted and tactical regulatory intelligence contributions during authoring and execution, are indispensable factors in thorough preparation and flawless execution of an interaction with FDA.

References


About the Author

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Managing Regulatory Intelligence for Medical Devices

By Richard Vincins

This article discusses how medical device guidance documents, regulations, standards and requirements are presented in increasing amounts and how regulatory professionals can access, assess, manage and ultimately report to their organizations on the potential impact of regulatory changes. The author covers where and how to access documents and methods for keeping up with regulatory changes using searchable databases, such as provided by FDA, as well as how to find information where such databases are not provided. The article includes “tips” for making the hard work of international regulatory intelligence for medical devices easier and more efficient, such as through subscribing to email feeds, attending conferences and “networking.”

Introduction

From an industry perspective, due to complexity of different devices, the medical device industry is one of the world’s most regulated and one of the most challenging in terms of regulatory requirements and compliance. For the quality and/or regulatory professional responsible for Class I, low-risk and non-sterile devices, Regulatory Intelligence (RI) may be straightforward. However, for the RI professional working with a Class III, high-risk, implant, electronic-based, sterile and attached to a software application (App), RI may often keep one awake at night. This reality is compounded by several factors requiring constant and careful management by medical device RI professionals. The first difficulty factor is to do more with less; the luxury of having staff of 20 people no longer exists and the RI professional may have to manage multiple work activities alone. The second factor has to do with the new, fast-paced, socially connected, “Internet of Everything Age,” where the proliferation of information is difficult to manage and continuously increasing, seeming exponentially and every day. These factors make the medical device industry challenging
not only from a regulatory perspective, but also just keeping up with the large amounts of information presented each day.

Several previous articles published on regulatory intelligence provide helpful information for managing regulatory intelligence.1-3 This article discusses how to keep up-to-date with regulatory intelligence primarily with US Food and Drug Administration (FDA), the European Union (EU) requirements and touches on ideas for other countries. This effort is compounded by there being (at last count) more than 30 countries each with some type of regulation for medical devices. Countries regulating medical devices for many years, such as FDA, Health Canada and the European Union, have well-established regulatory frameworks. They utilize their regulatory framework to continually release guidance, position papers and other industry notifications that can be challenging for an individual to keep up-to-date. This means that regulatory expectations are increasing, requiring continuous review, updates, adjustment and assessment on how new developments impacts each organization. Keeping up with these guidances, regulations, standards and other regulatory requirements can be a full-time function quality and regulatory professionals must find a way to “fit” into their already busy schedules.

In addition to local regulatory requirements for medical devices, there are a multitude of national and international standards published for wide-ranging application of quality management systems, regulatory requirements or product specific requirements. For example, ISO 13485 published by the International Standards Organization (ISO) as a management system standard has been around for more than two decades.4 ISO 14971 describes the fundamentals for implementing a risk management system and processes within the medical device industry. Many of these international standards have been recognized by regulatory authorities around the world to the point that expectation for compliance, even as a “voluntary” standard, is expected.5 Many national and international standards are beneficial in the medical device industry because they create a harmonized platform both regulators and industry can follow. For example, ISO 13485 was revised in 2016 to create more harmonized quality management system requirements rather than have 30 different quality system requirements around the world. Without these standards, because of the regulatory variations between each agency, the medical device industry would have a more difficult job in terms of compliance. Fortunately, national and international standards provide consistent ways to administer regulations, although they also create yet another level of regulatory intelligence to maintain.

**US FDA**

FDA was originally created to regulate drugs that may or may not be effective in treating ailments. Fast forward just over a hundred years since its creation, FDA is one of the strongest, well-funded and regulated administrations in the US or elsewhere. FDA is responsible for drugs, medical devices, food, cosmetics, blood and blood products and tobacco, along with many of the derivations of those. In the last 10 to 15 years, FDA also has implemented a number of regulations for medical devices, including one of the major and most recent ones, the **Medical Device User Fee and Modernization Act of 2002 (MDUFMA).**6 This act helped allow FDA to become almost self-funded to provide it with resources for regulating one of the world’s largest medical device markets. From time-to-time, FDA publishes guidance documents and now has funding for reviewing medical devices, but this function also created a need for the proliferation of ever more information. Fortunately, today, the Internet can be used to access information. FDA has established a process for releasing guidance documents outlining the agency’s current thinking and, more importantly, their expectations for regulating medical devices. Even with the Internet, finding this information is challenging on the best of days.

A few years ago, FDA consolidated their guidance documents into a centralized database, greatly assisting in locating draft and final guidance. **Figure 1** shows FDA’s guidance database with links provided in the sidebar allows different search categories along with
search criteria in a dynamic results page. This site is a “main-stay” website that should be bookmarked as a central location finding FDA information.

**Figure 1. Searching Guidance Documents**

![Search All Guidance Documents](image)

FDA also has an invaluable resource for identifying national and international standards they have recognized for quality system processes, product performance and product testing requirements. The website for recognized consensus standards, with link shown in the sidebar, also has a good search interface that can be used, including title, standard number, product code, etc., as seen in **Figure 2**. This information is important during any type of premarket submission to FDA, as expectations are that recognized consensus standards are utilized as part of product performance testing for safety and/or efficacy. As an example, almost all electronic or electrical medical devices must comply with the American National Standards Institute (ANSI) and Association for the Advancement of Medical Instrumentation (AAMI) ANSI/AAMI ES 60601-1, which is a recognized consensus standard by FDA.

**Figure 2. Search Database**

![Search Database](image)

With hundreds of pages of information on FDA’s website, how does one stay up-to-date? One way is by subscribing to a daily email list serve through which FDA sends notification of advisory meetings, newly published guidance, finalized guidance, webinars, premarket approvals, safety notices and myriad of other information. Do this by either bookmarking the “CDRH News and Updates” page using the link shown in **Table A** or subscribing to
email updates via the link shown in the sidebar. When subscribing, one may select a variety of areas, ranging across many branches of FDA, including CDRH specific information. This information should help in keeping up with large amount of regulatory intelligence FDA generates daily. While this is helpful, please note that you will be receiving emails at least daily and some do not like continuous emails cluttering their inbox. The option to visit the news page may be useful.

<table>
<thead>
<tr>
<th>Table A. Available FDA Weblinks</th>
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<tr>
<td>FDA Guidance Document Search Database</td>
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<tr>
<td>FDA Recognized Consensus Search Database</td>
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<tr>
<td>FDA CDRH News and Updates</td>
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<td>FDA Subscription Management Center</td>
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**European Union/European Commission**

The European Union recently published two new medical device regulations with a proliferation of new guidance documents with which quality and regulatory professionals must keep up-to-date.7,8 There are challenges on the European Union side for regulatory intelligence as their website is not easily navigable and information in the regulatory intelligence stream is not always transparent. Under the current Medical Device Directive (MDD) 93/42/EEC, there are a few guidance documents published under the “MEDDEV” designation with links shown in Table B. Several other informative documents and statements by the European Commission are also provided (Figure 3). With publication of the new regulations, Medical Device Regulation EU 2017/745 and In Vitro Diagnostics Medical Device Regulation EU 2017/746, expect many guidance documents to be published and existing guidance updated.

**Figure 3. EU Guidance Documents**

Guidance

The European Commission provides a range of guidance documents to assist stakeholders in implementing directives related to medical devices.

**New regulations**

Guidance documents to assist stakeholders in implementing the Medical Devices Regulations.

- MDCG documents

**Current legislation**

Guidance documents to assist stakeholders in implementing directives related to medical devices.

- Guidance MEDDEVS
- Consensus statements
- Informative documents

Like FDA, the European Union has published a listing of harmonized standards for current medical device-related directives, including the MDD 93/42/EEC. Unfortunately, as seen in the link provided in Table B, this list is a scroll-through list, not a searchable database. This
structure can make it difficult to locate current information as there is no notification of updates - searching must be done through the local browser search function. In addition, this information is not always updated on a regular basis, so there are out-of-date national and international standards which can cause difficulty during product technical reviews understanding which standards must be applied.

The European Commission also publishes other informative documents that, while not guidance or requirements documents, do contain helpful information. This publicly available information referred to as "DocsRoom," contains helpful references any quality or regulatory professional responsible for CE Marking will find useful (Table B). This is particularly important with the new regulations published along with a promise for more transparency by European authorities. Maintaining regulatory intelligence in the European Union also requires a larger net of capture information as there is not one centralized location, i.e., Notified Body Operating Group (NBOG) documents, Competent Authority for Medical Devices information and other trade industry groups.

### Table B. Available EU Weblinks

<table>
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<tr>
<th>Link</th>
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<tbody>
<tr>
<td>Guidance MEDDEV</td>
</tr>
<tr>
<td>Summary List of Harmonized Standards for the MDD</td>
</tr>
<tr>
<td>European Union DocsRoom</td>
</tr>
</tbody>
</table>

### Other Regulated Country Requirements

Outside the US or European Union, the two main markets, regulatory information can be sufficient to sporadic. Other larger medical device markets, such Canada and Australia, have regulatory authority websites dedicated to medical device information, while smaller markets, such as Malaysia or India, medical device information is more likely "buried" in pharmaceutical pages. An article previously published in *RAPS Regulatory Focus* has detailed links to various regulatory authorities around the world. While some may have changed, many are still the main site to visit for further links to specific medical device regulations. Other sources, such as the World Health Organization’s medical device atlas, provide links to regulatory sites. Regulatory intelligence also can be challenging in markets where local authorities only have information published in the local language. Japan, China and Brazil also are large medical device markets usually requiring local presence for regulatory intelligence because most information either on the website or publicly available is in the local language. Still, there are a variety of methods for keeping up with regulatory intelligence, including those in more obscure markets that can be significantly challenging.

### Methods for Regulatory Intelligence

The first step in understanding where to get regulatory intelligence is not only knowing when regulatory documents are new or changed, but also knowing how to keep track of these documents. There are a variety of methods, depending on each individual’s organization skills, resources available in the company, and availability of funds.

#### Manual Regulatory Intelligence

Developing regulatory intelligence can be daunting at first, but once a system is established it is not difficult to maintain, although it requires time each day or week to visit websites, read through email notifications, check electronic databases and update the information. A simple method for keeping track of documents is to create an Excel sheet with identification number, title, version, publication date, effective/transition date and impact assessment (other variations can be used). It is often helpful to keep track of archived regulatory documents, although usually this is not required. Below is a list of methods for manually keeping up-to-date on regulatory intelligence.
• Enter your email address in websites, list servers or email distribution with regulatory authorities for published information; many major regulatory agencies have some type of email notification system, i.e., FDA, Health Canada.
• Join mailing lists of consulting firms or other regulatory support groups, i.e., AdvaMed, that often give free webinars, white papers or other information about new and changing regulations/standards. The difficulty with this approach is in receiving even more emails based on marketing their products and services.
• Become part of a professional organization such as Regulatory Affairs Professionals Society (RAPS) or American Society for Quality (ASQ). These groups also provide learning sources, free educational webinars, forums and networking groups.
• There are other professional organizations and private companies such as Association for the Advancement of Medical Instrumentation (AAMI), Medtech Europe or Notified Bodies that once a member or customer usually have educational information on a regular basis.
• Network with friends and colleagues. When attending conferences, such as RAPS Convergence or other industry conferences, use the opportunity to get to know new people.
• Establish “regulatory intelligence time” in your schedule, perhaps an hour on Friday morning or afternoon devoted solely to gathering information from these sources.

Depending on the number of markets to which the organization distributes, manual methods may be appropriate; if part of a large organization or distributing in more than 10 countries, manual methods can prove difficult to manage.

**Electronic Automated Regulatory Intelligence**

In years past, there was little option beyond manually finding information. This entailed visiting the local library to search through articles or going to industry meetings. This has changed dramatically with the availability of information via accessible databases and cloud-based applications. However, depending on the service provided, these resources usually involve a subscription or a flat fee.

• A few organizations provide purchase of standards that sometimes - for a small additional fee - will notify you when the standard is updated. This usually applies only to standards such as ISO or IEC documents.
• Services providing access to standards usually do not cover guidance documents or other regulatory documents, leaving a gap in regulatory intelligence. There are an increasing number of providers bridging this gap by providing notification on other regulatory documents.
• As part of the service package, subscription-based service can not only provide notification of standards and guidance documents, but also electronic copies.
• Often these services have a cloud-based system, so this regulatory intelligence is kept in one location able to be accessed via the Internet. This is helpful for keeping all related standards, guidance documents, registrations, etc., in one central location.
• Electronic automated services are exceptional at filtering through identified regulatory markets by providing notification of standards, guidance documents, new regulations and other information. But this service comes at a price. It also should be noted that many companies, depending on their needs and depending on the markets they distribute product, use a mixture of both manual and automated methods.

**Conclusion**

During a training session or when going through a long list of standards from memory, the question ‘How do you keep track of everything, read everything and know how to get
regulatory intelligence?’ is often raised. The answer is fairly simple. Before you go to bed at night, close your laptop, put it under your pillow and hopefully, by osmosis, information gets into your memory cells! The real answer is, unfortunately, not so simple. We all know too well the challenges inherent in keeping track of so much regulatory information today, and it is not going to get any easier. Fifteen to twenty years ago, there were perhaps a half dozen, well-documented regulatory markets. Today, there are at least triple that number and the number will continue to increase. The citations, links and information provided in this article have been located, found and reviewed being on mailing lists, involved in RAPS forums, and being part of other regulatory forums. Using a method of osmosis for some people may work, though most will find that they need to establish methods that are manageable and appropriate for their organization.

Keeping up with new and revised regulatory requirements is the first step and probably the most challenging. With an understanding this is not a static process and depending on the organization, there are different methods that can be applied for regulatory intelligence. As regulatory requirements continue to increase, so will the bulk and speed of accompanying information increase. Once becoming aware of new and revised regulatory requirements, one must assess them for their potential to impact the quality system or product compliance. Because of continuing regulatory changes for the medical device industry, it is important for each organization to establish defined methods for gathering, reviewing, updating, and maintaining regulatory intelligence.

References


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By Pei-Ting Sarah Chou, RAC

This article discusses current and future Artificial Intelligence (AI) applications in healthcare and examines AI's potential for adding efficiency to pharmaceutical research and medical practice as well as AI potentially providing better healthcare and patient outcomes, especially in terms of diagnostics and treatment. The author presents ethical concerns of AI applications, the potential for AI misuse and the case for developing ethical standards.

Introduction

"AlphaGo" is a computer program that plays the board game "Go," developed by Alphabet Inc.'s Google "DeepMind" in London, England. In October 2015, the original AlphaGo became the first computer Go program to beat a human professional Go player. Having AlphaGo defeat the best Go players in the world demonstrates not only a milestone for Artificial Intelligence (AI) technology, but also a new era for AI. Not long after the AI Go victory, Google introduced DeepMind to the energy-saving system of its data center. This application of AI saved more than 30% of the system's energy and did so in ways never implemented by humans and, thus, paved the way for AI to be used in more future applications. Google has used DeepMind since then in collaborating with the UK's National Health Service (NHS) to build an eye-imaging machine learning system to help combat sight-threatening conditions, such as wet age-related macular degeneration, diabetic retinopathy and others.

By 2018, more AI applications had been developed for use in healthcare. For example, 2018 saw the first medical device using AI provide a screening decision without the need for the opinion of a clinician. The device was subsequently approved by the US Food and Drug Administration (FDA). FDA has
approved several AI applications for medical devices, including IDx-DR screening for patients for diabetic retinopathy. FDA determined there was no need for a second opinion from human expert. Also, ARTERYS liver and lung AI lesion spotting software for cancer diagnostics was approved, Viz.AI’s CT scan analysis along with healthcare provider notification of potential strokes in patients and Bayer's AI Software for Chronic Thromboembolic Pulmonary Hypertension (CTEPH) Pattern Recognition. These AI-driven medical technologies are being used today to diagnose and treat a variety of diseases. Most of these applications using AI are for medical imaging and disease pattern recognition and aim at both improving clinical decision-making and facilitating earlier disease diagnoses.

As demonstrated by the recent AI-driven technologies approved by FDA, AI has become increasingly used by medical professionals for image analysis, therapeutic selection, data filtering and quality control. As a result, forums for discussing the healthcare benefits of AI-driven technology have been increasingly organized. In 2018, two United Nations agencies, the International Telecommunication Union (ITU) and the World Health Organization (WHO), initiated focus groups on Artificial Intelligence for Health following the first program on Artificial Intelligence and Robotics conducted in 2015. Also in 2018, ITU and WHO co-organized the workshop on AI for Health workshop at Columbia University in which Deputy Director of the Office of Medical Policy (OMP) at CDER, Khair ElZarrad, addressed opportunities and challenges for AI therapeutic development.

Recently, AI applications for medical imaging, disease diagnostics, digital data and electronic health records have been developed, all of which have demonstrated the ability of AI to help protect privacy and assist in data security. These developments not only illustrate AI’s applicability along the healthcare supply chain, but also demonstrate how AI could potentially revolutionize healthcare systems by improving efficiency and patient outcomes.

As seen in Figure 1, emerging AI technologies can be further categorized according to their categorical roles in the supply chain:

- raw material
- data collection
- supplier
- healthcare professional training
- healthcare product or service
- vendor
- hospital/healthcare professionals
- end consumer
- patient/insurance company

Figure 1. Artificial Intelligence Application in the Healthcare Supply Chain
In the category of raw material, AI could assist with the manufacturing as well as research and development of therapeutic drug format selection using AI's ability to predict a potential drug's molecular structure, chemical composition and possible therapeutic effect. AI also could assist with the proper selection of material or stereo-presentation for constructing medical devices to be compatible with human engineering factors or for data collection. AI also could support data filtering, data classifying and data analysis throughout the data collection process and, in doing so, turn the electronic health record into a reliable predictor of risk as well as providing extensive vocabulary selection for data summarization.

For suppliers, AI could customize the service and the product to be supplied in such a way as to better meet the customer's needs. AI could adopt machine learning to develop customized tutorials for healthcare professional training and, in doing so, improve training outcomes. For healthcare products or services, AI could be used to improve diagnostic accuracy and efficiency by creating more precise analytics for photo images for disease diagnostics and advancing the use of immunotherapy for cancer treatment. For vendors, regardless of whether the need originates in wholesale or retail, AI could recommend proper marketing strategies for a particular disease therapy or healthcare product. For hospitals and healthcare professionals, clinical decision making could be revolutionized with AI at the patient's bedside where it could assist physicians in identifying which treatments are best for specific patients or for specific groups of patients. With AI at the bedside, the potential for the development of complications could be assessed sooner and possibly eliminate their potential. AI also could significantly improve therapeutic outcomes and reduce costs related to hospital-acquired conditions.

