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LEAD STORY

NMPA Regulatory Approval Process for Medical Devices

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FOREWORD

Hello All,

Here we go, with the 2nd Issue of Freyr CONNECT, Volume 10.

Freyr is growing from strength to strength. From successfully implementing Freyr SUBMIT Track for a leading US-based pharma company to spearheading the life sciences digital transformation with new product launches (Freyr ARTWORK 360), and from adding new locations to our global presence to strengthening our teams with a diversified global workforce, the year 2022 has been incredible for us, so far..

With that said, as always, we would like our patrons to acquire the best possible industry insights. Hence with this Issue, we briefly bring to you global Regulatory nuances and compliance best practices pertaining to the NMPA Regulatory approval process for medical devices, a comparative analysis of dossier submissions in the EU and US, the top fifteen (15) FAQs on US Agents, Freyr's Thought Leadership on pharmaceutical promotional material in the global arena, etc. The Issue confirms Freyr's proven expertise in Regulatory services and solutions with comprehensive case studies.

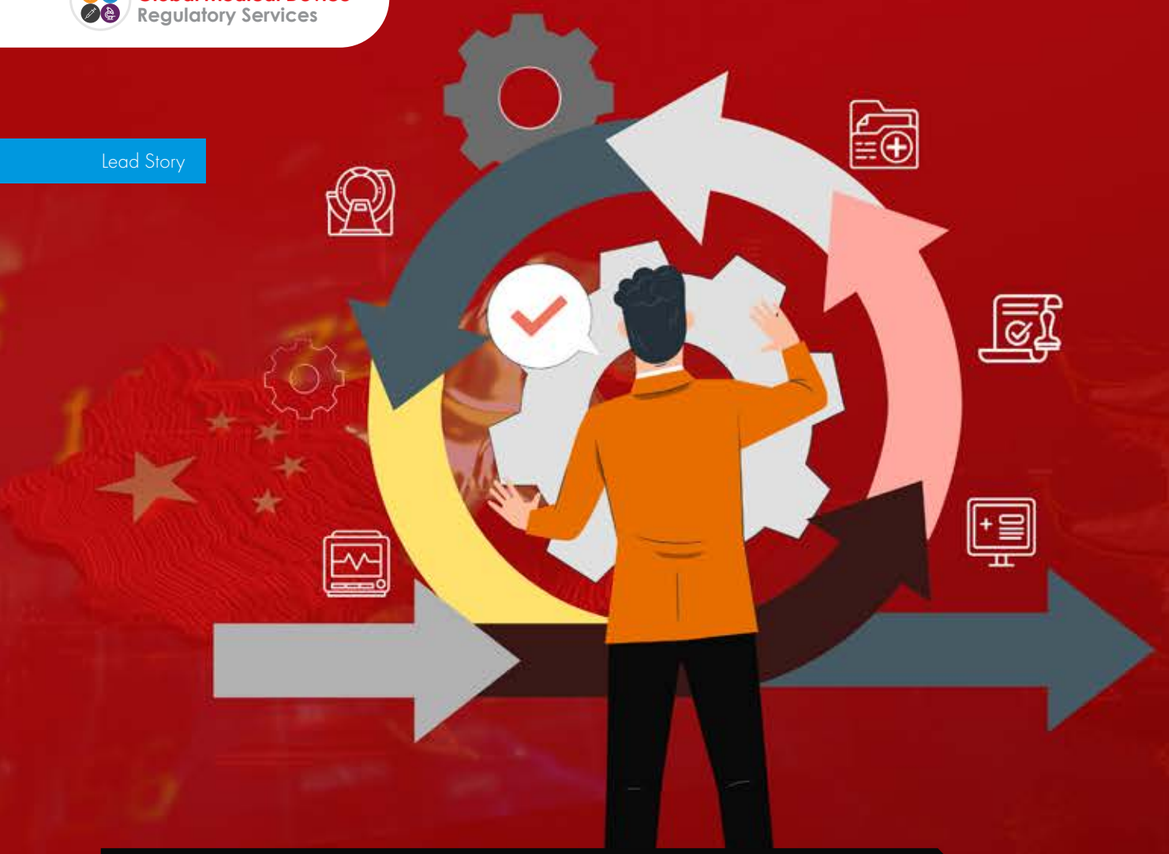
In conclusion, this Issue helps you choose the best Regulatory strategy with actionable insights. If you want to receive the updated newsletters as and when they get published, kindly subscribe now!