For healthcare consumers, AI could assist with self-monitoring one's health status and recommend proper healthcare product selection and purchase. For patients or health insurance companies, AI applications for mobile devices could expand healthcare access for underserved populations or for people living in developing, remote regions of the world. Finally, AI could help identify homogeneous populations within a disease category and calculate the cost of medical insurance in terms of both risk and safety considerations.

Because the recent development of AI technologies covers a broader range of applications when compared to previous innovative technologies, AI's impact on human health will be on a larger scale and come at greater speed than offered by previous technologies. However, there is insufficient information and a lack of studies about the accountability of AI devices, which means there is an inherent risk in integrating these technologies too soon. There can be drawbacks and caution may be necessary. For example, if we become highly reliant on the human decision patterns designed by AI, and if the AI decision pattern is built upon a biased data pool, such decisions may not reflect a logical neutral result but, rather, be based on a prejudicial view. This issue could drive potentially risky outcomes if users falsely believe the decisions provided by AI are based on neutral analysis. There is also the possibility that AI could be used for committing crimes by generating undetectable fraudulent images or videos mimicking authentic ones in order to mislead decision-makers. Further, preventing personal information and medical records from being used without personal consent of disclosure, and having data being wrongfully accessed via the advanced AI technologies by an unauthorized party is also an issue to consider.

Because serious ramifications can result from AI misjudging or misdiagnosing, challenges include examination of decisions related to whether we should rely highly on the decision patterns recommended by AI.

**Conclusion**

AI applications can offer support for the healthcare provider, strengthen the delivery of healthcare to better ensure healthy lives and work to promote well-being for humans of all ages. However, ethical concerns regarding the use of AI must be considered before introducing such powerful technology into our daily lives. Accordingly, a team from the Massachusetts Institute of Technology established a platform for studying the moral
decisions and ethical standards related to new technologies. However, developing ethical standards does not guarantee that behavioral transformation will follow. Legal professionals will likely develop consensus for adopting some of the standards pertaining to international human rights and apply them to governing the use of AI, but a simple and straightforward approach to the current trends and demands for AI applications also may serve a variety of industries in advance of formal and legal ethics and standards. As shown in the proposal published by the Data and Society Research Institute, technology companies are encouraged to borrow from the opinions of civil rights groups and ethics researchers and use these considerations when developing a human rights impact assessment throughout their AI systems’ lifecycle. Some reports on AI have been published by the Wellcome Trust, the think-tank Future Advocacy and the European Group on Ethics in Science and New Technologies, all of which illustrate some of the ethical, political and social impacts of AI. The relationships between economic growth and AI have also been discussed in a report offered by the McKinsey Global Institute.

For the healthcare domain, it may be that Institutional Review Boards (IRBs)/Ethics Committees (ECs) will face greater challenges in AI-related clinical trial applications and in research protocols seeking to adopt AI technologies. Proposed standards for AI should be accommodated within a global framework to avoid the inherent risk of having AI used by authoritarian leaders in their efforts to deprive people of their dignity and rights. There is also a need to develop standards addressing the potential harm caused by the misuse of AI.

As Albert Einstein, still a pillar in contemporary physics, once said, “It has become appallingly obvious that our technology has exceeded our humanity.” His observation should remind us that only when pioneering research in healthcare is advanced on basis of human concern and ethics can it contribute to genuine good deeds in the long term. As we debate the value of AI in healthcare, it would be prudent to reflect upon the current debate regarding stem cell and embryonic research.

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5. Ibid.


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Pei-Ting Sarah Chou, RAC, is a US-certified regulatory professional with scientific and professional training in the US, Europe and Taiwan. Chou is a founding member of the RAPS Taiwan Chapter board. She served as an adjunct research fellow for a non-profit intellectual property foundation, a lecturer at professional training programs organized by IRB and the Ministry of Economics in Taiwan, ROC, a member of AHWP working group, a roundtable contributor of ISO conference, an article reviewer and a medical writer. She is currently RA/QA/IP manager at Sourcing Overseas and Vigilant Health. She can be contacted at pchou@alumni.princeton.edu.


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Regulatory Intelligence Communication for Business Impact

By Kirsten Messmer, PhD, RAC and Charity-Anne M. Schuller, PharmD, MS, RAC

This article focuses on maximizing Regulatory Intelligence (RI) in response to specific stakeholder requests and offers best practices recommendations for RI communication. The authors provide an overview of information delivery methods and their applicability and present general considerations for communicating RI information by spreadsheets, text documents, slide presentations, strategy reports and competitive intelligence reports. They also highlight the use of due diligence and carrying out gap analyses. The article concludes by noting future trends in RI.

Introduction

RI professionals support the drug development process with strategic information, serve as liaisons with regulatory agencies and channel RI to the appropriate stakeholders. Typically, an RI professional is asked for an outline of the regulatory requirements and asked to identify existing precedent for regulatory actions and landscape opportunities for a certain product in a specific country, region or globally. Project-specific assimilation and analysis of the relevant information available through public sources, internal experience and/or subscription services to avoid regulatory pitfalls, requires the necessary skills for seeing “the big picture,” evaluating the details involved and developing a specific and creative regulatory strategy to support a time- and cost-efficient product development program. However, strategy needs to be reviewed throughout the drug development process to update the strategy with regard to any changes in the development plan and/or regulatory requirements. This article concentrates on information provision approaches to maximize the use of RI in response to a specific stakeholder request (for proactive RI communication see Huddle and Messmer.1)
RI Requests

Requests (both ad hoc and project-specific) for RI can vary widely in content and purpose. The purpose, requested content and teams involved determine, in part, the presentation method and level of detail provided. However, the RI professional also needs to include her/his own judgement on what level of content and information delivery method provides the best strategic support to the requestor. Knowing the information needs and presentation preferences of the customer is paramount, as noted in the previous article on proactive RI communication by Huddle and Messmer.\(^2\) In ad hoc requests, the primary customer is the person requesting the information. However, the RI ultimately might be presented to a secondary customer, as would be the case if the internal business development (sales) department requests RI to support a proposal to a specific customer. In this case, the RI professional needs to cater to both the internal and external customer based on the request specifications and any prior experience with similar requests.

RI Communication: General Considerations

The RI provided should always be concise, complete, current and accurate. Independent of the presentation vehicle, the writing always should be of the highest quality and free of spelling and grammatical errors. The material should be presented in an easy-to-understand manner, yet without being overly simplified to suit the requestor’s background understanding of the subject matter, perhaps for someone who is likely not as intimately familiar with the material as is the RI professional.

The most powerful reports combine text, tables and graphics to communicate the RI. Overly lengthy and text-dense reports are generally not helpful due to the significant time pressures of drug development. RI is an exciting, fast-moving field with a potentially high business impact. It is important to translate that ‘buzz’ into the key outputs needed by the customer.

Original sources need to be cited whenever possible as this will help avoid any potential issues regarding copyright infringement. Although one might consider the risk to be limited, it is always advisable to err on the side of caution and, when in doubt, seek input from the legal department. Second, and perhaps more importantly, citing original sources allows for easier updates and vetting of the information. While this practice might be less necessary for responses to specific questions and time-limited use information, such as the assessment of a clinical trial feasibility, citing original sources will become more important for regulatory strategy reports, competitive intelligence and due diligence. These latter works will likely be used as “roadmaps” for extended periods of time. In an ever-changing regulatory environment, it is important to revisit the information provided in regular intervals or even more frequently because guidances can change swiftly. It is paramount for any updated assessments to have access to the original information sources to be able to accurately compare the new information to that provided in the initial report. The ability to time-efficiently update RI will add value for the customer. “Re-inventing the wheel” for every update of RI reports adds unnecessary cost.

Spreadsheets and Text Documents

With a specific customer request or notification, probably the simplest presentation of large amounts of information is represented as a spreadsheet, or a briefing document, focused on key elements relevant to the request. Information topics, such as a set of specific regulatory questions, can be represented against target countries in tables. For spreadsheets, the topic covered in each column or line needs to be focused and precise. The breadth and depth of the information should be comparable for each data point for a given topic (e.g., country when assessing regulatory questions for various countries) while succinctly providing key information.
While a “yes” or a “no” answer might be preferable, in regulatory affairs such simple answers are not possible. Thus, it becomes paramount to fully understand the question in relation to the general context and to subsequently formulate the response as precisely, and as to the point, as possible. The shorter the presented information can be for each country (and overall) the better; additional information always can be provided in further commentary.

The main advantage of spreadsheets is that they can present large amounts of information in a concise and consistent format (Figure 1). However, this type of presentation requires further data analysis to draw the pertinent conclusion. The RI professional should analyze the collected data and provide the main findings, including conclusions drawn based on that information, as well as the RI professional’s experience to the ‘customer’ as an analytical overview.

Figure 1. A spreadsheet can provide a lot of information, but often requires further data analysis to draw the pertinent conclusion.

Slide Presentations

Generally, most of us can take in and understand large amounts of information much faster if conveyed in a visual medium, such as a slide presentation. However, there are typically two manners in which slide presentations are provided - summaries of information without commentary for each single slide sent to the customer, and slides presented to the customer in a meeting.

Slides presented during a customer-facing meeting should contain enough text to summarize main messages. It is the speaker’s responsibility to provide the context and crux of the slide’s message by verbally capturing the attention of the audience. It is equally important to create the slides so they tell ‘the story’ by guiding the listener and, at the same time, conveying critical information. Wherever possible, pictures and graphics should replace text to convey complex concepts.

While an Internet search for “slide presentation rules” generates an abundance of articles, all results provide suggestions that lead to the same general principles - slides presented verbally should not contain full sentences unless they are direct quotes. Large amounts of text on slides – particularly in complete sentences – entices the audience to read the slides rather than listen to the information provided by the speaker. Figure 2 and Figure 3 show two presentations of the same information. While Figure 2 is crowded with text, Figure 3 represents the same information graphically.
Other things to consider when designing the slides include font size, font color, and background color. Although presentation of RI to a specific requestor is likely to be conducted in a smaller room, there might be an opportunity for follow-up with a larger audience. Choosing the largest font size possible for the text will ensure readability from the back rows in large conference rooms. When choosing colors, it is important to use high-contrast differences and test the chosen colors for any colorblindness impediments. Although slide deck presentations provide the opportunity for visualizing complex information, any images, graphics, and infographics used should all support key points, not detract from them.
Strategy Reports

Strategy reports are probably one of the most valuable presentations of RI because they often combine the information, knowledge and experience of various experts. A good strategy report begins with an executive summary outlining a “roadmap” for tackling the project at-hand. The summary frames the discussion for the audience and, if possible, includes a high level SWOT analysis (Strengths, Weaknesses, Opportunities and Threats) outlining strategies for taking advantage of opportunities and to address the threats. The summary will conclude with a succinct outline of the strategy and suggested actions. The main text of the strategy report depends on the question(s) asked, so it is important to ensure a complete understanding of the question(s) and the purpose of the report. For example, if the aim of the report is to propose a strategy for developing a medicinal product in a select group of countries, the presentation of information will differ from a strategy report aimed at filling in gaps for a specific product identified during due diligence. Considering the first issue for developing a gene therapy and gaining approval for the first clinical trial (Figure 4) could suggest the submission sequence needed to obtain clinical trial approvals at approximately the same time.

In the select country example, the executive summary likely will be followed by a side-by-side overview of information for all countries considered, before addressing each country in more detail. The concluding section will then provide the proposed strategy to ensure smooth execution of the development program in as many suggested countries as possible, or for a core group of priority countries.

Figure 4. Sample Regulatory Strategy to Accompany a Strategy Report for Obtaining Gene Therapy Approval in Several Jurisdictions at the Same Time

In the specific product example, due diligence may have identified gaps in a submission package that need to be addressed before the submission can proceed. The executive summary should include a brief overview of the product, the product’s development status, and a listing of the issues identified. The report should then address each issue in detail and provide steps to achieve resolution. The summary will outline steps to be taken in order of priority.
Competitive Intelligence

The RI professional as a strategist provides internal and external customers with competitive intelligence to guide successful product development and commercialization. Competitive intelligence may include information on:

- Commercialized products for the same indication and/or mechanism of action,
- Revenues for these products,
- Products under development for a specific indication including the development stage,
- Product availability in various markets, indication prevalence and
- Clinical trial information and precedents (case studies).

The type of information obtained during intelligence gathering depends on the questions asked. Common questions include, but are not limited to:

- How many other products are at the same development stage and how do they compare? (e.g., mechanism of action, expedited program designation)
- How many clinical trials are conducted in countries A, B, C, etc., that would directly compete with a trial the requestor may be considering (e.g., prevalence of indication, number of trials and patient enrollment target number, available marketed treatments)?
- Requestor wants to use a specific approval pathway – Has this been done before; if so, how was it done and was it successful? (e.g., precedent, publicly available agency interactions for similar product/pathway; Figure 5 would support the report by illustrating the search strategy employed to develop the precedent)?

Figure 5. Sample Search Strategy For Development of a Regulatory Precedent

Spreadsheets and slide deck presentations may be suitable for some of the smaller requests, such as showing products under development against development phase. Figure 6 provides a mock-up of a development landscape. However, most competitive intelligence-informing product development questions will require a formal report, one illustrated by graphics summarizing the information obtained from all available information.
sources, and provides a clear analysis and shows the conclusions drawn in respect to the specific questions asked. Key information, processes, and data should be highlighted by appropriate illustrations throughout the report.

Figure 6. Sample Product Development Landscape Showing Development Stage for Various Products

Like the strategy reports, competitive intelligence reports will provide a regulatory strategy of product development based on RI analysis but also will add an operational and/or commercial strategy for product development and positioning.

Due Diligence and Gap Analysis

Although due diligence and gap analysis have slightly different meanings, they require similar thought processes to generate a high-quality RI output, one providing actionable recommendations.

Due diligence is defined as "action that is considered reasonable for people to be expected to take in order to keep themselves or others and their property safe." This term might be best known from the business and real estate world where due diligence is performed to ensure that a purchase (acquisition, merger) provides the desired return on investment with no potential loss. In RI or regulatory affairs, due diligence may be called upon to lead or contribute to product and/or entity. In the case of a medicinal product, this entails ensuring that the product development pathway is adequate, including assuring that regulatory requirements have been met and all necessary documentation is available.

Gap analysis is defined as "a system that compares how a company works now with how it would like to work, and then calculates how the company can use time, money, etc. to achieve the success it would like." Paraphrased: how does it look now and what does it need to look like to be successful? In the regulatory world, a gap analysis is generally performed on an individual product to determine whether all regulatory requirements have been met and to identify any ‘gaps’ needing to be addressed before the product can be successfully developed, approved and commercialized.
Gap analysis likely will form a vital part of the overall due diligence process. For due diligence/gap analysis during product development, it is paramount to understand the product itself to be able to accurately assess the current product status and any actions (and potential costs) needed to move the product through development to approval and commercialization.

The pharmaceutical market necessitates accurate and precise product assessment and regulatory outcome predictions to support corporate goals. The RI professional must ensure regulatory precedents have been correctly interpreted and applied, that all regulatory requirements are noted, and any opportunities to use expedited pathways are highlighted to maximize benefits for the requestor. The most appropriate format is a detailed and concise report supplemented by well-designed graphics and summary tables with pertinent information.

What does the future hold?

The ever-increasing pace of pharmaceutical product development and subsequent regulatory updates necessitates engaging new tools to support effectiveness and efficiency in the delivery to clients. Also, quick access to key points supports faster decision-making and process adjustments.

The use of Artificial Intelligence (AI) has dramatically increased over the recent years. AI applications in RI include “trend spotting” and identification of differentiators for a customer’s product against competitors. AI can support many process of gathering, assimilating and reporting of information. This activity includes looking for gaps, identifying trends and testing new ideas. However, responsibility for the interpretation will still fall to the RI professional. Because innovation is guided by novelty and not existing regulations and laws, RI delivered to the customer needs to go beyond the regulations, pathways and guidelines, many of which are set retrospectively. For example, as a result of a novel efficacy endpoint created during the development of a gene therapy product for the treatment of a hereditary retinal disorder, FDA specifically began encouraging sponsors to develop and propose novel endpoints in the guidance addressing gene therapies for retinal disorders. Regulators are generally open for early discussions of innovative products and product development processes in order to understand the drug developers’ rational since there is no comparable benchmark. It becomes the RI professional’s responsibility to ‘read between the lines,’ link trends across multiple disciplines, and assimilate the information available for fast and accurate communication. The RI professional must also possess the skill to separate fact from fiction and the practical from publicity headlines to be able to create RI communications beneficial for clients, regulators and colleagues.

Conclusion

RI is an important, ever-evolving, always changing science. The pace of information release by regulatory agencies and other stakeholders continues to accelerate, reflecting the increase in experience with medicinal product development and approval. Additionally, the complexity of products has been increasing significantly in recent years (e.g., advanced therapy approvals). Information acceleration and complexity necessitates gaining an intimate understanding of the product at-issue and the regulatory requirements to guide product development and approval at every step. Also, taking advantage of innovative pathways regulatory agencies are implementing to support faster product approval is important. While RI delivery can take on many formats, support multiple objectives, and be developed using a variety of tools, the skillsets and methods for obtaining, providing and maintaining information remain the same. It will always be important to know the intended customers, utilize the most appropriate resources, carrying out thorough searches, and obtain an attentive secondary review. All of these processes go into ensuring successful RI provision and strategic support for drug development.
References

2. Ibid.

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This article covers recent changes to China’s healthcare regulatory authorities and healthcare policy administration. The author explains the responsibilities and functions of the many government departments, agencies and regulatory bodies responsible for overseeing drugs, food, medical devices, testing and evaluation since the reorganization and restructuring of the former Chinese Food and Drug Administration (CFDA) and several other organizations in March 2018.

Introduction

China is a large country with a territory of 9.6 million square kilometres and a population of 1.39 billion people. The nation has 23 provinces, five municipalities, four municipalities directly under the Central Government (namely Beijing, Shanghai, Tianjin and Chongqing) and two special administrative regions. A variety of authorities, administrations, agencies, bureaus, affiliates and institutions are involved in the national and local level in developing health policy as well as drafting, formulating, implementing and supervising healthcare regulations. The roles and responsibilities of these agencies have been subjected to a series of reformation and reorganization efforts. The latest and perhaps the most important reorganization occurred in March 2018, when the State Council was restructured during the first meeting session of the 13th National People’s Congress. Since this restructuring, it has become important to understand the health and regulatory authority organization and the various responsibilities and processes for successfully placing medical products on the Chinese market.
The Health Administration Organization in China

Organization

In China, the health administration organization is comprised of bodies at the central and local levels. The State Council of the People’s Republic of China is the highest executive body of the state and the highest-level body of the state administration, also called the “Central People’s Government.” The State Council oversees 26 ministries and commissions, 10 organizations, nine institution, and 16 administrations and bureaus.

The National Health Commission (NHC) is one of the 26 ministries and commissions. It was newly established on 21 March 2018. Its establishment effectively reorganized the roles and responsibilities of the former National Health and Family Planning Commission (NHFPC) and several other organizations. Having replaced the former Ministry of Health (MOH) and the former National Population and Family Planning Commission (NPFPC), the NHC has a number of key responsibilities, including:

- drafting laws and regulations concerning national health policies, and plans for the development of public health services
- coordinating the reform of the medical and health system
- implement the plans for disease prevention and control and the national immunization program
- organizing and implement the health policies for the aging population
- organizing the formulation of national drug policies and the national essential medicine catalogue, and other health policy related responsibilities

The State Administration for Market Regulation (SAMR) is one of the 10 organizations directly under the State Council. It was newly established on 21 March 2018. After reorganization, the key responsibilities include:

- managing NMPA and National Intellectual Property Administration (NIPA)
- drafting laws and regulations concerning marketing supervision
- business registration and grants
- organizing and providing the instruction for market supervision
- implementing anti-monopoly rules
- quality relevant issues and the general supervision for food safety

The National Healthcare Security Administration (NHSA) is another one of the 10 organizations directly under the State Council. It, too, was newly established in March 2018. The establishment of this new organization aimed at improving the medical insurance system and ensuring insurance funding is manageable and controllable. Its key responsibilities include:

- drafting and implementing laws and regulations concerning medical insurance, maternity insurance, medical assistance
- formulating and implementing the administration of medical insurance funding
- formulating the list of reimbursement and payment standards for medical products and services
- establishing a dynamic adjustment system
- formulating the rules for granting reimbursement
- developing and supervising the implementation of the regulation for bid invitation and procurement of medical products and medical consumable materials
- determining the price of medical products, consumable materials and medical services
- establishing the pricing system and the dynamic adjustment system
The China National Medical Products Administration (NMPA)

At the local level, there are 31 provincial and municipal administration bodies for market regulation. Accordingly, the 31 local drug administrations are responsible for local health policy and regulatory affairs within their local jurisdiction.

The following discussion covers the important regulatory bodies and presents their key regulatory responsibilities.

Table 1. Chinese Drug Administration: Historic Overview

<table>
<thead>
<tr>
<th>Year</th>
<th>China’s National Health Authority’s Name</th>
<th>Organizational Level/Remit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>State Drug Administration (SDA)</td>
<td>Directly report to the State Council</td>
</tr>
<tr>
<td>2003</td>
<td>State Food and Drug Administration (SFDA)</td>
<td>Added food administration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Directly report to the State Council</td>
</tr>
<tr>
<td>2008</td>
<td>SFDA</td>
<td>Reporting to the former Ministry of Health (MOH)</td>
</tr>
<tr>
<td>March 2013</td>
<td>China Food and Drug Administration (CFDA)</td>
<td>Name change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reporting to the State Council</td>
</tr>
<tr>
<td>March 2018</td>
<td>China National Drug Administration (CNDA)</td>
<td>Name change as food was excluded from the remit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reporting to the State Administration for Market Regulation (SAMR)</td>
</tr>
<tr>
<td>August 2018</td>
<td>National Medical Pharmaceutical Administration (NMPA)</td>
<td>Name change and reporting to the SAMR</td>
</tr>
</tbody>
</table>

The former CFDA, now the National Medical Products Administration (NMPA), directly reports to SAMR. NMPA is responsible for the administration of drugs, including chemicals, biologics, Traditional Chinese Medicines (TCM), medical devices and cosmetic products. Food is excluded. The responsibilities of NMPA include, but are not limited to the following:

- supervising the safety for drugs, medical devices and cosmetic products
- managing the standardization, such as formulating and publishing the Chinese Pharmacopeia (ChP), formulating and publishing the standards for medical devices and cosmetic products, drafting and publishing the National Essential Medicine List
- managing the registration of drugs, medical devices and cosmetic products, including drafting the registration regulation, improving and implementing the marketing authorization review and approval system
- conducting quality management for drugs, medical devices and cosmetic products
- conducting postapproval risk management for drugs, medical devices and cosmetic products
- inspecting drugs, medical devices and cosmetic products

The 31 provincial and municipal drug administrations, such as the Beijing drug administration or the Shanghai drug administration, have the following roles and responsibilities:

- manufacturing authorization, inspecting and penalizing companies in case of compliance violations within their local jurisdiction
- authorizing and managing the supply licenses for retailers, pharmacy chain stores and headquarters, internet marketing
- monitoring and inspecting the use of drugs, medical devices and cosmetics
The Center of Drug Evaluation (CDE)

Early in 1985, the first review commission was established within the former Ministry of Health and the drug review office was established, responsible for the technical evaluation of drugs. As a directly affiliated agency within NMPA since 2015, this regulatory authority underwent organizational reform. Staff numbers were increased significantly from around 190 in 2015 to 700 in 2018. In addition, CDE changed their project management system to streamline the technical review and approval process. As the most important regulatory body for drug authorization, CDE has the following key responsibilities:

- performing technical evaluation of drug regulatory affairs applications
- providing protocol assistance, scientific advice and regulatory consultation
- performing generic drug consistency evaluation
- participating in the formulation of drug registration law, regulations, guidance, opinions, etc.
- organizing and implementing good evaluation practice
- assisting with relevant inspections and testing
- performing ICH guidance adoption activities
- performing research into the technical evaluation related theory, technology and development trends
- conducting other activities assigned to CDE by NMPA

CDE has 19 departments. The following are the main departments relevant to technical evaluation and clinical trials:

- Department of Traditional Chinese Medicine (TCM) - CMC and clinical
- Departments I and II for Chemical Products - CMC and clinical
- Department of Biological Products - CMC and clinical
- Department of Pharmacology and Toxicology
- Department of Statistics and Clinical Pharmacology
- Department of Clinical Trial Management

The Center of Medical Devices Evaluation (CMDE)

CMDE performs the technical evaluation of medical devices. The following are its main responsibilities:

- performing technical review of medical devices
- drafting medical device relevant law, regulations, guidance and best practices
- providing training and consultation
- participating in inspections and other relevant activities

CMDE has about 100 employees working in 14 departments. Six departments are responsible for technical evaluation of the various types of medical devices and two departments cover clinical trials and biostatistics evaluation for medical devices.

The Center for Food and Drug Inspection (CFDI)

CFDI is directly affiliated with NMPA and plays an important role in safeguarding the quality of drugs, medical devices, cosmetics and food. CFDI is organized into several departments responsible for managing inspections and administrative tasks. The main responsibilities include, but are not limited to the following:
formulating and amending inspection relevant regulations for drugs, medical devices and cosmetics
performing clinical trial and non-clinical trial site authorization
performing R&D site inspections, inspections for the purpose of registration, for-cause inspections during manufacturing and overseas inspections
performing inspections of medical device clinical trials and for-cause inspections during manufacturing and conducting overseas inspections
performing inspections of Research and Development (R&D) for cosmetics and for-cause inspections during manufacturing and conducting overseas inspections
performing food establishment inspections
managing the certification of national inspectors, providing consultation, conducting research into inspection related new theories, technology and development trends and regional/international cooperation

CFDI is expected to increase overseas inspections for drugs and medical devices. The inspection scope will be extended from manufacturing to include R&D. NMPA published an administrative regulation concerning overseas inspections of drugs and medical devices.  

CFDI has 10 departments, six of which are responsible for conducting inspections of a variety of products. NMPA regularly updates the list of inspectors who are responsible for conducting specific inspections.

The National Institutes for Food and Drug Control (NIFDC)

NIFDC has been directly affiliated institution within the former China Food and Drug Administration (currently named NMPA) since 1998 and is the statutory body and the highest technical arbitration institution for testing the quality of drugs in China. NIFDC covers the testing for drugs, medical devices, health foods, cosmetics, ingredients and packaging materials. NIFDC has the following responsibilities:

performing testing for the purpose of product registration and conducting specification verification
conducting testing for the purpose of safety supervision for these products
performing batch release for biological products
formulating and performing validation and specification verification for ingredients and packaging materials
performing testing of ingredients and packaging materials
formulating and updating the technical standards/requirements, specifications and analytical methods
organizing the standard reference planning, development, distribution and management, and conducting other testing relevant activities

NIFDC has about 800 employees and is comprised of 28 departments and agencies. The following comprise the important testing relevant agencies within NIFDC:

Testing Agency for Food
Testing Agency for Traditional Chinese Medicine (TCM)
Testing Agency for Chemical Products
Testing Agency for Biological Products
Testing Agency for Medical Devices
Testing Agency for In-Vitro Diagnostics
Testing Agency for Cosmetics
Testing Agency for Ingredients and Packaging Materials
Institution of Medical Devices Standards Management
• Re-Evaluation Center for the Safety of Cosmetics
• Management Center of Reference Standards and Standardization

In addition, NIFDC plays an important role in testing of biological products. In special circumstances, it is mandatory to perform testing of biological products, such as the testing for obtaining marketing authorization approval or for the batch release of biological products.

The Chinese Pharmacopoeia Commission (CPC)

CPC\textsuperscript{28} is an agency within NMPA. It is responsible for reviewing and granting product names before marketing authorization can be obtained. In addition, the following are some of its responsibilities:\textsuperscript{29}

• compiling and updating the Chinese Pharmacopoeia (ChP) and its addendums
• evaluating the implementation status of the ChP
• formulating and updating the standards, requirements and specification for drugs, ingredients and packaging materials
• providing relevant ChP training and consultation

CPC has nine departments and approximately 50 employees.

The Center for Drug Re-Evaluation – National Center for ADR Monitoring (CDR-ADR)

CDR-ADR\textsuperscript{30} is directly affiliated agency with NMPA and is responsible for safety re-evaluation and adverse events monitoring for drugs, medical devices and cosmetics. CDR-ADR has the following responsibilities:\textsuperscript{31}

• performing adverse events monitoring for drugs, medical devices and cosmetics
• monitoring drug abuse
• drafting regulations and technical standards for the following items:
  o adverse event re-evaluation and monitoring for drugs and medical devices
  o drug abuse monitoring
  o adverse events monitoring for cosmetics
• performing the safety re-evaluation for drugs and medical devices
• participating in the formulation of the national essential medicines catalogue
• participating in the formulation of the Over-the-Counter (OTC) medicines catalogue and other relevant activities

CDR-ADR has approximately 60 employees working in eight departments.

Figure 1 describes the structure of Chinese health and regulatory authorities.
Figure 1. Chinese Health and Regulatory Authorities Structure

Conclusion

This article provided a “snapshot” of the history of the Chinese government’s willingness to reform and reorganize the structure of the administration if and when necessary. Staying up-to-date with the changes is essential for those involved with regulatory affairs for products manufactured in China or products placed on the market in China. Most of the information regarding these issues and regulations is only available in Chinese.

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9. Ibid.

About the Author

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This article compares and contrasts several aspects of biological products versus biosimilar products. The author defines both biologics and biosimilars and explains how and why the two differ in terms of their organic natures. She also guides the reader through the biologic vs. biosimilar developmental and testing stages and through agency approval and postmarketing surveillance. The author clarifies important points to consider when developing biologic and biosimilar products, including approval processes for both, comparing data requirements, the step-wise process for biosimilar approvals, clinical and nonclinical trials and issues of “interchangeability.” She concludes by suggesting the impact biosimilar products will have on the market will not be unlike the market impact of generic drugs.

Introduction

Biomedical research is advancing rapidly, and a key part of that advancement is in the analytical capabilities allowing comparison between a reference biological product and a biosimilar product. To understand how biological products and biosimilar products differ, it is first necessary to understand how a biological product is different from a standard drug product.

What is a biological product?

A biological medicinal product is defined as one with an active substance made by or derived from a biological source, such as living cells or organisms. These organisms may include viruses, therapeutic serum, toxin, antitoxin, vaccine, blood, blood components or derivatives, allergenic products and proteins (except any chemically synthesized polypeptide). Biologics also may include growth factors, hormones, enzymes, allergenic
products and proteins, such as insulin and growth hormones, coagulation factors and monoclonal antibodies. These substances are isolated from natural sources, such as humans, animals, plants or microorganisms, often using cutting-edge biotechnology methods.\textsuperscript{1-6}

While small molecule drugs have a fixed molecular formula allowing their structure to be completely defined and easily copied by generic manufacturers,\textsuperscript{7} biological products (usually proteins), by contrast, are molecularly large and complex. Differences can occur in protein structure, including amino acid sequence, post-translational modifications (glycosylation) and protein folding. Once more, they are not easily characterized and are often immunogenic, which means they can cause an immune response within the body. Their structure may not be completely defined or known, and there are often natural variations between products because they are made from living organisms.\textsuperscript{8} Protein complexities must be carefully considered because even minor differences in protein structure can significantly impact a product’s safety and efficacy profile. Advanced analytical methods, such as mass spectrometry, peptide mapping and cell assays are used to identify a biological product’s physiochemical and functional properties, such as protein modifications, biological activity and molecular structure.

Fragility in biological molecules makes manufacturing complicated. Too, differences in the biological system used to manufacture the product can cause post-translational modifications. Aseptic processing and careful storage and handling are required as there is potential for microbiological contamination because the molecules tend to be heat sensitive. Higher order structure and protein modifications can be affected by the formulation and by certain environmental conditions, such as light, temperature, moisture, packaging materials, container closure system and delivery device materials. These alterations in the protein product all have the potential to adversely affect the safety and efficacy of the biological product. These minor variations, which can be within and between batches of the same biological medicine, particularly when scaling up a production batch, must fall within acceptable ranges to ensure consistency in terms of safety and efficacy.\textsuperscript{9}

**Guidance and Approval Process for Biological Products**

**United States**

In the US, the US Food and Drug Administration’s (FDA’s) Center for Biologics Evaluation and Research (CBER) issues guidance on how to submit a Biologics Licence Application (BLA). There are a variety of guidance documents available for each type of biological, such as blood products or rDNA derived vaccines. Information can be found on FDA’s website.

Reviewing and approving a biological in the US follows a pathway similar to that of a New Drug Application (NDA). If nonclinical testing is successful, the product moves into clinical trials with an Investigational New Drug Application (INDA). If the product proves to be safe and efficacious in the intended patient population, the manufacturer can submit a BLA to CBER to gain a marketing approval. The BLA should contain both nonclinical and clinical data demonstrating safety, purity and potency along with a description of manufacturing methods, stability data supporting the expiry date. The addresses of the manufacturing sites, as well as the proposed labelling, closures and containers, should be included.\textsuperscript{10}

**European Union**

In the EU, the European Medicines Agency (EMA) issues scientific guidelines for biological products. Available on the EMA website.

Review and approval of a biological in the EU follows much the same pathway as a Marketing Authorization Application (MAA). Once preclinical testing is successful, clinical
trials are required. The Clinical Trial Directive and Clinical Trial Regulation\textsuperscript{11,12} describes the general requirements for clinical trials for medicines, including biologicals. The company also must submit an Investigational Medicinal Product Dossier (IMPD).\textsuperscript{13} If the product is safe and efficacious, the manufacturer can apply for an MAA. The MAA must meet standard dossier requirements (Directive 2001/83/EC) complying with CTD format and including Module 1 (administrative information and labelling/mockups), Module 2 (expert summaries), Module 3 (chemical, pharmaceutical and biological information), Module 4 (nonclinical reports) and Module 5 (clinical study reports).\textsuperscript{14}

Table 1 provides details of some other guidances to be considered, including those developed by the International Council for Harmonisation (ICH).

| Table 1. Other Guidance to Consider When Developing a Biological Product |
|---------------------------------------------------|---------------------------------------------------------------|
| **ICH S6 Preclinical Testing**                   |                                                               |
| **ICH Q5A – Q5E: Quality**                       |                                                               |
| Guideline on Preclinical Safety Evaluation of Biotechnology Derived Pharmaceuticals (ICH S6) (CPMP/ICH/302/95) |                                                               |
| Guideline on the Requirements for Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials. EMA/CHMP/BWP/534988/2008 |                                                               |
| EMA/CHMP/ICH/731268/1998 (July 2011) (ICH S6 addendum) |                                                               |
| Regulation (EC) No 141/2000 on Orphan Medicinal Products |                                                               |
| The Small and Medicine Sized Enterprises (SME) Regulation – (EC) No 2049/2005 |                                                               |
| Guideline on the Quality, Nonclinical and Clinical Aspects of Gene Therapy Medicinal Products CHMP/GTWP/671639/2008 |                                                               |
| Guideline on Human Cell-Based Medicinal Products EMEA/CHMP/410869/2006 |                                                               |

**Data Requirements for a Biological Product**

Both FDA and EMA have adopted the International Council for Harmonisation of Technical Requirements (ICH) guidelines, making the data requirements for a biological product generally similar for both the US and EU. The guidelines are also similar to those for a drug product. However, assessment of immunogenicity is a critical aspect for biologicals. Evaluation of the viral safety of biological products derived from characterized cell lines of human or animal origin (i.e., mammalian, avian, insect) is also required.\textsuperscript{15}

The manufacturer of a biological product must clearly demonstrate safety and efficacy in the intended indication and with the appropriate number of patients in clinical trials. The first step is to produce an analytical package specifying the product’s composition and formula. Then, before moving into clinical trials, laboratory and animal testing are carried out to understand the pharmacological and potential toxicity of the biological.

Biologics often cannot be tested in standard rat and dog species due to their biological or tissue- specific activity. As such, a variety of tests are required, including in vitro binding assays and functional tests, to identify one or two relevant species. If a relevant species cannot be found in animal models, homologous proteins or transgenic animals, human receptors are an alternative approach to gathering the required animal data.

Many biologicals are immunogenic, which means they can elicit an immune response within the body, affecting the preclinical results. If these effects are not desired (for example in the case that the product is not a vaccine), samples are needed for antibody testing during repeat dose toxicity studies. The effects of antibody formation on pharmacokinetics (PK), pharmacodynamics (PD) and adverse events must be carefully considered. Immunogenicity in animal models is important in terms of exposure and toxicity as Anti-
Drug Antibodies (ADAs) can result in reduced exposure. Nonclinical studies are not useful in predicting potential immunogenicity in humans.\textsuperscript{16}

Sponsors will need to perform single and multiple dose PK and/or toxicokinetic studies to provide information on the Absorption, Distribution, Metabolism, Excretion (ADME) and dose response. These studies help predict safety margins for clinical trials. PD studies must be conducted including \textit{in vitro} binding assays and \textit{in vivo} studies conducted to define pharmacological activity and mechanism of action. Both single and repeat dose toxicity studies using a relevant species are needed as well as safety pharmacology to evaluate the product’s effects on major body systems, specific organs and local tolerance. Carcinogenicity studies may be warranted based on duration of dosing, patient population and/or biological activity. Reproductive and developmental toxicity studies may not be needed depending on the product, indication and patient population. Classic biotransformation studies are not required as biologics generally degrade into peptides and amino acids; genotoxicity studies are usually not applicable to biotechnology derived products because they are not expected to interact with DNA or chromosomes.