Happy Reading!

Suren Dheenadayalan
CEO

Center of Excellence
Global Medical Device
Regulatory Services

Lead Story

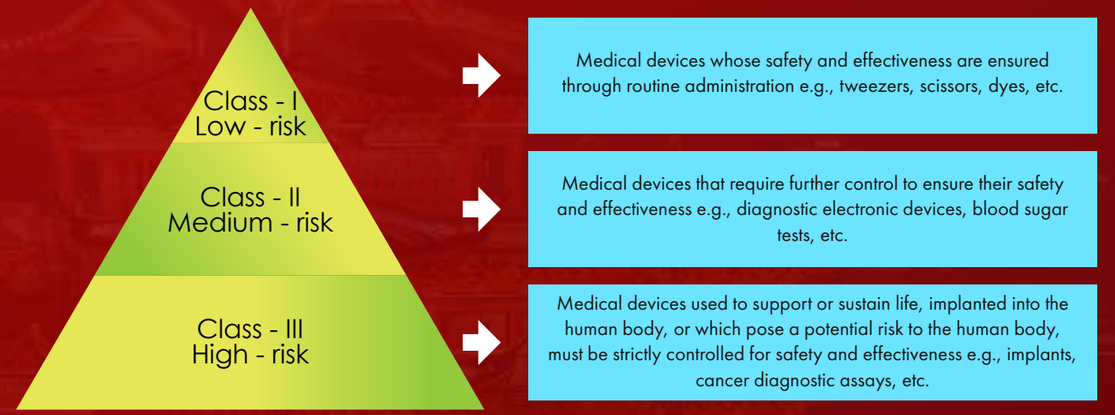


NMPA REGULATORY APPROVAL PROCESS FOR MEDICAL DEVICES

China is one of the most populous countries and has the world's largest medical devices market. As per a 2018 statistical report, by 2030, China is expected to hold more than 25% share of the global medical device industry at over US$200 billion, which is second to the USA with an expectation of a US$300 billion growth rate. China's medical devices market growth rate is driven by a growing customer base in terms of population and health centers, expanding health insurance schemes, the rising prevalence of diseases and disorders, and the rapidly growing geriatric population. Thus, China offers a wealth of opportunities for medical device companies. However, like all other nations, China has stringent Regulatory requirements and a competitive environment. The medical device manufacturers willing to access the China market must have a clear-cut understanding of the local regulations and technical standards. This article will provide insights on China's Regulatory approval process for medical devices, and the varied premarket or product registration procedures for imported and local domestic products.

Classification of Medical Devices

Depending upon a medical device's potential risk to patients, the NMPA categorizes medical devices into three (03) classes. As per the degree of risk (from low to high), medical devices are divided into Class I (low-risk), Class II (medium-risk), and Class III (high-risk) in due order. A medical device's degree of risk is determined comprehensively according to the intended purpose, the pattern of use, structural characteristics, and whether the device is body contacting or not.



Medical Device Classification in China

Registration of Medical Devices

- Earlier, China's medical device registration term was only four (04) years. Currently, it is five (05) years.
- To renew a device's registration, a renewal application must be submitted six (06) months before the expiration date.
- Overseas medical device manufacturers must provide device samples to the NMPA for testing and meeting China's testing standards. A test protocol describing the device's test methodology, parameters, and standards used to prove the device's safety and performance must be documented. This document is called Product Technical Requirement (PTR).
- Class II and Class III devices require registration. Class I devices do not require registration but are required to file the device according to the file list. To register Class II and III devices, manufacturers must send the appropriate documents like CE mark, 510(k) letter, ISO 13485 certification, and approved premarket approval application to the NMPA, along with supportive clinical data. All the device information, including labeling and packaging, must be translated into Chinese.
- Foreign manufacturers must hire a China-based registration agent/legal agent to register their devices in China. The agent's responsibilities include:
  - providing technical services and maintenance support for the devices
  - assisting in device recalls when needed
  - overseeing the registration and clinical trial process and ensuring all the documents meet China's registration requirements
  - supporting the manufacturer in case of any adverse events
- Manufacturers must provide the name, address, and contact number of their designated agents in the registration application.