To start clinical trials in humans, an Investigational Medicinal Product Dossier (IMPD) in the EU or Investigational New Drug (IND) in the US is required to allow the agencies to assess safety issues and patient risk. This investigational new drug application package must provide information on everything learned to date regarding the product’s pharmacological effects, mechanism of action and ADME to conclude clinical trials are reasonably safe. The package should include an investigational plan with protocols for the planned studies. It must also contain manufacturing information to allow safety evaluations.\textsuperscript{17}

As with drug products, the clinical development of biological products has three phases, but also must include an assessment of immunogenicity because antibodies could be raised against the medicine, thereby reducing efficacy or affecting its activity.

Phase 1 studies introduce the biological to a small number of humans (generally patients rather than volunteers as is the case with drugs for ethical reasons) to provide information on the product’s metabolism, pharmacology and safety with escalating doses. The maximum tolerated dose and optimum therapeutic dose are established, and the bioactivity assessed. Immunogenicity is also assessed in terms of antibody development after administration, then again 28 days after administration to determine if there is a link to PK, PD, or adverse events.\textsuperscript{18,19}

Phase 2 studies in a few hundred patients are controlled and provide information on the short-term adverse events and specific use for the product as well as exposure and response relationships, PK, PD and immunogenicity. This information aids decision making regarding appropriate size, study population, and endpoints for the Phase 3 studies.

Phase 3 studies are typically large, randomized, double-blind, controlled, multi-center trials. Placebo controls are used if considered ethical. These studies are the main source of information for the risk benefit assessment for the product and its label claims. The patient population needs to represent those for which the sponsor will be seeking approval. The endpoint selected should be an established clinical outcome measure to demonstrate a clinical benefit in that patient population. Data from these clinical studies will form the majority of the BLA and MAA packages.

Biologics are sensitive to changes in the manufacturing process, such as scaling up from pilot production to full scale manufacturing, changes to improve efficiency or a change in production facility. The manufacturer must assess the effects of these changes using appropriate analytical testing, functional assays and, in some cases, animal or clinical studies to prove that the change does not affect product safety and efficacy.\textsuperscript{20,21} The manufacturer also may need to perform additional tests on the released product and FDA may request samples from each lot to perform their own tests.
What is a biosimilar product?

FDA defines a biosimilar product as a biological product shown to be highly similar to an existing FDA-approved reference biological product. The high similarity is demonstrated using analytical animal and clinical studies and allowing for minor differences in clinically inactive components, providing there are no clinically meaningful differences in safety, purity and potency.\textsuperscript{22-24}

EMA defines a biosimilar product as one similar to a biological medicinal product which has already been authorized in the EU. Similarity must be in terms of structure, bioactivity, safety, efficacy and immunogenicity based on comprehensive comparability studies. These studies provide evidence that the biosimilar is highly similar, notwithstanding natural variations inherent to all biological medicines and with no clinically meaningful differences.

The biosimilar approach is more likely to be applied successfully for biotechnology-derived products, which are highly purified and can be more thoroughly characterized using state-of-the-art analytical methods. It is more difficult to apply a biosimilar approach to other types of biological products, such as those extracted from biological sources, as they are more difficult to characterize.

If the active substance is a protein, the biosimilar is expected to contain the same amino acid sequence (protein) and folding pattern (3D structure) as the reference product. These factors determine biological activity. The biosimilar also must have the same posology and route of administration as the reference product. In the US, if the indication or condition for use corresponds to a particular presentation of the reference biological product, the applicant must use the same presentation. However, not all presentations for which the reference product has been approved are required for the biosimilar’s approval.

As biosimilars are types of biological products, the same natural variability seen in biologics applies. The manufacturing process will be unique to each manufacturer and, as a result, minor differences, ones not affecting safety and efficacy, may occur between the biosimilar and the reference product, e.g., formulation (different excipients), presentation (reconstituted powder rather than solution for injection) or administrative device.

Approval Process and Guidance on Biosimilars

The EU has been a pioneer in regulating biosimilar medicines since in 2006 when they approved the first, which was a human growth hormone. By shaping their development globally and establishing a framework for their approval, the EU has gathered considerable experience over the last 10 years in showing how biosimilars, in their approved indications, are as safe and efficacious as biologicals.

To improve patient access to biological medicines, FDA introduced the \textit{Biologics Price Competition and Innovation Act (BPCI Act)} in 2009. This act authorized FDA to create an abbreviated licence approval pathway for biosimilar products. FDA did this to provide more treatment options for patients, increase patient access to life saving medicines and lower the cost of these types of medicines through competition.\textsuperscript{25}

Both FDA and the EMA have similar guidelines.

The World Health Organization also has issued guidance for the development of biosimilars following the same principles as those of the EU and FDA.\textsuperscript{26}

The goal of a biosimilar development program is to confirm similarity with the reference medicinal product based on PK and PD equivalence and a confirmatory comparative clinical study in a representative indication evaluating safety, efficacy and immunogenicity. The scientific principles for these comparability studies are based on ICH guidance for evaluating the impact of changes in the manufacturing process for a biological medicinal product.
product. It is not necessary to independently establish safety and effectiveness for the proposed biosimilar product as this has already been done with the reference product. If biosimilarity is proven through comparative studies, the manufacturer can rely on existing scientific knowledge about safety and efficacy drawn from the reference product data, thus avoiding repetition of completed clinical trials with the reference product.

If the product is proven to be highly similar, as well as safe and efficacious in one therapeutic indication, the safety and efficacy data for other indications approved for the reference product may be extrapolated. This allows the biosimilar product to be approved for an indication without direct studies and also avoids unnecessary repetition of clinical trials with the reference product.

Generally, in both the EU and US, comparability studies should be conducted with an EU/US licensed product. However, both agencies have taken steps to facilitate global development programs by allowing the use of non-licensed products in comparative clinical studies if adequate scientific justification is provided to bridge the non-licensed product to one that is licensed. The sponsor is invited to discuss such an approach with the agencies to ensure other points for consideration are covered, such as whether the facility used to produce the non-licensed product is up to agency standards.

In the US, determination of interchangeability is also a consideration. An interchangeable biosimilar product is one expected to offer the same clinical result as the reference product. There should not be a risk of increased safety or diminished efficacy if alternating during repeat dosing between the biosimilar and the reference product. FDA has issued guidance for this.

Data Requirements for a Biosimilar

Reproducing a biosimilar product is a challenge quite different from that for manufacturing a small molecule generic drug. Biosimilars are not generics of the biological reference product due to the natural variability of proteins and because their complicated manufacturing processes do not allow for making an exact copy. Therefore, the data package for biosimilars must be more extensive than for a generic to ensure any minor differences in structure and function will not impact product safety, efficacy and immunogenicity.

A generic product is produced by chemical synthesis and can be copied exactly from the reference product, which is smaller and is easier to characterize. The manufacturer of a generic product also must produce a full pharmaceutical quality dossier demonstrating bioequivalence, meaning the active substance is released into the body at the same rate, and to the same extent, under the same conditions. PK bioequivalence studies are the only clinical data requirements as all indications can be approved based on bioequivalence.

By contrast, because a biosimilar product is obtained from a biological source, it can only be reproduced to a high degree of similarity due to the natural variability and unique manufacturing methods. Once more, biosimilars are made of structurally complex molecules needing advanced technologies to characterize them. As a result, the biosimilar manufacturer must demonstrate biosimilarity with robust pharmaceutical quality data as well as comprehensive comparison studies (both nonclinical and clinical) with the reference product to show that structure, biological function, PK and PD, efficacy, safety and immunogenicity are all highly similar. Efficacy and safety must be justified in each indication; however, extrapolation of data to other indications may be justified if biosimilarity is demonstrated.
Table 2. Comparison of Development and Characteristics Between a Generic and Biosimilar

<table>
<thead>
<tr>
<th>Generic Drug Product</th>
<th>Biosimilar Product</th>
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</thead>
<tbody>
<tr>
<td>Chemical synthesis</td>
<td>From natural sources</td>
</tr>
<tr>
<td>Exact copy can be obtained</td>
<td>Can only reproduce to a high degree of similarity due to natural variability and unique manufacturing processes</td>
</tr>
<tr>
<td>Small and easy to characterize</td>
<td>Large and complex. Advanced analytical technologies required for characterization</td>
</tr>
<tr>
<td>Full quality data package required</td>
<td>Full quality data package required with additional process and product characterization plus comparison with reference product</td>
</tr>
<tr>
<td>Demonstrate bioequivalence</td>
<td>Demonstrate biosimilarity using comparability studies assessing chemical structure, biofunction, efficacy, safety and immunogenicity</td>
</tr>
<tr>
<td>N/A</td>
<td>Abbreviated preclinical program based on complexity and residual uncertainty from quality</td>
</tr>
<tr>
<td>Clinical PK bioequivalence studies</td>
<td>Comparative PK and PD equivalence studies (plus safety and efficacy if complex)</td>
</tr>
<tr>
<td>All indications approved based on bioequivalence</td>
<td>Efficacy and safety in at least one indication if mechanism of action is the same. Extrapolation to other indications if there is scientific knowledge available</td>
</tr>
</tbody>
</table>

A totality-of-evidence approach is recommended in the guidance for biosimilars, along with a step-wise development program focusing on demonstrating similarity in structure and functional equivalence. This analytical data will form the foundation of the development program to include animal studies, a human PK/PD equivalence study and a clinical study in a sensitive population with appropriate endpoints to confirm similar efficacy. Safety and immunogenicity must be confirmed as well as allowing any clinically meaningful differences to be detected. A robust manufacturing process also must be established to ensure a high-quality biosimilar product is consistently produced.

Advances in analytical technologies, such as mass spectrometry, have meant that some protein products can be extensively characterized in terms of their physicochemical and biological properties, which include higher order structures and functional characteristics. This ability has greatly improved identification and characterization of the drug substance of a protein product as well as excipients and impurities.

Comparability studies are used to demonstrate the physicochemical properties and biological activity of the biosimilar and the reference product are highly similar. This is achieved in a step-wise process.
Table 3. The Stepwise Process for Biosimilar Development

<table>
<thead>
<tr>
<th>Stepwise Process for Biosimilar Development</th>
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<tbody>
<tr>
<td><strong>STEP 1</strong></td>
</tr>
<tr>
<td>Demonstrate analytical similarity</td>
</tr>
<tr>
<td>Compare all predicted functions and confirm no enhanced function</td>
</tr>
<tr>
<td><strong>STEP 2</strong></td>
</tr>
<tr>
<td>Nonclinical PK/PD and toxicology as required</td>
</tr>
<tr>
<td><strong>STEP 3</strong></td>
</tr>
<tr>
<td>Human PK and PD</td>
</tr>
<tr>
<td>Additional clinical data as required</td>
</tr>
</tbody>
</table>

**Step 1: Comparative Quality Studies**

The main part of a biosimilar application is the direct comparison demonstrating analytical similarity between a reference product and the proposed biosimilar product.

First, using state of the art technology, an in-depth analysis of the structure and function of both the reference biological product and the biosimilar is carried out. This serves to establish a target profile and to define, through analytical characterization, the Critical Quality Attributes (CQAs) impacting the PK, safety or efficacy. Analysis includes aspects such as primary structure (amino acid sequence), higher order structure (receptor binding), biological properties (mechanism of action), impurities, particle and aggregates and stability profiles.\(^{27,28}\)

In vitro studies compare protein structure and biological function of both products using sensitive methods to identify minor differences in clinical relevance between the biosimilar and the reference product. The amino acid sequence should be the same as the reference product, but there may be variations due to mutation or modification occurring during manufacture. These studies are much more accurate than clinical trials because of the variability among human subjects. Any differences discovered during this analysis must be carefully evaluated and their relationship to function assessed. Even subtle differences in structure can significantly impact the product’s pharmacokinetics (PK), efficacy, safety and immunogenicity. The clinical significance of these differences can be investigated through a series of PK (exposure) and PD (response) studies, and by assessing clinical immunogenicity.\(^{29}\)

**Step 2 - Comparative Nonclinical Studies**

In vitro PD studies can confirm whether the biosimilar matches the reference product in terms of its action within the body, such as antigen binding and activation (or inhibition) of physiological targets and the immediate physiological effects in cells. This is accomplished through a variety of activity-relevant assays.\(^{30}\)

In vivo disease models can be used to compare dose response efficacy and demonstrate equivalence in activity. They also can be used to compare PK, PD, toxicology and immune response.

If there is enough confidence in the analytical and in vitro pharmacological similarity, the need for testing in animals can be reduced or eliminated. In vivo PD studies using animal models are only performed if there is no suitable in vitro model (cell based bioactivity models) or if toxicological studies are required, such as the biosimilar is produced in a new type of cell or organism or there are differences in formulation (new excipients not used before), which may affect efficacy or raise potential toxicity concerns.
A PK/PD comparative single dose study or toxicity study may be required if there is uncertainty regarding similarity. Immunogenicity studies to detect differences between the reference and the biosimilar may be performed, but these will not predict similarity in clinical immunogenicity.31

**Step 3 - Comparative Clinical Trials**

Clinical studies are not designed to demonstrate safety and efficacy in patients, *per-se*, but to confirm biosimilarity and address any questions from the analytical or functional studies to exclude clinically meaningful differences.

The extent of differences will be determined by the degree of similarity demonstrated during the analytical and preclinical studies. This could include PK, PD, efficacy, safety and immunogenicity studies. At the very least, it will likely require **one sufficiently large randomized PD study to demonstrate clinical equivalence, comparable safety and immunogenicity in an informative population.**

A PK study must first be carried out in either healthy subjects or in patients within the study population needing to be scientifically justified. If equivalence exposure can be demonstrated in the PK study, the pivotal clinical study can be conducted using the same therapeutic dose as used for the reference product, thereby eliminating the need for phase II studies. A PD study should be conducted if there is a marker relevant to the mechanism of action available to provide information on efficacy. In addition, a safety, efficacy and immunogenicity study should be carried out in a sensitive population to allow detection of any clinically meaningful differences. Study populations should represent the indication for which approval is being sought. However, regulators generally allow extrapolation between indications if efficacy relies on a similar mechanism of action and equivalence has been demonstrated in one of them.

**Totality-of-Evidence**

The agency may determine that not all of the above studies are required; however, they may request companies to meet with them to discuss their proposed biosimilar product development plan and to establish a schedule of milestones to serve as “landmarks” for future discussions with the agency. Each product is assessed on a case-by-case basis.

**Use of a non-EU or US Licenced Product in the Comparative Clinical Studies**

In both the EU and US, comparability studies for biosimilars should, ideally, be conducted with a locally approved reference medicinal product. For approval in the US, the manufacturer should prove biosimilarity to a US licence reference medicinal product; the same applies in the EU. However, both agencies will accept the use of foreign sourced comparators in the comparability studies if an adequate scientific justification or rationale can be provided to “bridge” the foreign product to one that is licenced in either the US or the EU. This scientific bridge will include a comprehensive analytical assessment (structural and functional) comparing all three products: the biosimilar, the licensed product and the non-licensed product. It is also likely to include a clinical PK and, if appropriate, a PD study for all three products to establish bioequivalence unless justification can be provided as to why such a study is not required. It is recommended to discuss the acceptability of such an approach with the agencies in advance.

**Interchangeability**

For a biosimilar product expected to be administered to a patient more than once, a “switching study” to determine interchangeability is required. This requirement is unique to the US. The risk, in terms of safety or diminished efficacy of switching or alternating
between the biosimilar and the reference medicinal product, should not be greater than if only the reference medicinal product is used without switching.

The study should evaluate changes in treatment resulting from two or more alternating exposures (switch intervals) between the biosimilar and the reference product to demonstrate the same clinical result as the reference medicinal product would be expected to provide for all indications of use in any given patient. The study should be carried out in an appropriate patient population with endpoints assessing PK (and PD if a suitable market is available) as PK (and PD) are expected to be more sensitive to potential changes in immunogenicity. Postmarketing data is important for monitoring the safety of interchangeable products.32

For biological products not administered more than once, switching studies are generally not needed, although a justification for why they are not needed is expected. There are no specific EU guidelines on interchangeability as individual member states make substitution policies.

How and why Data Requirements for Biological and Biosimilar Medicines Differ

In both the US and the EU, biological products undergo a rigorous evaluation to ensure safety, efficacy and quality. However, a biosimilar product has an abbreviated approval process and different data requirements. For example, the manufacturer of the reference product must produce a “stand-alone” application containing all data and information needed to affirm efficacy and safety have been demonstrated through extensive clinical trials for the disease indications being sought.

By contrast, the development of a biosimilar product focuses only on demonstrating its high similarity to the reference product. It is not necessary to establish safety and efficacy with a full clinical package, as this has already been done for the reference product. Biosimilarity is proven first with detailed comparative analysis of structure and function of the reference and biosimilar products, and then through animal studies and comparative clinical studies if there are differences needing to be assessed for clinical significance. Once biosimilarity is demonstrated, the manufacturer can rely on the scientific knowledge from the reference product regarding safety and efficacy in the therapeutic indications.

<table>
<thead>
<tr>
<th>Table 4. Comparison of Data Requirements for a Biological Reference Product and a Biosimilar Product</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biological Reference Product</strong></td>
</tr>
<tr>
<td>Pharmaceutical quality studies – full process and product characterization</td>
</tr>
<tr>
<td>N/A</td>
</tr>
<tr>
<td>Full preclinical program</td>
</tr>
<tr>
<td>Clinical studies</td>
</tr>
<tr>
<td>Phase 1</td>
</tr>
<tr>
<td>Phase 2</td>
</tr>
<tr>
<td>Phase 3 in all indications</td>
</tr>
<tr>
<td>Risk management plan (EU only) Pharmacovigilance</td>
</tr>
</tbody>
</table>
For a biosimilar product, there are more detailed Chemistry, Manufacturing and Controls (CMC) and analytical (comparative) requirements, but less clinical data is expected. Once analytical and nonclinical similarity is confirmed, the clinical studies are only required to answer questions about minor differences between the biosimilar and the reference product.

Summary and Conclusion

Biological medicines are large, complex molecules with inherent variability. These molecules are difficult to characterize in the laboratory and are sensitive to minor changes in manufacturing processes, storage and handling conditions.