Documentation and Approval

The NMPA requires comprehensive documentation, and all the documents must be submitted in Chinese and original language if applicable. The documents required for new registration and registration extension are mentioned below.

Documents for New Registration:

- Regulatory information includes application form, product list, associated documents, conformity statement, etc.

- Products description, applicable scope and contraindications, and product registration history
- Certification documents like EC, EC DoC, and ISO 13485
- Authorization for a legal representative
- A document referring to the commitment of an agent and business license of an agent
- List of basic requirements for safety and effectiveness of a medical device
- Clinical evaluation document
- Risk analysis of products
- Product technical requirement
- Research information
- NMPA test report
- User manual and label sample
- Conformity declaration and other documents according to the latest regulation or tendency, e.g., cyber security documents
- Quality management system documents, etc.

Documents for Registration Extension

- Application form
- Certification documents like authorization for a legal representative
- A document referring to the commitment of an agent and business license of an agent
- Declaration on no change of product, copy of original registration license (and change approval license), and attachment
- Conformity declaration
- Copies of the original medical device registration certificate and its attachments, and copies of previous medical device change registration (filing) documents and their attachments
- Other documents according to the latest regulation

The new electronic registration system makes it possible to initially register for electronic Regulated Product Submissions (eRPS) and have assigned access. While uploading approval documents, manufacturers can use the eRPS to track the documents' approval status, re-submit the documents or submit answers to the questions raised by the Health Authority. Electronic submissions can be used for:

- The initial registration/approval of medical devices (including IVD devices)
- Changes to an existing registration of domestic Class III medical devices and foreign Class II and III medical devices
- Applications for clinical investigations for foreign Class III medical devices
- Changes to a medical device's Instructions for Use (IFU)
- Extension of medical device licenses
- Applications for approval of innovative medical devices
- Changing, correcting, and deregistering licenses for medical devices

Clinical Evaluation

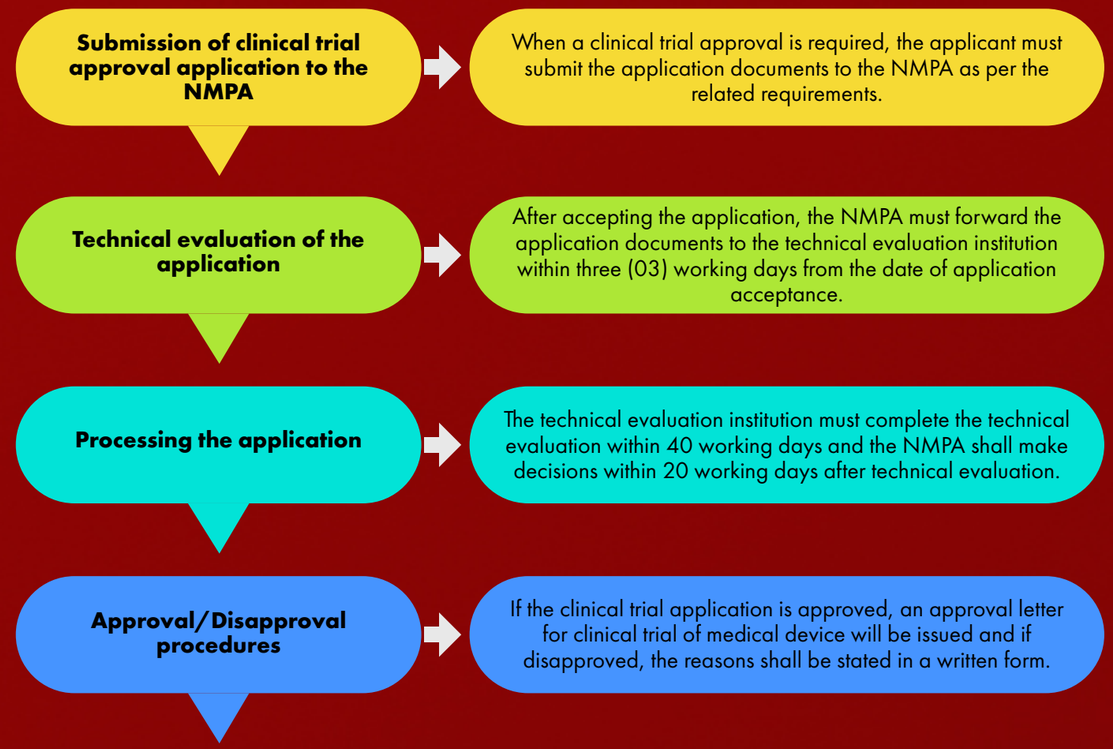
China has stringent clinical trial requirements for medical devices. Clinical evaluation is a process in which the applicant validates whether the devices under registration can meet their intended use and indications based on the information from clinical literature, clinical trials, and clinical experience data. The latest amendment of the regulation has allowed foreign manufacturers to get the clinical trials done in their home country only on the condition to follow all the norms specified in the regulation. Clinical trials are not required for Class I medical devices but are mandatory for Class II and III devices. However, clinical trials may be exempted in one of the following circumstances:

- When the safety and effectiveness of the device can be proved through non-clinical evaluation
- When a medical device's safety and effectiveness can be demonstrated through the analysis and assessment based on the data obtained from clinical trials or application of a medical device of the same variety
- When the functional mechanism of the device is definite, the production process is well-established, the design is finalized, the marketed medical device of the same variety has been in clinical use for years with no record of serious adverse events, and its conventional purposes of use are not changed

NMPA updated the medical device exemption catalog containing the list of Class II and III medical devices that are exempted from clinical trials. According to the requirements of the Good Clinical Practice (GCP) for medical devices, the clinical trials of medical devices must be conducted in a qualified clinical trial institution. The production of samples used for clinical trials must meet the relevant requirements of a Quality Management System (QMS) for medical devices and be filed with the NMPA of the province, autonomous region, or municipality directly under the central government where the clinical trial sponsor is located. The local NMPA department that accepts the clinical trial filing must inform the local NMPA department and the competent health department at the same level of the location of the clinical trial institution of

the filing. If the clinical trial of Class III medical devices has a high risk to the human body, it shall be approved by the NMPA under the State Council.

Clinical Evaluation Approval Process for High-risk Devices

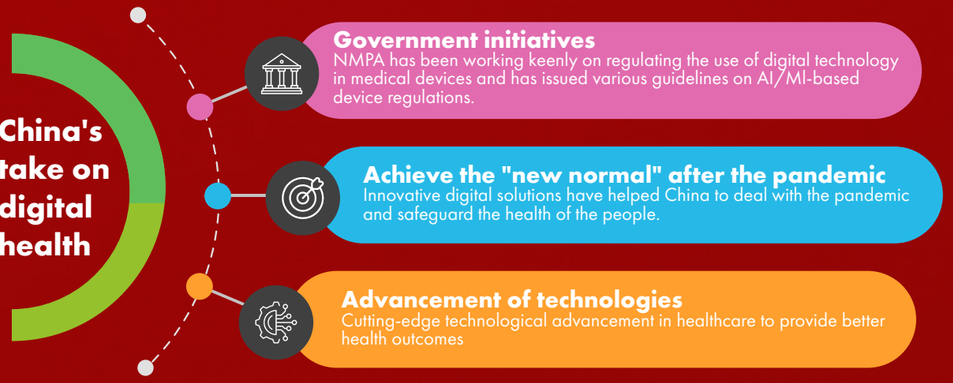


Pre-and Post-market Requirements

The NMPA is taking effective measures to monitor the device's performance after being placed on the market, like an adverse event monitoring system, annual periodic risk evaluation report, recalls, and frequent random quality inspections. Instead of focusing on only pre-and post-market requirements, the NMPA emphasizes the administration through the device's lifecycle. Therefore, the legal manufacturer is responsible for the safety and effectiveness of the device during its entire lifecycle. The manufacturers are required to establish a QMS and ensure its effective operation and implementation of post-market surveillance and risk control plan, active adverse event monitoring and re-evaluation, and the establishment and implementation of the product tracing and recalling system.