The difference between a biological medicine and a biosimilar is that biologics are developed in living organisms, whereas biosimilars are pharmaceutical drugs synthesized outside of the living organism. Biosimilars mimic the biological medicine, but they are not identical in nature.

Biological products must undergo a rigorous evaluation to ensure safety, efficacy and quality. By contrast, the development of a biosimilar product focuses on demonstrating its high similarity to the reference product through comparative studies. In other words, it is not necessary to establish safety and efficacy with a full clinical package. However, any differences emerging between the biosimilar and the reference product must be assessed for clinical significance.

Biosimilars are likely to have a great impact on the pharmaceutical industry, an impact similar to how generic drugs have impacted the industry by making more medicines affordable and available to patients. In addition, the cost of developing a biosimilar is much lower than the developing biosimilars due to the abbreviated clinical trial program. Risk of failure is also much lower than for a biosimilar’s reference product. Reduced cost should broaden the availability of such drugs to patients. Because they are better characterized than their reference product due to the extensive analytical studies required for regulatory approval, there is a more complete picture of the drug and how it will affect the patient. However, one disadvantage to biosimilars is the risk of differences due to structure, which can impact clinical and safety profiles. If there is enough justification to provide totality of evidence, agencies are likely to be open to many different approaches in development. However, sponsors are advised to request scientific advice to discuss their proposed development program. Finally, the truncated clinical development program and exposure in fewer patients means that companies must be extra vigilant in their postmarketing surveillance.

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By Suzanne Schwartz, MD, MBA and Michelle Jump, MS, MSRS, RAC

This article reviews past and current efforts to protect medical devices and other connected healthcare infrastructure from security breaches. The authors cover recent regulatory efforts in Australia, Canada, China, Europe, Japan and the US aimed at enhancing cybersecurity and industry’s efforts in cybersecurity regulatory compliance to protect patients as well as healthcare infrastructure.

Introduction

What are the Issues?

The US healthcare and public health critical infrastructure sector represents a significantly large cyberattack surface. Intrusions and breaches occur through weaknesses and vulnerabilities in the system’s architecture and medical devices. As with all other computer systems, medical devices that use software are vulnerable to cyberattacks and hospital network operations using software and the Internet are also subject to disruption. If vulnerabilities are not addressed and remediated, they can serve as points of access and entry into medical devices, hospital and other healthcare networks, resulting in compromised data confidentiality as well as compromised patient safety.

Strengthening healthcare cybersecurity and the critical infrastructure within and across sectors is imperative. Doing so requires fostering an incentivized culture that encourages proactive behavior, especially with regard to information sharing, as well as developing a framework to strengthen cybersecurity and critical infrastructure.
**Australia**

In the fall of 2018, the Australian government’s Therapeutic Goods Administration (TGA) announced cybersecurity consultation through The Commonwealth Scientific and Industrial Research Organisation (CSIRO), an independent Australian federal government agency responsible for scientific research, in the areas of Software as a Medical Device (SaMD) and Cybersecurity for Medical Devices (CSfMD).¹ The collaboration aims at generating reports for both SaMD and CSfMD that can help move regulation forward.² According to CSIRO, TGA engaged CSIRO to conduct research to build an understanding of Australia’s Software as a Medical Device innovators and learn how and when TGA can support them in demonstrating the safety of their products. To accomplish this, CSIRO conducted research into medical device cybersecurity in an effort to support the development of a TGA guidance document to assist the medical devices ecosystem implement best practices for cybersecurity. On 20 December 2018, CSIRO posted draft regulatory guidance and other informational materials on their website and invited comments from interested parties on the applicability and usefulness of the content contained in the draft regulatory guidance and information materials.³ The comment period deadline was 14 February 2019.

The Australian guidance stresses a Total Lifecycle (TPLC) approach, similar to the Canadian guidance and also refers to AAMI TIR57 and UL 2900, as well as ISO 27799, ISO/IEC 290147, ISO/IEC 30111 and others. It also focuses on the importance of information sharing, vulnerability disclosure and supply chain assessment. Cybersecurity-specific considerations have been added for each essential principle.

**Canada**

In the fall of 2018, Health Canada sought “input” on its approach to medical device cybersecurity from the Scientific Advisory Committee on Digital Health Technologies. That input was published on 7 December 2018 on the Health Canada website as a draft guidance document on the premarket requirements for cybersecurity of medical devices.⁴,⁵ The draft guidance⁶ outlines a set of high level goals, including security design and risk control activities, as well as specific license application requirements such as an SBOM, list of recalls related to cybersecurity, risk management reports and evidence of a cyber framework as part of device development. It also references the NIST cybersecurity framework and references standards such as AAMI TIR57 and UL 2900.

**China**

China’s National Medical Product Administration (NMPA), founded on the basis of the former China Food and Drug Administration (CFDA) was rebranded and restructured as the China NMPA in 2018.⁷

Now, CFDA has new, codified medical device cybersecurity expectations prior to product registration that include the expectation that companies will conduct a self-assessment of cybersecurity standards and measures. The measures are not mandatory, but the new cybersecurity law suggests that failure to do an assessment may delay product registrations. The latest CFDA cybersecurity guidelines, published in 2018, covers devices connected for data exchange, remote control or those devices used to store media for the exchange of information.

NMPA’s medical device cybersecurity focus follows a three-part, CIA Model: Confidentiality, Integrity and Availability.⁸ “Confidentiality” means data can only be accessed by authorized users within an authorized time frame through authorized means. "Integrity” means data must be accurate, comprehensive and cannot be altered without authorization. “Availability” means data must be accessible and utilized as expected. Once more, the CIA model focus must cover the entire process, from data generation through data usage and consider the entire lifecycle. That data, says NMPA, is the patient’s personal information protected by encryption and embedded software “controls” for monitoring, security and tracking capabilities.
Europe

The European Union Agency for Network Information Security (ENISA), now a permanent agency in the European Union (EU), is developing a Single Digital Market strategy as proposed in the EU Cybersecurity Act on 29 May 2018. The Single Digital Market includes the concept of the Internet of Things (IOT), which merges physical and virtual worlds, creating smart environments. The European Commission actively cooperates with industry, organizations and academic institutions to unleash the potential of the IOT technology across EU Member States and beyond.

Baseline security recommendations have been crafted for IOT. The recommendations include cybersecurity recommendations focused on critical information infrastructures where their destruction or disruption that could bring about major consequences for the health, safety and economic wellbeing of EU citizens. Section 4 of the EU IOT recommendations focuses on security “best practices” in terms of policies, organizational, people, process measures and technical measures. System safety and reliability recommendations include designing systems with operational disruption in mind and preventing the system from causing unacceptable risk of injury or physical damage. Also included is the recommendation for a mechanism with the ability of “self-diagnosis” and self-repair to recover from a failure, malfunction or compromised state. Ensuring a “standalone” operation, in which essential features of the device should continue to work in a loss of communications or negative impacts from compromised devices or cloud-based systems is a goal.

Gap analysis is also recommended in the context of IOT design and development. In all, IOT recommends the following 24 categories of detailed security measures:

1. security by design
2. privacy by design
3. asset management
4. risk and threat identification and assessment
5. hardware security
6. trust and integrity management
7. strong default security and privacy
8. data protection and compliance
9. system safety and reliability
10. secure software/firmware updates
11. authentication
12. authorization
13. access control
14. cryptography
15. secure and trusted communication
16. secure interfaces and network services
17. secure input and output handling
18. logging
19. monitoring and auditing
20. end-of-life support
21. proven solutions
22. management of security vulnerabilities and/or incidences
23. human resource security training and awareness
24. third party relationships

Japan

In July 2018, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) published Guidance for Ensuring Cybersecurity in Medical Devices (Notification No. 0724-
Since breaches of cybersecurity are now seen as a foreseeable hazard, the primary focus of the guidance is on risk management and with a dual focus on both technical controls and procedural protection.

**Federal Efforts to Strengthen US Cybersecurity**

Federal policy framework for cybersecurity and critical infrastructure resilience emphasizes a collaborative approach among government, industry and other stakeholders. Executive Order 13636, “Improving Critical Infrastructure Cybersecurity” seeks partnerships with the owners and operators of critical infrastructure to improve cybersecurity while Presidential Policy Directive 21, “Critical Infrastructure Security Resilience” promotes better security. In addition, Executive Order 13691 promotes the establishment of Information Sharing and Analysis Organizations (ISAOs) and Executive Order 13800 aims at strengthening the cybersecurity of federal networks and critical infrastructure networks.

**FDA’s Cybersecurity History and key Principles, Premarket and Postmarket**

The US Food and Drug Administration’s (FDA) recent medical device cybersecurity efforts include releasing the 2018 Medical Device Safety Action Plan, issuing safety communications and cybersecurity guidances, convening several public workshops (2014, 2016 and 2017), partnering with the Health ISAC, supporting ISAO efforts and organizing independent security researchers, medical device manufacturers and the Department of Homeland Security for coordinated vulnerability disclosure, among other activities. These efforts continue to enhance multi-stakeholder engagements for cybersecurity initiatives including cooperation and collaboration with the following groups and agencies:

- Medical Device Innovation Consortium (MDIC)
- National Telecommunications and Information Administration (NTIA): US Department of Commerce
- Healthcare and Public Health Sector Coordinating Council (HSCC) Cybersecurity Working Group

Key principles of FDA’s premarket cybersecurity guidance have emphasized shared responsibility between stakeholders (including healthcare facilities, patients, healthcare providers and manufacturers of medical devices), addressing cybersecurity during the design and development of medical devices, establishing design inputs for devices related to cybersecurity and establishing a cybersecurity vulnerability and management approach as part of software validation and risk analysis as required by 21 CFR 820.30 (g).

FDA is also driving efforts to improve the postmarket management of cybersecurity in medical devices by incentivizing “right behavior.” For example, FDA advocates for a risk-based framework to assure risks to public health are addressed in a continual and timely fashion. The emphasis articulates manufacturer responsibilities by leveraging existing Quality System Regulation and postmarket authorities. FDA also continues to foster a collaborative and coordinated approach to information sharing and risk management while aligning with Presidential executive orders and National Institute of Standards and Technology (NIST) frameworks.

Over the years, there have been many cybersecurity lessons learned. Accordingly, FDA’s thinking with regard to cybersecurity in the healthcare space has evolved. For example, when investigating device vulnerabilities it is necessary to get to “ground truth” as quickly as possible so that mitigations can be proactively communicated and executed. FDA has observed that non-coordinated disclosure of vulnerabilities may result in delayed assessments. In addition, the impact of cyberattacks, such as WannaCry, on critical infrastructure has the potential to disrupt critical patient care and can therefore result in delayed treatment and patient harm.
These lessons have led to efforts to further advance medical device cybersecurity. FDA’s “Medical Device Safety Action Plan” considers the need for the Agency to seek additional premarket and post-market authorities, including to require:

1. companies to build and update security capabilities into a product’s design and to include appropriate data supporting these design capabilities into premarket submissions to FDA
2. manufacturers to develop a Software Bill of Materials (SBOM) to be shared with customers and as part of regulatory submissions
3. firms adopt policies and procedures for coordinating disclosures about vulnerabilities as they are identified

**FDA’s Current and Future Efforts: Medical Device Safety Action Plan**

FDA released an updated draft *Medical Device Cybersecurity Premarket Guidance* in October 2018. The new draft guidance outlines tiers that separate products into two categories, dependent on their potential risk to patients. In addition, MITRE, in collaboration with FDA, has developed a *cybersecurity preparedness and incident response playbook* which involves using testing scenarios for medical devices in the clinical environment to help foster regional and national preparedness. To enhance information sharing of medical device vulnerabilities across the ecosystem, FDA has executed Memorandums of Understanding with emerging ISAOs emphasizing information sharing relevant to patient safety and treatment.

Also, with MITRE’s expert support and guidance, efforts to develop a clinical rubric for *Common Vulnerability Scoring System* as a Medical Device Development Tool (MDDT) continue to progress with active multi-stakeholder engagement. Finally, the Medical Device Innovation Consortium (MDIC)—a public private partnership with FDA—published a white paper in late 2018 that provided a compelling analysis for adoption of coordinated vulnerability disclosure policies and processes.¹⁸

**Summary and Conclusion**

**A Common Cybersecurity Thread**

Around the globe and across regulators, four consistent themes are emerging with regard to medical device cybersecurity: risk management, security by design, standardization and documentation. Cybersecurity risk management starts with an understanding of risk and its control, which means “security-by-design” or designing technical controls to ensure comprehensive and robust medical device protection for patient health and their personal data. As standards are being developed, assessed and implemented, methods and rules for manufacturers to show they are doing “the right things” are also being incorporated. However, global medical device cybersecurity will depend on three expectations of industry—that there will be enhanced collaboration, greater transparency and increased awareness of the security risks inherent in medical devices.

**References**


About the Authors

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By Meredith Brown-Tuttle, RAC, FRAPS

If you thought 2017 had a lot of changes, 2018 was even busier (and 2019 seems to be shaping up just the same if not busier). This article explores the major changes during 2018 including guidance documents drafted and finalized, new legislation, other areas of interest and some tools to help you explore additional areas.

**Strategic Policy Areas (Drug/Biologic Specific Only) Summary**

The following four priority areas were identified in [FDA’s 2018 Strategic Policy Roadmap](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/2018-strategic-policy-roadmap) issued in January 2018:

1. reduce the burden of addiction crises threatening US families
2. leverage innovation and competition to improve healthcare, broaden access and advance public health goals
3. empower consumers to make better and more informed decisions about their diets and health and expanding the opportunities to use nutrition to reduce morbidity and mortality from disease
4. strengthen FDA’s scientific workforce and its tools for efficient risk management

Number 2 impacts industry and #4 is internal to FDA but will ultimately affect/help industry. Within the document, specifics are given to support these goals including:

- **improve product development and strengthen FDA’s Gold Standard (#2)** which was implemented through the Advanced Manufacturing Strategy Roadmap (assure the availability of safe and effective medicines by modernizing the drug manufacturing methods to make the processes more reliable, efficient and high quality)
• promote Generic Drug Competition (#2) implemented through the Drug Competition Action Plan and Biosimilar Innovation Plan
• modernize FDA’s Regulatory Toolbox (#4) started through both the Building a Strong FDA and Scientific Computing Work Plan (internal to FDA)

Major Legislation/Regulations

What major legislation was passed this year and will be implemented through the passage of regulations? While new bills/laws were scarce, there were a few new regulations (Table 1) and many guidance documents recapped below (Table 2).

Right to Try

On 30 May, President Trump signed the “Right to Try” bill into law. This law is another way for patients who have been diagnosed with life-threatening diseases or conditions who have tried all approved treatment options and who are unable to participate in a clinical trial to access certain unapproved treatments. FDA encourages companies to accommodate these patients’ requests; watch for more action to follow about this.

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<td>21 CFR Part 600</td>
<td>Removal of Certain Time of Inspection and Duties of Inspector Regulations for Biological Products Proposed Rule</td>
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<td>21 CFR Part 3</td>
<td>Modification of Product Jurisdiction Proposed Rule Update</td>
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<td>21 CFR 310</td>
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<td>21 CFR Parts 20 and 720</td>
<td>Public Information - Amend Regulations (FOI)</td>
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<td>21 CFR Parts 50, 312 and 812 add § 50.22 to part 50 (21 CFR part 50)</td>
<td>FDA takes steps to allow greater flexibility for clinical investigators about informed consent in minimal risk situations. FDA is proposing to amend its regulations to implement section 3024 of the 21st Century Cures Act.</td>
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<td>21 CFR Parts 314 and 601</td>
<td>Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products: Withdrawal</td>
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Guidance Documents

In 2018, FDA published a number of draft and final guidance documents in the Federal Register (Table 2). Also included in Table 2 is the Federal Register notice or press release associated with each guidance document, when available (and the newly designed FDA website captures information like this as well…great minds think alike). Why would a link to the Federal Register notice be important? Often the background of the guidance document, definitions used in the guidance document, rationale for why needed and comments received on a previous draft are included in the Federal Register notice. Below are some helpful links to help you explore this critical body of knowledge:

• new guidance documents posted by FDA
• search guidance documents
• 2018-2019 guidance document agenda
• withdrawn guidances (Table 3)
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### Table 3. 2018 Withdrawn Guidance Documents

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<td>19 May 2016</td>
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<td>Sinusitis: Designing Clinical Development Programs of Nonantimicrobial Drugs for Treatment</td>
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<td>Statistical Approaches to Evaluate Analytical Similarity Guidance for Industry</td>
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**Action Plans and Related New Programs**

While Action Plans are not technically legislation or regulations, they lay out FDA’s plans for how they plan to modify functions, processes and structure to meet the challenges posed by scientific innovation, globalization, the increasing breadth and complexity of the products that FDA regulates and new legal authorities. While the Action Plan process was technically rolled out in 2014, there were quite a few issued during 2018 or progress made on those issued in years past.

**Drug Competition Action Plan (DCAP): Generic Drug Review Enhancement**

Technically, this is from 2017 but a lot of work was accomplished on this during 2018 (see below). FDA took two new, important steps to increase competition in the market for prescription drugs and facilitate entry of lower-cost alternatives. The agency published a list of off-patent, off-exclusivity branded drugs without approved generics and also implemented, for the first time, a new policy to expedite the review of generic drug applications where competition is limited. To encourage generic drug development, FDA posted a list of branded drugs that have no listed patents or exclusivities and for which the agency has yet to approve a generic drug application (known as an Abbreviated New Drug Application [ANDA]). The agency also intends to expedite the review of any generic drug application for a product on this list to ensure they come to market as expeditiously as possible. FDA will continue to refine and update the list periodically to ensure continued transparency around drug categories where increased competition has the potential to provide significant benefit to patients.

FDA is also announcing a change to its policy on how the agency prioritizes its review of generic drug applications and will expedite the review of generic drug applications until there are three approved generics for a given drug product. The agency is revising the policy based on data that indicate that consumers see significant price reductions when there are multiple FDA-approved generics available.

- Statement from FDA Commissioner Scott Gottlieb on new Steps to Facilitate Efficient Generic Drug Review to Enhance Competition, Promote Access and Lower Drug Prices
- Advancing Toward the Goal of Global Approval for Generic Drugs: FDA Proposes Critical First Steps to Harmonize the Global Scientific and Technical Standards for Generic Drugs
- FDA Tackles Drug Competition to Improve Patient Access
- Statement from FDA Commissioner Scott Gottlieb Responding to Report From GAO and Updating on FDA's Ongoing Efforts to Increase Access to Complex Generic Drugs
- Statement from FDA Commissioner Scott Gottlieb on new Agency Actions to Further Deter 'Gaming' of the Generic Drug Approval Process by the use of Citizen Petitions

**Competitive Generic Therapy (CGT) Designation**

Under new authorities provided to the agency in the FDA Reauthorization Act of 2017 (FDARA), a drug can be designated as a Competitive Generic Therapy (CGT) if there is inadequate generic competition for that drug, meaning there is not more than one approved drug in the active section of the Orange Book. Applicants for drugs that receive a CGT designation may receive review enhancements and expedited review of their ANDA. Applicants for drugs that receive a CGT designation are also eligible for a 180-day period of marketing exclusivity if they are the first approved applicant for that CGT and meet certain other conditions. Under a special forfeiture rule for CGTs, the applicant must commercially market the CGT within 75 days after the date of approval of its ANDA or it will forfeit its...
exclusivity. FDA approved several strengths of potassium chloride oral solution as the first generic drugs to receive a Competitive Generic Therapy (CGT) designation.

- **FDA Approves First Generic Drug Under new Pathway Aimed at Enhancing Market Competition for Sole Source Drugs**

### ANDA Suitability Petitions

Certain differences between a Reference Listed Drug (RLD) and a proposed generic drug product may be permitted in an ANDA if these differences are the subject of an approved **suitability petition**. An applicant may submit a suitability petition to the FDA under section 505(j)(2)(C) of the *Federal Food, Drug, and Cosmetic Act (FD&C Act)* and pursuant to 21 CFR 314.93 requesting permission to submit an ANDA for a generic drug product that differs from an RLD in its route of administration, dosage form, strength or that has one different active ingredient in a fixed-combination drug. An ANDA citing a suitability petition that has not been approved will be refused for receipt because the application lacks a legal basis for the submission. FDA issued a MAPP establishing the policies and procedures of the OGD for responding to suitability petitions submitted to it by or on behalf of prospective abbreviated new drug application (ANDA) applicants.

- **Manual of Policies and Procedures (MAPP)**
- **Patent Certifications and Suitability Petitions**

### ANDA New Guidance Documents Issued

- **FDA provides scientific and regulatory clarity for generic drug developers through the issuance of 43 new or revised product-specific guidance documents, including hard-to-copy complex generics and abuse-deterrent formulations of opioids.**
- **Product-Specific Guidances for Generic Drug Development**
- **Product-Specific Guidances: Draft and Revised Draft Guidances for Industry: Availability**

### FDA Disallows use of REMS to Block Generics

Sponsors have sometimes been able to use their Risk Evaluation and Mitigation Strategy (REMS) requirements to block timely generic entry. FDA feels the REMS requirements has been exploited in two ways. One occurs at the front end of the drug development process, when generic drugs are being developed. The other occurs at the back end of the process, after necessary testing has been completed, when a generic drug seeks approval and market entry. On the front end, brand drug makers sometimes use REMS as a way to restrict the sale of their drugs, keeping the drug out of the hands of generic firms. The generic drug makers typically need up to 5,000 doses of a brand drug in order to run bioequivalence and bioavailability studies to prove the generic medicine is the same as its brand drug. The other obstacle occurs at the back end, after a generic drug seeks FDA approval and market entry because brand and generic drug makers are required to develop a single shared REMS program—the generic drug maker has to negotiate with the brand firm to enter into a shared REMS programs before the generic drug can be approved and these negotiations can be protracted for the branded manufacturers advantage and bar entry of the generic. Through a new policy, supported by a draft guidance document, FDA's aim is to help generic drug makers get their products through the development and approval processes efficiently while maintaining the safety controls sought by the REMS. The first draft guidance, **Development of a Shared System REMS**, describes general principles and recommendations to assist sponsors with developing these programs. The goal is to improve the clarity and efficiency for developing shared system REMS, which will enable timelier market entry for products that are part of these REMS.
Statement from FDA Commissioner Scott Gottlieb on new Policies to Reduce the Ability of Brand Drug Makers to use REMS Programs as a way to Block Timely Generic Drug Entry, Helping Promote Competition and Access

FDA’s Proposal to Harmonize Standards for Generic Drugs (ICH Involvement)

FDA has submitted a proposal to ICH recommending the development of internationally harmonized guidelines on scientific and technical standards for generic drugs. ICH is the global venue for harmonization of standards for pharmaceutical products, including both new drugs and generic drugs. Although many existing ICH guidelines are applicable to generic drugs, historically ICH has focused on standards for new drugs. As a result, there are areas specific to generic drugs where harmonized guidance is lacking.

Citizen Petition Modifications

Further to support generic competition and market entry, FDA issued a revised draft guidance, Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act, designed to allow for a more efficient approach to 505(q) petitions and allow them to focus more reviewer resources on scientific reviews instead of Citizen’s Petitions and stop manufactures from gaming the system and stopping generics market entry.

Biosimilars Action Plan

FDA released the Biosimilars Action Plan (BAP) to provide information about the key actions the agency was taking to encourage innovation and competition among biologics and the development of biosimilars. The BAP is focused on four key areas:

- improving the efficiency of the biosimilar and interchangeable product development and approval process
- maximizing scientific and regulatory clarity for the biosimilar product development community
- developing effective communications to improve understanding of biosimilars among patients, clinicians and payors
- supporting market competition by reducing gaming of FDA requirements or other attempts to unfairly delay competition

The BPCI Act requires a marketing application for a “biological product” (that previously could have been submitted under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)) must be submitted as a Biologics License Application (BLA) under section 351 of the Public Health Service Act (PHS Act). Certain biologic products regulated by CDER were previously approved as drugs and need to be reclassified as biologics (i.e., insulin and other proteins) and this reclassification will take place over a 10-year transition period ending on 23 March 2020. On 23 March 2020, the BPCI Act requires an approved marketing application for a “biological product” under section 505 of the FD&C Act shall be deemed to be a license for the biological product (i.e., an approved BLA) under section 351 of the PHS Act. To support the BPA, FDA released the following documents related to the “Deemed to be a License” Provision of the BPCI Act:

- Draft Guidance for Industry: The “Deemed to be a License” Provision of the BPCI Act: Questions and Answers
- Proposed Rule on “Definition of the Term Biological Product”
- **MAPP on Responsibility in the Office of Pharmaceutical Quality (OPQ) for the Integrated Quality Assessment of Products Containing Drug Substances Composed of Amino Acid Polymers**
- **Preliminary List of Approved NDAs for Biological Products That Will be Deemed to be BLAs on March 23, 2020**
- **A new webpage that contains information and resources related to the ‘Deemed to be a License’ Provision of the BPCI Act**
- **Federal Register Notice of Availability and Request for Comments**

**“Deemed to be a License” Provision of the BPCI Act**

- **Remarks from FDA Commissioner Scott Gottlieb as Prepared for Delivery at the Brookings Institution on the Release of the FDA’s Biosimilars Action Plan**
- **Biosimilars Action Plan: Balancing Innovation and Competition**

**Biosimilar Pay-For-Delay Reporting Bill Introduced in House**


**Drug Supply Chain Security Act (DSCSA): 2018 Updates**

The _Drug Quality and Security Act (DQSA)_ was enacted by Congress on 27 November 2013. Title II of DQSA, the _Drug Supply Chain Security Act (DSCSA)_ , outlines steps to build an electronic, interoperable system to identify and trace certain prescription drugs as they are distributed in the US. This will enhance FDA’s ability to help protect consumers from exposure to drugs that may be counterfeit, stolen, contaminated or otherwise harmful. The system also will improve detection and removal of potentially dangerous drugs from the drug supply chain to protect US consumers.

Additionally, the DSCSA directs FDA to establish national licensure standards for wholesale distributors and third-party logistics providers, and requires these entities report licensure and other information to FDA annually.

In May 2018, FDA announced a new _Drug Supply Chain Security Act (DSCSA) Pilot Project Program_.

Additionally, _five new guidance documents_ were issued this year to support the DSCSA.

**FDA’s Predictive Toxicology Roadmap**

The Predictive Toxicology Roadmap is a six-part framework for integrating new predictive toxicology methods into safety and risk assessments of FDA products. FDA’s collaborative efforts to advance toxicology toward a more predictive science with NIH, EPA and other federal agencies through programs like Tox21 and ICCVAM.

During the past decade, FDA scientists have taken significant steps to upgrade their toxicology toolboxes. However, a comprehensive strategy is needed to evaluate new methodologies and technologies for their potential to expand FDA’s toxicology predictive capabilities and to potentially reduce the use of animal testing. Acceptance of any new toxicology methods will require sufficient convincing data as well as continuous dialogue.
and feedback among all relevant stakeholders from development to implementation, including qualification and acceptance by regulatory authorities. To ensure FDA continues to employ cutting-edge science to assess the safety and effectiveness of its regulated products and to leverage advances being made in toxicology, the FDA Commissioner tasked the Agency’s Toxicology Working Group with developing a roadmap for integrating predictive toxicology methods into safety and risk assessments.

- **FDA’S Predictive Toxicology Roadmap**

### Tools to Turbo Charge Drug Development

**Real World Evidence Action Plan**

**Framework for FDA’s Real-World Evidence Program Framework**

While this is from the *21st Century Cures Act* of 2016, the process of implementation is a continuum and there were strides to further define how to implement this clinical development option with issuing a framework document for evaluating the potential use of Real-World Evidence (RWE). The goal of the framework was to:

- help support the approval of a new indication for an already approved drug or
- help support or satisfy drug post-approval study requirements

This framework applies to drug and biological products approved under section 505(c) of the *FD&C* and biological products licensed under the *Public Health Service Act*. The framework does not cover medical devices.

The RWE Program outlined will evaluate the potential use of RWE to support changes to labeling about drug product effectiveness. This includes adding or modifying an indication, such as a change in dose, dose regimen or route of administration, adding a new population or adding comparative effectiveness or safety information. The RWE Program will establish demonstration projects, engage stakeholders, get input from FDA senior leadership when evaluating RWE and promote shared learning and consistency in applying the framework. FDA also will develop guidance documents to assist sponsors interested in using RWE to support drug development.

In the framework, FDA identifies a three-part approach for assessing whether the use of Real-World Data (RWD) to generate RWE is appropriate to answer a regulatory question:

- Are the RWD fit for use?
- Can the trial or study design used to generate RWE provide adequate scientific evidence to answer or help answer the regulatory question?
- Does the study conducted meet FDA regulatory requirements (e.g., for study monitoring and data collection)?

### FDA RWE Framework Issued in December 2018

- [FDA’s New Efforts to Advance Biotechnology Innovation](#)
- [Real-World Evidence](#)
- [Framework for a Real-World Evidence Program: Availability](#)
- [FDA Budget Matters: A Cross-Cutting Data Enterprise for Real World Evidence](#)
- [FDA’s Real World Evidence and Data Page](#)

### Master Protocols

Master protocols might be the way of the future for all fast track and breakthrough products; but for now, the guidance document was issued just for oncology products. A Master Protocol is used for oncology drugs and biologics regarding the design and conduct of clinical trials, other than First-In-Human (FIH) trials, intended to simultaneously evaluate more than one investigational drug and/or more than one cancer type within the same
overall trial structure (master protocols) in adult and pediatric cancers. In contrast to traditional trial designs, where a single drug is tested in a single disease population in one clinical trial, master protocols use a single infrastructure, trial design and protocol to simultaneously evaluate multiple drugs and/or disease populations in multiple sub studies, allowing for efficient and accelerated drug development. Master Protocols have been used by both Keytruda and Opdivo to rapidly test and expand labeled indications.

**Complex Innovative Designs (CID) Pilot**

FDA launched a pilot meeting program for Complex Innovative Designs (CID) to facilitate the advancement and use of novel clinical trial designs. The pilot meeting program offers sponsors who are selected an opportunity to engage with FDA experts from CDER and/or CBER to discuss CID approaches and analyses in medical product development. The pilot program period will run through fiscal year 2022 and is being conducted to fulfill FDA’s performance commitment under PDUFA VI, incorporated as part of the FDA Reauthorization Act of 2017. During the pilot, FDA has committed to accepting up to two meeting requests quarterly, about 120 days apart, to offer feedback on the proposed CID approach within a specific drug development program and to providing regulatory advice. FDA is exploring the use of CIDs to inform regulatory decision-making and to enhance the understanding and review capacity of CID.

- Complex Innovative Designs Pilot Meeting Program
- Promoting the Use of Complex Innovative Designs in Clinical Trials

**Pilot Meetings Program for Model-Informed Drug Development (MIDD) Approaches**

MIDD approaches use a variety of quantitative methods to help balance the risks and benefits of drug products in development and when successfully applied, can improve clinical trial efficiency, increase the probability of regulatory success and optimize drug dosing/therapeutic individualization in the absence of dedicated trials. The pilot program provides sponsors or applicants who are selected to participate the opportunity to meet with agency staff to discuss MIDD approaches in medical product development.

The program period will run from fiscal years 2018 to 2022. FDA subject matter experts from relevant fields such as clinical pharmacology will lead the meetings. Experts from CDER and/or CBER will participate as needed. The pilot program is being conducted to fulfill a performance goal under PDUFA VI, incorporated as part of the FDA Reauthorization Act of 2017. Under the pilot, FDA has committed to accepting two to four paired-meeting requests quarterly each fiscal year.

**Increased Transparency on Clinical Data: CSR Pilot Program**

For this program, FDA will include the study report body, the protocol and amendments and the statistical analysis plan for each of the participating product’s pivotal studies. Once the clinical trial transparency pilot program is complete, FDA will seek public feedback through a Federal Register notice and docket for public comments. Please note that some larger companies already post these in full or redacted on their company website or are included in New England Journal of Medicine (and other scientific journals) articles about pivotal trials in the supplemental section.

- FDA Commissioner Scott Gottlieb on new Steps FDA is Taking to Enhance Transparency of Clinical Trial Information to Support Innovation and Scientific Inquiry Related to new Drugs

**Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure**
FDA’s surrogate endpoint table provides valuable information for drug developers on endpoints that may be considered and discussed with FDA for individual development programs. This table also fulfills a 21st Century Cures Act requirement to publish a list of “surrogate endpoints which were the basis of approval or licensure (as applicable) of a drug or a biological product” under both accelerated and traditional approval pathways.

According to section 507(e)(9) of the FD&C Act “(t)he term ‘surrogate endpoint’ means a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is not itself a direct measurement of clinical benefit, and—

“(A) is known to predict clinical benefit and could be used to support traditional approval of a drug or biological product; or

“(B) is reasonably likely to predict clinical benefit and could be used to support the accelerated approval of a drug or biological product in accordance with section 506(c).”

This surrogate endpoint table includes surrogate endpoints that sponsors have used as primary efficacy clinical trial endpoints for approval of New Drug Applications (NDAs) or Biologics License Applications (BLAs). The table also includes surrogate endpoints that may be appropriate for use as a primary efficacy clinical trial endpoint for drug or biologic approval, although they have not yet been used to support an approved NDA or BLA. FDA believes this list should facilitate consideration of potential surrogate endpoints when developers are designing their drug development programs.

**Division Musical Chairs**

FDA has proposed an important series of new steps to modernize the organization and functions of CDER’s Office of New Drugs. These changes are intended to free up resources so that reviewers have more time to focus on drug development, particularly for unmet medical needs, and on the multiple collaborations needed to make sure candidate drugs are developed and assessed properly, with appropriate input from external scientists, expert physicians and patient communities. The proposals include regulatory and review process changes, as well as organizational restructuring. FDA also intend to strengthen the support structures, including personnel and Information Technology (IT), that underpin the regulatory process. So what this means to companies is that if you go to the GI Division to talk about Nonalcoholic steatohepatitis (NASH), you will get NASH or hepatic experts to aid in the development process and not an oncologist.

- [Advancing Toward the Goal of Global Approval for Generic Drugs: FDA Proposes Critical First Steps to Harmonize the Global Scientific and Technical Standards for Generic Drugs](https://www.fda.gov)
- [FDA’s Comprehensive Effort to Advance New Innovations: Initiatives to Modernize for Innovation](https://www.fda.gov)
- [Statement from FDA Commissioner Scott Gottlieb on Proposed Modernization of FDA’s Drug Review Office](https://www.fda.gov)

**Military Breakthrough Designation**

- [FDA and DoD Launch Program to Expedite Availability of Medical Products for the Emergency Care of American Military Personnel](https://www.fda.gov)

FDA’s Department of Defense’s (DoD) Office of Health Affairs announced the launch of a joint program to prioritize the efficient development of safe and effective medical products intended to save the lives of American military personnel. The framework for the program was put in place through H.R.4374, which authorized DoD to request, and FDA to provide, assistance to expedite development and FDA’s review of products to diagnose, treat or prevent serious or life-threatening diseases or conditions facing American military personnel. Utilizing this law’s expanded authorities, FDA will work closely with Health Affairs to better understand the military’s medical needs for deployed personnel, give the
highest level of attention to and expedite its review of priority DoD medical products in a manner similar to products under the breakthrough designation program, provide ongoing technical advice to Health Affairs to aid in the rapid development and manufacturing of medical products for use by the military and take a closer look at products currently under development to determine opportunities to expedite their availability.

**Material Threat Medical Countermeasure Priority Review Vouchers**

Per the provision of the 21st Century Cures Act that added a new section to the FD&C on priority review vouchers, the first voucher for material threat medical countermeasure applications was issued for TPOXX. The program was put in place through the 21st Century Cures Act (Cures Act) that adds a new section to the FD&C Act on priority review vouchers for material threat medical countermeasure applications. This program was designed to encourage development of medical countermeasures by offering additional incentives for obtaining approval of new drug or biological medical products for the prevention and treatment of harm from a biological, chemical, radiological, or nuclear agent identified as a material threat.

- Material Threat Medical Countermeasure Priority Review Vouchers - Draft Guidance for Industry
- Fee for Using a Material Threat Medical Countermeasure Priority Review Voucher in Fiscal Year 2019
- FDA Approves the First Drug With an Indication for Treatment of Smallpox

**Tropical Diseases Added to Voucher Program**

FDA added four tropical diseases to priority review voucher program to encourage drug development in areas of unmet need, the addition included: Lassa fever, chikungunya virus disease, rabies and cryptococcal meningitis. Applicants who submit applications for drug or biological products to prevent or treat these diseases may qualify for a tropical disease Priority Review Voucher (PRV). A tropical disease PRV can be used to obtain priority review of a subsequent drug application that does not itself qualify for priority review.

- Tropical Disease Priority Review Vouchers

**Patient Engagement**

There has been strides forward by FDA to include patients in the drug development process; so now besides a dedicated Advisory Committee meeting, patients can now ask for meetings and suggest draft guidances.