NMPA's Take on Digital Health

The COVID-19 pandemic has fast-forwarded the spread and penetration of digital health technologies with China at the forefront of this revolution. The adaption of digital health technologies in the medical device sector in China is rapidly evolving with considerable changes happening in the Regulatory landscape. Government initiatives, advancement of technologies, and an urge to achieve the "new normal" after the pandemic are driving these swift changes.



Government Initiatives for Domestic Manufacturers

China's current contribution to the global device market share is about 20% and is attributed to the aging population, affordability, increased incidence of chronic diseases, and lifestyle disorders that offer great opportunities to medical device manufacturers. To strengthen the domestic production of devices, the Chinese government has taken initiatives like setting up medical device industrial zones, rent reductions, settlement bonuses, or product registration bonuses to help domestic manufacturers upscale their businesses. The Chinese government encourages hospitals to procure domestically produced devices. At present, the majority of the domestic manufacturers are small-mid scale businesses manufacturing low-value consumables and dominate the mid-low-end device market. China is still largely dependent on imports for high-end devices. The government's "Made in China 2025" policy will strengthen the domestic manufacturing of high-end devices in China in the coming years.

China's Device Market Post-COVID-19

In view of COVID-19, the Chinese government has taken some steep steps to bring the China medical device industry back to its pace. The government has now enabled three (03) policies for the MedTech market that will ensure its smooth functioning:

Volume-based purchasing
Bulk procurement of high-value medical consumables to reduce the inflated prices of these products. This initiative has led to decrease in the overall cost by 80%, thus facilitating quality devices to the patients

Focus on digital health
Many alternative pathways of healthcare like online consultation, telemedicine, AI/ML based imaging equipment, and telehealth apps have changed the traditional process consultation and caregiving

Enhanced localization
Implementation of various policies and initiatives has resulted in an increased supply of domestic devices into China market

China's MedTech Industry for Foreign Manufacturers

China is still greatly dependent on foreign manufacturers for high-value devices. Foreign manufacturers can enter China market in three (03) possible ways:

Imports	• Fastest method to enter the market • Challenges in maintaining brand image, no local presence
Direct investment	• More capital investment required • Longer time to enter the market
Joint venture	• Manufacturers need to understand the business culture of China • Foreign manufacturers must find suitable partners with whom they can build the business in China

Future Trends

With the increasing aging population, lifestyle changes, and increased disposable income, China's medical device market holds an important place in the global device industry. The stringent regulations ensure that safe and effective devices are available for use. The right Regulatory strategy helps device manufacturers to overcome the challenges and seize the market potential. The adoption of digital health is already at the forefront in China, and it will disrupt and dominate the global MedTech industry. In the coming years, foreign manufacturers will have vast opportunities to enter the Chinese MedTech market owing to the Regulatory and governmental reforms. With the right entry approach, they can capture a stake in this ever-growing market.

Conclusion

China's medical device market is growing rapidly with accelerating technological transformation in medical devices, overall rising demand for healthcare reforms, increasing aging population, rising prevalence of chronic diseases, and heightened public health awareness. Simultaneously, the NMPA has laid down stringent regulations to ensure safe and effective medical devices are accessible. Therefore, medical device manufacturers willing to enter or expand their presence in China should consider and adopt the industry-specific regulations for a compliant market entry.

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Featured Article

A FRESH LOOK AT DIGITAL TRANSFORMATION IN LIFE SCIENCES R&D PROCESSES

by Simon Howe

I have seen many suggestions that Digital Transformation is about changing marketing practices in the new digital age. It is way more than that. Big Data, targeting, analytics, new channels, personalization, deep learning, push and pull...all these terms get floated around without ever really clarifying what it is and more important, really understanding the benefits. In this article, I hope to show how Digital Transformation is relevant to Life Sciences R&D and can deliver huge benefits. Because my customers are Life Sciences companies - Pharma, Medical Devices, Chemicals, Cosmetics, Food Manufacturers and more - this will be the backdrop and context of my guide.