**Request a Meeting on Drugs: Stakeholder Engagement**

FDA now allows patients to submit a request for a meeting on drug-related topics which will be handled by the Professional Affairs and Stakeholder Engagement (PASE) Staff; this is not an option for industry stakeholders. These meetings are not intended to establish binding agreements pertaining to drug development programs or to discuss proprietary information pertaining to specific drug development programs under FDA review. To support this process FDA launched a new External Stakeholder Meeting Request (ESMR) system. This system will help external, non-industry stakeholders more easily request meetings with CDER on drug development and drug safety matters. The ESMR system will ensure these requests are managed appropriately and consistently.

- Request a Meeting on Drugs
Submitting Drafts of Proposed Guidance Documents Electronically

Under FDA’s good guidance practices regulations at 21 CFR 10.115(f)(3), external parties can submit drafts of proposed guidance documents for FDA to consider. All proposed draft guidance documents should be marked “Guidance Document Submission” and be submitted either in paper to the address found on the Dockets Management page or electronically.

- Instructions for Submitting Drafts of Proposed Guidance Documents Electronically

Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank

History of clinicaltrials.gov Legislation Includes:

- 1997: Congress Passes Law (FDAMA) Requiring Trial Registration
- 2000: NIH Releases ClinicalTrials.gov Web Site
- 2004: ClinicalTrials.gov Wins the Innovations in American Government Award
- 2005: International Committee of Medical Journal Editors Requires Trial Registration
- 2005: State of Maine Passes Clinical Studies Registration Law (Repealed in 2011)
- 2006: World Health Organization Establishes Trial Registration Policy
- 2007: Congress Passes Law (FDAAA) Expanding ClinicalTrials.gov Submission Requirements
- 2008: ClinicalTrials.gov Releases Results Database
- 2008: Declaration of Helsinki Revision Promotes Trial Registration and Results Dissemination
- 2009: Public Meeting Held at the National Institutes of Health
- 2013: European Medicines Agency Expands Clinical Trial Database to Include Summary Results
- 2014: Notice of Proposed Rulemaking (NPRM) for FDAAA 801 Issued for Public Comment
- 2014: NIH Draft Policy on Registration and Results Submission of NIH-Funded Clinical Trials Issued for Public Comment
- 2015: National Cancer Institute Issues Clinical Trial Access Policy
- 2016: Final Rule for FDAAA 801 Issued
- 2016: Final NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information Issued
- 2017: Revised Common Rule (45 CFR 46) Issued

There has been an issue with Sponsors not posting the initial trial or the subsequent results on clinicaltrials.gov even though the International Committee of Medical Journal Editors won’t allow the publication of the trial results in a major journal if the trial is not posted with 21 days after the first patient was dosed.

The ClinicalTrials.gov registration requirements were expanded with FDA Amendments Act of 2007 (FDAAA); section 801 specifically requires more types of trials to be registered, results information to be submitted and the submission of FDA Form 3674 to show compliance. FDAAA 801 also established penalties for failing to register or submit the results of trials. To date, penalties, which could have been levied at a rate of $10,000/day for failure to comply, have not been enforced. The guidance document addresses the following questions:

- How do the Centers intend to identify whether responsible parties have failed to submit required clinical trial registration and/or results information to the
ClinicalTrials.gov data bank or submitted false or misleading information to the data bank, or whether submitters have failed to submit to FDA the certification required by section 402(j)(5)(B) of the Public Health Service Act (PHS Act) or knowingly submitted a false certification to FDA?

- Under what circumstances may a Center decide to seek civil money penalties against a responsible party or submitter?
- What procedures apply when a Center seeks civil money penalties?
- What civil money penalty amounts may be assessed for:
  - failing to submit required clinical trial registration and/or results information to the ClinicalTrials.gov data bank
  - submitting false or misleading information to the data bank
  - failing to submit the required certification to FDA
  - knowingly submitting a false certification to FDA

Bottom line: FDA is getting ready to implement its ability to levy fines and has given industry 12 years to comply with the requirements.

FDA Collaborations

**Biotech Working Group**

In early May, FDA formed a new Biotech Working Group. This Working Group is comprised of representatives from multiple FDA centers and offices. The Biotech Working group will develop an Action Plan that lays out the steps they intend to take to ensure FDA has a flexible regulatory framework for evaluating the safety of products that also supports plant and animal biotechnology innovation.

**Clinical Trials Transformation Initiative**

FDA announced a collaboration with the Clinical Trials Transformation Initiative (CTTI) and are cohosting a Patient Engagement Collaborative (PEC) (Federal Register 60749 / Vol. 82, No. 245/Friday, 22 December 2017). The PEC will be an ongoing, collaborative forum coordinated through the Patient Affairs Staff, Office of Medical Products and Tobacco (OMPT), Office of the Commissioner and will be hosted by CTTI. Through the PEC, the patient community and regulators will be able to discuss an array of topics regarding increasing meaningful patient engagement in medical product development and regulatory discussions at FDA. The activities of the PEC may include, but are not limited to:

- providing diverse perspectives on topics such as systematic patient engagement, transparency, and communication
- providing considerations for implementing new strategies to enhance patient engagement at FDA
- proposing new models of collaboration in which patients and patient advocates are partners in certain aspects of the medical product development and FDA: review process

**Manufacturing**

**Quality Metrics for Drug Manufacturing**

FDA announced two new programs to gather feedback on the use of quality metrics to modernize pharmaceutical quality systems and advance innovation. These efforts, the Quality Metrics Feedback Program and the Quality Metrics Site Visit Program, build on stakeholder comments requesting continued dialogue on quality metrics and provide ways for industry to engage the agency and inform FDA’s use of quality metrics. Feedback from early adopters, manufacturers who implemented quality metrics programs to address
significant manufacturing problems, and independent academic research indicates that manufacturers’ overall quality programs benefit from an establishment’s quality metrics program. The new programs provide an opportunity for FDA to continue learning about the advantages and challenges companies have experienced in implementing quality metrics programs.

FDA is encouraging new drug application holders to request Type C Formal Meetings and Abbreviated New Drug Application (ANDA) holders to submit pre-ANDA meeting requests to FDA to initiate discussions on quality metrics for specific products.
The Quality Metrics Site Visit Program

This voluntary site visit program is designed to offer experiential and firsthand learning opportunities to FDA staff involved in development of FDA’s Quality Metrics Program.

Staff will gain exposure to robust quality metrics programs through on-site visits, tours of operations, and discussions with establishments to assist staff in further developing FDA’s Quality Metrics Program. FDA staff also will observe how quality metrics data are gathered, collected, and reported to management.

Continuous Manufacturing Progress

- FDA Supports Critical Research to Spur Innovation for Continuous Manufacturing Technology to Support and Advance Drug and Biologics Development

For more than 50 years, pharmaceuticals have been produced using a method known as “batch manufacturing,” a multi-step, lengthy process that involves the use of ungainly, large-scale equipment. However, recent advances in manufacturing technology have prompted the pharmaceutical industry to consider moving away from batch manufacturing to a faster, more efficient process known as continuous manufacturing. FDA is taking proactive steps to facilitate the drug industry’s implementation of emerging technologies, including continuous manufacturing to improve product quality and address many of the underlying causes of drug shortages and recalls.

The continuous manufacturing process has been discussed for years, but now FDA has awarded three grants, using its authority under the 21st Century Cures Act to institutions of higher education and non-profit organizations to study and recommend improvements for the continuous manufacturing of drugs and biological products, as well as similar innovative monitoring and control techniques.

Emerging Technology Program (ETP)

The ETP was created to promote the adoption of innovative approaches to pharmaceutical product design and manufacturing. Through the program, industry representatives can meet with Emerging Technology Team (ETT) members to discuss, identify and resolve potential technical and regulatory issues regarding the development and implementation of a novel technology prior to filing a regulatory submission.

New Inspection Protocol Project (NIPP)

This New Inspection Protocol Project (NIPP) uses standardized electronic inspection protocols to collect data in a structured manner for more consistent oversight of facilities and faster and more efficient analysis of FDA findings. The protocols also include additional questions related to quality culture observed in facilities. The new tool is being applied to FDA inspectional work related to sterile injectable drugs, which have been the subject of sterility problems and shortages in the past. The primary focus of this new tool is to ensure a more streamlined and consistent coverage and reporting of FDA inspectional activities.

Approvals

Division Specific Approvals

- Hematology/Oncology (Cancer) Approvals and Safety Notifications
- 2019 FDA Approved Drugs
Novel Drug Approvals

- Center for Drug Evaluation and Research Advancing Health Through Innovation 2017 New Drug Therapy Approvals
- Novel Drug Approvals for 2017
- Novel Drug Approvals for 2018

Why is this report so cool? It gives a breakdown of all drugs approved and what accelerated approval options they carried with them in a graphic, no longer do you need to hunt and peck through recent approvals to pull this information together—FDA gives it to you in their annual report.

Figure 1. Novel Drug Report Breakdown

New Class of Drugs Fulfills Promise of RNA-Based Medicine

The approval of a new drug to treat polyneuropathy caused by a rare and frequently fatal disease called hereditary transthyretin-mediated amyloidosis (hATTR) marks the arrival of a game-changing new class of therapeutics. The new drug, called patisiran (Onpattro), is a small interfering RNA (siRNA) that is part of a class of therapeutics that can target hereditary diseases by affecting gene function. With this ability to target specific RNA "messages," there is the potential to design therapeutics for a wide range of diseases. Patisiran is the first drug approved to treat hATTR. Why are these drugs unique? This class of drugs is unique because the drugs work at the RNA level to specifically silence the production of a disease-causing protein. siRNAs can be designed to interfere with the production of abnormal proteins throughout the body, and are often chemically modified to ensure they are not destroyed by enzymes in the body.
Just Interesting

FDA created and made Bayer use a “Patient Decision Checklist” to make sure patients were informed about the use of the device “Essure” (postmarketing).

About the Author

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All the website links in this article were verified as of 26 April 2019. Subsequently, the US Food and Drug Administration (FDA) relaunched its website, which changed or deactivated many of the links connecting to agency information. Due to this article’s publication schedule, it was not possible to update all the URLs referenced, so some FDA links may not be accessible. RAPS apologizes for any inconvenience this may cause.

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The Value of Engagement With Trade Associations in Policymaking, Regulation and Standardization

By Léa Coulet

This article presents an argument for the value that trade associations bring to healthcare in terms of promoting best practices, policies, regulations and standards. The author defines trade associations and lays out their functions and the value of those functions for regulators and policy makers and also presents defining characteristics of good regulations and good policies. The focus is on foods for special medical purposes and the author shares examples from the work of the Medical Nutrition International Industry (MNI) in these areas.

Introduction

Trade associations play an important role in promoting best practice, informing public policies and regulations and developing standards. In the complex and fast-moving healthcare area, which is driven by innovation, data technologies, patient demand and budget constraints, policymakers and regulators face tremendous challenges to formulate effective, evidence-based and future-proof policies that serve the public interest. Productive engagement with stakeholders and trade associations is increasingly necessary. This article aims to present the value that trade associations bring to the debate, based on the experience of the Medical Nutrition International Industry (MNI).

Several questions can be posed regarding the role of trade associations in developing good policies, regulations and standards. Why is their involvement necessary, and how do they bring value?
What is a trade association?

There are many standard definitions for ‘trade association.’ Wikipedia proposes a definition that emphasizes the activities of a trade association:

“A trade association, also known as an industry trade group, business association, sector association or industry body, is an organization founded and funded by businesses that operate in a specific industry. An industry trade association participates in public relations activities such as advertising, education, lobbying and publishing, but its focus is collaboration between companies. Associations may offer other services, such as producing conferences, networking or charitable events or offering classes or educational materials. Many associations are non-profit organizations governed by bylaws and directed by officers who are also members.”

By contrast, the Cambridge English dictionary definition emphasizes the objective of the trade association:

“An organization that supports companies and employers of a particular type of industry and protects their rights.”

These definitions focus on the services trade associations provide to their industry. However, in the regulatory context, it is also important to look at the services that trade associations offer to the community and their stakeholders, including policymakers and regulators.

The Value of Trade Associations for Regulators and Policymakers

Although every trade association is different, they have similar characteristics enabling them to serve the community and bring value to their stakeholders.

Trade associations represent the “voice” of their sector.

Trade associations act as a main point of contact, thereby facilitating dialogue with industry. Regulators find it easier talking to a trade association, rather than to every company active in the sector. It is the role of the trade association to consolidate the industry viewpoint and make the link between industry and regulator and, by doing so, allow a structured, representative and transparent dialogue.

Trade associations provide access to a vast pool of expertise and information.

Trade associations have an extensive knowledge of their sector and a strong culture of knowledge sharing, which can be quickly passed on to regulators and policymakers.

Trade associations are well equipped to assess the impact of policy/regulatory measures on their sector and are, therefore, essential interlocutors for ensuring government action achieves its desired purpose. They can also provide access to a vast pool of experts and expertise. In the area of medical nutrition, for example, companies are well-connected and work with doctors, scientists, nutritionists, researchers and patient advocacy groups.

Trade associations guarantee a dialogue with respectable and trustworthy industry partners to regulators.

Trade associations have membership criteria to ensure their members are reputable and trustworthy businesses. Engaging with a trade association is a guarantee for regulators to deal with respected and committed partners.
MNI, for example, has detailed membership criteria to ensure its members are representative of the sector, respectable businesses, and committed to providing better care through better nutrition to all patients, across all care settings and age groups.

**Trade associations facilitate multi-stakeholder cooperation.**

Trade associations are part of a broader community and an “eco-system” that consolidates industry, regulators and citizens who are willing to work cooperatively with them to find solutions. They are generally able to support multi-stakeholders’ platforms, organize forums and conferences and develop joint positions on questions submitted by authorities. Rather than cultivating diverging and competing interests, trade associations are great allies with whom to work towards convergence and reach consensus.

**Shaping an Adequate Environment: Key Principles**

All sectors, including the medical nutritional sector, need a stable environment, one shaped through policies, regulations and standards.

**What makes a good regulation?**

According to Wikipedia, a regulation is “an abstract concept of management of complex systems according to a set of rules and trends.”

The European Union defines a regulation as “a binding legislative act. It must be applied in its entirety across the EU.”

The Cambridge English dictionary defines regulation as “an official rule or the act of controlling something.”

The term regulation is, rightly or wrongly, associated with a negative connotation. One often hears about too much regulation, rigid regulation, red-tape, administrative burden, brake on innovation, etc.

The fact is that regulation is necessary in open market economies, including:

- to protect the rights and the safety of citizens/patients
- to create trust in the market, provide certainty and a level-playing field for business
- for the state’s control over the market players
- to translate legislation and policy into practical implementation

Getting regulation right is important; therefore, it is critical to understand what makes a good regulation.

The immediate response is very simple: a good regulation serves the public interest. Beyond this principle statement, a few key subordinate principles are essential to make a good regulation. The principles outlined below are particularly important in the area of healthcare.

**Evidence-Based**

Regulations should be evidence-based. They should be based on science, rooted in proven facts and data, looking at health technology assessments and patient outcomes.

**Necessity**

The regulation should respond to a need, and the measures should be targeted to responding to that specific need, while avoiding side effects. The triangle (the regulators,
the regulated community and the beneficiaries of the regulation) need to cooperate to agree on the need and on how to respond to it via a mix of binding rules and general principles.

**Transparency**

The regulation should bring confidence to the regulated system. This can be achieved by consulting all relevant stakeholders in a transparent and documented manner, following a public consultation framework.

**Proportionality**

A regulation should provide measures and rules proportionate with the risks of the issue at stake. The advantages of the regulation should outweigh the potential disadvantages of the regulation and avoid unnecessarily stringent measures. Compliance costs should be examined and minimized as much as possible.

**Effectiveness**

A regulation needs to work in practice. Consultation with the parties implementing the regulation is absolutely crucial to ensure legal instruments adopted can be easily understood, implemented and followed, without creating additional cost or burden. The regulated community should be given time and support to comply.

**Flexibility (or Future-Proof)**

Regulations should be flexible enough to allow for future developments. This is particularly important in the area of healthcare where regulation should allow and support innovation.

**What makes a good policy?**

The quick answer is a policy is good if it reaches its objectives.

However, policy is one of these “buzzwords” very commonly used without a clear understanding of its meaning. For instance, policy and regulation are often mixed up. This article will focus on public policies initiated and driven by government.

Wikipedia defines public policy as “*the principled guide to action taken by the administrative executive branches of the state with regard to a class of issues, in a manner consistent with law and institutional customs.*”

The Cambridge dictionary uses the following definition:

“A *government policy that affects everyone in a country or state, or these policies in general.*”

A major difference between a public policy and a regulation lies in the fact that policies are general, country-wide frameworks based on principles which affect the entire country through a set of principles, measures, actions and budget. A regulation aims to implement a policy by providing a frame to a given domain.

A good policy – as for a good regulation, includes:

- serves public interest
- has well-defined objectives
- benefits from a budget in line with its ambition
- has an implementation plan
• has evaluated its impact

What makes a good standard?

A quick answer to the question is: a standard is good if it is adopted. In healthcare, one would argue that a standard is good if it secures patient safety.

Other elements define a successful standard:

• clarity
• practicality
• ease of implementation
• consensus-based
• improve performance
• reduce risk

CEN, the European Committee for Standardisation, defines a standard:

"A technical document designed to be used as a rule, guideline or definition. It is a consensus-built, repeatable way of doing something."9

Others define it as "an agreed way of doing something. It could be about making a product, managing a process, delivering a service or supplying materials—standards can cover a huge range of activities undertaken by organizations and used by their customers."10

Typically, industry produces standards in order to create agreement on technical specifications for health, safety and the environment and to achieve interoperability.

Trade associations are key role players in standards development. They help to develop standards based on consensus among their members, ensure the standards reflect the reality of the market, and encourage and facilitate adoption by industry.

Why Trade Associations can Help Getting Policies and Regulations Right

When developing a regulation in the health sector, regulators must “tick” all the above boxes. To be successful, they have a vested interest in consulting all relevant stakeholders including industry.

Trade associations, such as the MNI, can help them define the need, run the sanity checks, run impact assessments, anticipate future developments, assess costs and risks, and help in crafting robust, fit-for-purpose, future-proof policies and regulations that will provide long-term benefits to patients and the healthcare system.

The Role of Trade Associations in Informing Policies, Regulations and Standardization: MNI Example

In the previous section, insights have been shared on what makes a good public policy/regulation or standard and how trade associations are equipped to inform these processes meaningfully.

This section will focus on the healthcare area and share examples of how the MNI, the trade association federating the medical nutrition industry at a global level, can bring value to the policy, regulatory and standardization process.
MNI Introduction

The Medical Nutrition International Industry (MNI) association\(^{11}\) was created in 2005 to represent the voice of the medical nutrition industry at an international level.

MNI represents companies providing solutions for nutritional therapy, including oral nutritional supplements, enteral tube feeding (enteral nutrition via the gastrointestinal tract) and parenteral nutrition (intravenous feeding) as well as other actors operating in the medical nutrition market.

MNI works to achieve better care through better nutrition, across all ages and healthcare settings, and supports multi-stakeholder cooperation to improve the quality of nutritional interventions for patients.

Defining the EU Regulatory Framework for Medical Nutrition

The development of the regulatory framework covering medical nutrition, also called Food for Special Medical Purposes (FSMPs) in the EU, is an excellent example of consultation of the industry and its trade association (MNI).

Defining FSMPs: A Headache for Regulators

FSMPs are foods for special medical purposes. They are foods for helping patients meet their disease-related nutritional requirements when these cannot be met via the normal diet. FSMPs can take different forms, such as liquids, thickening powders, sip-feeds or naso-gastric solutions and must be used under medical supervision.

The first commercial products reached the market in the 1950s, yet their regulatory category status typically evolved from being put under drug law, then Food for Special Dietary Uses (FSDUs). Ultimately, by the 1980s and 1990s, they were properly defined as Foods for Special Medical Purposes (Codex Stan 180-1991)\(^{12}\) supporting among other objectives their development as products for patients. Still, these ‘food products for patients’ often did not lose their “drug-like” characteristics or image.\(^{13}\)

When the first products were commercialized, there was no understanding of these products and how they could support malnourished patients. It was, therefore, necessary to define the regulatory category with a clear definition.

However, defining such specialized products is not a simple task for those not involved in their development. MNI, as the association of manufacturers providing FSMPs contributed to the discussion and helped define the key characteristics of FSMPs. The definition for FSMPs is today enshrined in the so-called FSG regulation (EU)609/2013:\(^{14}\)

“…food specially processed or formulated and intended for the dietary management of patients, including infants, to be used under medical supervision; it is intended for the exclusive or partial feeding of patients with a limited, impaired or disturbed capacity to take, digest, absorb, metabolise or excrete ordinary food or certain nutrients contained therein, or metabolites, or with other medically-determined nutrient requirements, whose dietary management cannot be achieved by modification of the normal diet alone.”

In addition, FSMPs are also classified in three categories in the European Commission Delegated Regulation (EU) 2016/128:\(^{15}\)

- Nutritionally complete food with a standard nutrient formulation which, used in accordance with the manufacturer’s instructions, may constitute the sole source of nourishment for the persons for whom it is intended.
• Nutritionally complete food with a nutrient-adapted formulation specific for a disease, disorder or medical condition which, used in accordance with the manufacturer's instructions, may constitute the sole source of nourishment for the persons for whom it is intended.
• Nutritionally incomplete food with a standard formulation or a nutrient-adapted formulation specific for a disease, disorder or medical condition which is not suitable to be used as the sole source of nourishment.

The article "Revising the EU FSMP Regulatory Framework: Laying the Foundation for Future Nutritional Patient Care" provides an excellent summary of the provisions covering FSMPs in the EU.

While the regulatory framework for FSMPs is now adopted and implemented in the EU, many countries and regions are looking to the EU for inspiration to build their own regulation on FSMPs.

MNI is regularly invited to share its expertise on medical foods in countries and regions where regulation is being considered, initiated or reviewed.

Industry also can add value by information sharing and promoting good practice and regulatory convergence across the globe.

**Malnutrition and the Value of Medical Nutrition: Creating Awareness**

Today, there is still very limited knowledge of medical nutrition among regulators and the general public. There is also little awareness of the burden of malnutrition, also called disease-related malnutrition. It is MNI’s responsibility to inform and educate regulators and the general public to fill the knowledge gap.

The prevalence of malnutrition is very high across the globe. In Europe, malnutrition—or the risk of malnutrition—affects 25% of hospitalized patients and one third of people living in the community.

In Europe alone, an estimated 33 million people are malnourished or at risk of malnutrition. The additional cost of managing the malnutrition of these patients is estimated to cost healthcare systems 170 billion Euros ($191.2 billion) per year.

Malnutrition is a serious public health issue. It is crucial that health authorities (government, policymakers, regulatory authorities) take measures to manage malnutrition effectively. These measures should prevent malnutrition and provide access to nutritional therapies, including FSMPs.

MNI has developed case studies to help authorities and the general public understand medical nutrition, the indications for using such products, the different forms that they can take to fit healthcare professional and patient needs, why they should be used under medical supervision, and the science behind these products.

More recently, MNI has published a comprehensive dossier entitled Better Care through Better Nutrition: Value and Effects of Medical Nutrition. The Dossier is a unique and comprehensive summary of the evidence base on the prevalence of malnutrition and the value and effects of medical nutrition. Data are presented by age group, healthcare setting, and, where possible, by patient group. With forewords from key stakeholders, it is a credible and valuable resource to address malnutrition and the health and economic benefits of nutritional care. The dossier is also available in a summarized booklet for a lay audience - Figure 1.
To date, no one else has provided such an extensive and documented summary on the burden of malnutrition. MNI believes much more needs to be done to support malnourished patients and is committed to supporting health authorities in articulating effective nutritional care policies.

Supporting the Nutritional Care Community and Fostering Multi-Stakeholder Dialogue to Inform Nutritional Care Policies

As mentioned in the first part of this article, trade associations are willing to work with other stakeholders. MNI takes multi-stakeholder cooperation very seriously and supports activities building a vibrant and empowered nutritional care community.

- In 2008, MNI launched the MNI Grant to raise awareness on malnutrition and to reward initiatives tackling malnutrition at national level. Over the years, the MNI Grant has supported and stimulated ambitious initiatives which have contributed to improving nutritional care policies at national levels.

- MNI is an active member of the Optimal Nutritional Care for All (ONCA) campaign, a European public-private partnership that promotes screening for malnutrition and
good nutritional care. The campaign started in eight countries in 2014 and is now rolling out in eighteen countries. In each country, stakeholders with an interest and expertise in nutritional care (including the academic world, authorities, patient groups and manufacturers) work together to drive and enhance nutritional care policies and provide access to quality nutritional care for patients. This campaign was described in this review in the article Innovating Patient Driven Nutritional Care Across Europe: The Optimal Nutritional Care for All (ONCA) Multi-Stakeholder Initiative.24

- MNI also cooperates with the clinical and academic worlds. For instance, MNI has a long-standing cooperation with the European Society for Clinical Nutrition and Metabolism (ESPEN). The cooperation focuses on initiatives to improve clinical practice, such as the dissemination of ESPEN guidelines or initiatives aiming at strengthening the education of medical students on nutrition. Every year for the last ten years, MNI, ONCA and ESPEN have joined forces to bridge the gap between the academic/clinical worlds, and health decision-makers by inviting senior officials to the ESPEN Congress in a spirit of knowledge sharing.

Promoting Adoption of International Standards That Reflect Common Practice and Ensure Patient Safety: Case Study

Background

Enteral feeding therapies rely on devices to administer nutrition solutions to patients. These include giving sets, feeding tubes, syringes, pumps, connectors, etc. known as enteral feeding systems – Figure 2.

Figure 2. Overview of an Enteral Feeding System

The design and the testing of enteral feeding systems will be described by an international standard: ISO 20695.25 The draft ISO20695 standard reflects current practice in the market and it is being increasingly adopted around the globe with a proven track record of guaranteeing the safety of patients on enteral feeding by minimizing risks linked to misconnections between various devices for different medical applications.
**Threat**

The standard was under review as part of the regular ISO standards creation process, and there were calls to change the design of certain devices. MNI analyzed the situation and anticipated how a modification to the design of devices would create confusion among users:

- Users would need to be trained to the new design.
- Users would need to phase two or more different designs, which might not be interconnectable with each other. This might result in the impossibility to start a feeding therapy; or in the need to replace parts of the enteral feeding system or to use adapters to facilitate a connection.
- Using adapters should be avoided as this might cause confusion or even distress and again opens the possibility for accidental misconnections again between systems for different medical applications leading to potential safety risks for the patients.

**Action**

MNI and the Global Enteral Device Supplier Association (GEDSA) joined forces to support the adoption of ISO 20695 and developed a joint position paper.

The adoption of the standard will be an important and much-needed milestone to provide a unique set of rules at the global level for enteral feeding devices. It will provide clarity and certainty for uses and will strengthen safety of patients on enteral nutrition.

**Outcomes**

As this article goes to press, it is not possible to share a clear outcome as the review process for ISO 20695 is ongoing. However, it is important to note that the active involvement of trade associations such as MNI and GEDSA have been instrumental to federate industry around an international standard, providing for a single design for enteral feeding devices worldwide.

**Conclusion**

Trade associations are key actors on consultations to have a balanced and future proof policies, regulations and standards. Cooperation between industry associations and government is very important for the policy making process. In the healthcare sector, there are many ways that trade associations can make an impactful and beneficial contribution to their community including patients and healthcare professionals.

In turn, trade associations can gain government’s and stakeholders’ trust and respect by following a few basic guidelines:

- act as a consolidate, co-ordinated voice of the sector
- provide evidence-based information
- share commercially neutral positions that reflect the consensus views of the sector
- work towards convergence
- be trustworthy, patient and transparent
- support the community

Trade associations should continuously ask themselves: How can we participate to make the process better and ensure my input helps to reach the objectives set by the community?
References

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Disclaimer

This article reflects the personal opinion and experience of the author. It should not be construed as an official position by any organization with which the author is affiliated.

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The Botanical Safety Consortium (BSC): The Development of a 21\textsuperscript{st} Century Framework for Assessing the Safety of Botanical Dietary Supplements

By Daniel S. Marsman, DVM, PhD, Joseph T. Dever, PhD, Stefan Gafner, PhD, Cynthia Rider, PhD, Sibyl Swift, PhD and James C. Griffiths, PhD

This article discusses steps to improve the safety of botanicals in dietary supplements. The authors discuss several US legislative initiatives and efforts by several nongovernmental organizations, such as the Council for Responsible Nutrition and the American Botanical Council, to track patterns of botanical use, and the Congress of the European Societies of Toxicology’s efforts to approach safety issues, including its establishment of the Botanical Safety Consortium and its working groups.

Introduction

Natural health products, often considered a safe and natural alternative to conventional medicine, have exhibited a resurgence in Western society. In the US, since the introduction of the \textit{Dietary Supplement Health and Education Act of 1994 (DSHEA)},\textsuperscript{1} the dietary supplement market has flourished. Concomitantly, the dietary supplement market has further morphed into various product streams, a most rapidly expanding one being products containing one or more botanical/herbal ingredients. In parallel with this market expansion, substantial advancements in analytical methodologies have led to a better understanding of the complexity and diversity of botanical chemistry and botanical preparations. This increased knowledge has led to a growing awareness of the potential safety concerns associated with botanicals, especially their impurities, and contaminants.

Tracking use of Botanical Dietary Supplement Products

Because of the success of the dietary supplement industry and the pursuit of an ever-broadening array of products, it is not surprising the industry needed to turn greater focus toward assuring the safety of these products. For the botanical dietary supplement...
products, a plethora of botanical compounds are currently “in vogue” and an increasing number and diversity of botanical preparations have been incorporated into innovative multi-botanical products continually entering the market. To track their success, the Council for Responsible Nutrition (CRN) conducts an annual survey of consumer activity. Their data clearly indicate how the use of botanicals continues to grow year-by-year. For example, in 2018, their survey indicated that 75% of Americans take supplements and of those, 41% have used herbals/botanicals during the previous year. This represents a 13% increase for herbals/botanicals use over the last five years. Similarly, the American Botanical Council tracks consumer use patterns and has published data indicating interest in and use of herbal and other natural products has continued to rise at a substantial rate, with US sales in 2017 exceeding $8 billion dollars. This increased use, and the entrance into the market of newer and more ethnically focused botanicals from emerging regions and countries, such as India, China and Latin America, should be a focus of attention for those in the scientific and regulatory community charged with product stewardship and consumer safety.

Safety and Testing Revisions

To establish the reasonable expectation of safety, companies have had to rely on outdated botanical safety frameworks. These frameworks employ the same methodologies used for discrete and pure drug compounds and other chemical moieties, and they primarily depend upon a significant number of animal toxicity tests. From a global regulatory perspective, there are essentially no specific safety tests required, allowing each manufacturer to use their own best judgment on which testing approach is needed for the New Dietary Ingredient (NDI) variant in question. Traditional premarket safety testing, with reliance on in vivo animal test methods, has become increasingly difficult for addressing botanical safety, both due to the complexity and variability of the ingredients as well as the combination of a multitude of discrete botanical ingredients into ever-increasing combinations and co-use scenarios. These concerns for testing botanicals in traditional animal studies is in addition to the many criticisms of these studies. These concerns include high-dose, non-physiologic dosing regimens, additional uncertainty factors for extrapolation to humans, significant financial and labor costs, time consumption (often in years) and the questionable ethics associated with the use of animal models. In addition to direct challenges to use of traditional pre-clinical studies, another confounding factor is the large number of potential variants of each potential botanical material due to seasonal variations, harvesting practices, processing and manufacturing differences, among others.

Innovation within the dietary supplement sector often focuses on subtle—and not so subtle—“tweaks” to currently popular botanical ingredients so that different levels of marker compounds, active moieties and changes in Absorption, Distribution, Metabolism and Elimination (ADME), may be realized. When higher concentrations of marker compounds/putative actives are achieved, safety studies may focus solely on these substances. However, it is often unclear, or unlikely, that the active constituent for nutritional efficacy is the most toxic constituent. Therefore, the traditional toxicological challenges with complex mixtures apply to botanicals. These uncertainties may include questions around synergistic or antagonistic action between botanical constituents, or actions with other botanical constituents in the mixture.

New Approaches for Safety Assessment

Given the continued interest in botanicals in a variety of consumer care products, coupled with a strong desire to minimize or eliminate animal testing and the recent developments regarding in vitro and in silico safety testing methods, the time is ripe to consider new approaches for the safety assessment of botanicals intended for use in food/dietary supplements. These approaches could include capturing adverse event data from clinical studies and postmarket surveillance, but this should be carried out by relying on new methodologies to assess specific safety endpoints. Human use data can be used as a filter to assist in the decision-making for further testing. In addition, modern analytical
characterization of a botanical ingredient can be potentially coupled with a suite of endpoint evaluations to create a tiered approach to assessing toxicity based on existing data as well as new data generated specifically for safety assurance.\(^4\)

In order to expand on the topic of botanical safety assessments, representatives from industry, academia and the regulatory community participated in a scientific session, “Botanical Safety Evaluation in the era of Alternatives” at the 53\(^{rd}\) Congress of the European Societies of Toxicology (Eurotox 2017). This session was followed by a roundtable building on the elements shared by presenters during the scientific session. The roundtable panel and participants discussed—and provided perspective on—a “decision tree” approach (i.e., is there general alignment to the key elements that are needed to build a robust botanical safety evaluation) and inherent vulnerabilities of such an approach.\(^5\) Key elements discussed and carefully considered included the accurate identification and advanced multi-detector analytical characterization of botanical raw materials and the \textit{in silico} approaches potentially used to address safety data gaps and inform the need for further studies. Other topics discussed included a discussion of scientific proof necessary to conduct similarity comparisons to commonly consumed foods or botanicals (i.e., with a well-established safety profile and a systematic evaluation of relevant toxicity data of botanical constituents utilizing structure-activity relationships. Included as well was the application of established Threshold of Toxicologic Concern (TTC) principles to botanical constituents, in the absence of data and where safety endpoint gaps are identified which cannot be resolved without \textit{in vitro} or \textit{in vivo} studies, and the botanical compositional data that essential to inform study design. The 2017 Eurotox session was used as a “springboard” to add these perspectives to the public discourse and the scientific literature, as evidenced by the 2018 Society of Toxicology poster presentation\(^6\) and the 2019 Toxicology Letters manuscript\(^7\).

\textbf{The Botanical Safety Consortium}

The scientific discourse begun at Eurotox 2017 continued at the International Conference on the Science of Botanicals (ICSB 2018). At this meeting, interested parties from industry, academia, science-based trade associations and the regulatory community came together to propose the inauguration of a pragmatic strategy to explore scientific solutions through a multifunctional collaborative, later referred to as the Botanical Safety Consortium (BSC).\(^8,9\)

The objective of the BSC is to provide a sound scientific basis for integrating existing botanical safety/toxicity data with the latest toxicological tools, including, but not limited to, \textit{in silico} and \textit{in vitro} methodologies to more thoroughly evaluate botanical safety.

Some of the key areas the BSC will explore include the chemical characterization of complex botanical mixtures and fit-for-purpose assays and models for evaluating genotoxicity, hepatotoxicity, developmental and reproductive toxicity, cardiotoxicity and systemic toxicity. In addition, attention also will focus on \textit{in vitro} ADME and herb-drug and herb-herb interactions.

A botanical library containing ingredients with known \textit{in vivo} toxicity gained from animal studies or reports of adverse events in humans, will be created and evaluated in the recommended battery of assays. Results from the consortium will be shared through a publically available database and along with findings and recommendations published in peer-reviewed literature.

BSC Working Groups (WGs) will address analytical characterization and key safety endpoints. The two co-chairs of each BSC WG will be technical representatives from industry and from government or academia to maintain balance. A BSC Steering Team will provide oversight and guidance to the BSC WGs. The Steering Team includes representation from a variety of dietary supplement stakeholder segments including the Federal Government as FDA’s Office of Dietary Supplement Program (ODSP), National
Institute of Environmental Health Sciences (NIEHS), dietary supplement manufacturers, trade associations and other non-governmental organizations.

Conclusion

At this writing, the BSC is still in the early stages of coalescing and establishing its processes and procedures. In addition to this administrative work, the steering committee is working with the BSC WG co-chairs to identify additional scientists with specific expertise in the above-mentioned toxicologic endpoints. WG membership will be based on a capacity to carry out the work, interest, expertise and willingness to share internal data and experience in the design of future work. Active participation is an expectation in this ‘roll-up-your-sleeves’ exercise, including specific expertise in tests, assays and models to address the endpoints outlined above. The BSC WGs will be expected to provide input on the selection of candidate ingredients to be placed in the BSC’s assays and modeling exercises. There are plans to create a mechanism for stakeholder and scientific peer feedback, as well as an annual scientific meeting where information will be openly shared. Results from work undertaken by the BSC (via the targeted working group activities and data generation) will be published in the peer-reviewed literature.

The goal of the BSC will be to enhance the botanical safety toolkit and bring clarity to botanical safety assessments for manufacturers and regulators. With broad representation by interested and affected parties, the BSC Steering Committee and Working Groups will be designed to ensure collaborative and cooperative scientific recommendations.

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