Rethinking how we do business

A simple definition is that Digital Transformation is the use of digital technologies – IT, Cloud, Data Science, and Artificial Intelligence – to rethink and change the existing business practice. By doing so, we can dramatically modify current processes, streamline and speed up, or create new ones entirely. We are completely reimagining business.

The good news is that although Digital Transformation is best implemented from the top down, it can also be piloted, deployed, and proven to be effective at lower levels and then rolled out across the organization.

At Freyr, we take two basic approaches: Incremental Innovation and Disruptive Innovation.

Incremental Innovation is focussing on a single or small number of business processes and applying some simple improvements with the deployment of quick and smart automations. Think of an Excel macro that cuts through some routine data sorting and reporting jobs, or a Robotic Process Automation (RPA) algorithm that is designed to turn several steps in database analytics into a one-click process. For our customers, our primary objective is to deliver process improvement through well-defined small digital components such as bots, PDF scripts, Excel word macros, through to AI/ML components.

Perhaps best of all, you should not wait a long time and endure months or years of IT development programs to automate these processes and yield exponential business benefits. It should be simple and organic, simply improving how we use everyday tools such as Word, Excel and PowerPoint.

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Bringing it all together

The Disruptive Innovation approach brings all these components together into a larger whole, delivering automation for end-to-end workflows and sets of related use-cases. A recent example is a global pharma company for whom we developed an automation solution. This transformed completely their medical review process. Previously, they were spending approximately $300,000 per month for manually searching, reviewing, and pulling together reports from a range of sources - medical literature, journals, specialist websites, blogs, and forums. The journals alone numbered 5,000 and there were thirty (30) languages to cover.

Deploying a combination of Natural Language Processing (NLP), Artificial Intelligence (AI), and web crawling technologies means, the Freyr solution has significantly improved what previously took multiple days to now be achieved in a matter of hours. We have also greatly reduced the burden on expensive and expert resources with the pharma company now spending just $40,000 per month.

Although this use case was primarily designed and deployed for Pharmacovigilance function, it has a functional applicability way beyond this and can be used across R&D in areas like Medical Affairs, Labeling, and Regulatory Affairs.

Start with the right Digital Strategy

Now that I have established what Digital Transformation is, and that it can be both big and small and it delivers real benefits across a business, I thought it may be useful to look at a framework for approaching digital change.

Freyr Digital Strategy is focused on four (04) fundamental pillars:

1. Connectivity

The seamless and straightforward sharing of data, documents, outcomes, and actions across platforms and applications should be a key goal of Digital Transformation. Unfortunately, there is still a great number of siloed processes and business applications in all industries. For Life Sciences companies, this means choosing vendors who are enhancing their existing solutions - to deliver comprehensive interoperability - or at least are planning to develop their new products from the ground up. All the solutions you are considering offer the highest levels of interoperability and can be integrated and extended easily, and then applied across all product and service innovations. Your vendor partners need a good record of planning, designing, building, and sharing APIs and including more complex concepts such as RESTful APIs.

2. Innovation

Incremental innovation-based Digital Transformation should provide three (03) basic business benefits - speed, simplification, and exponential business benefits. Ideally, a multi-step business process should be reduced to a couple of clicks. Finding, analyzing, and reporting on sets of patient records or drug trial data should take hours, not days.

This is not as obvious or easy as it sounds. So while all bases should be covered - better interfaces and improved navigation, new functionality, richer and more granular reporting, deployment on mobile devices, fully scalable Cloud services - sadly many vendors simply offer a shiny look-and-feel interface upgrade, with nothing really changing underneath.

Avoid this by choosing a vendor with deep domain expertise and a keenness to talk about their product roadmaps and innovation plans.

3. Automation

Think little as well as big. At a simple level, automation involves developing macros and scripts in Office applications that improve accuracy and streamline everyday tasks - Regulatory intelligence searches, report building, validation - through to the more complex AI, Machine Learning, and Robot Process Automation (RPA) development of fully automated workflows.

For our pharma customers, this helps them achieve the highest levels of Regulatory compliance and critically, get new drugs to market faster. This applies equally to any business and sector.

At Freyr, we already apply this automation across our portfolio of products and services, including submissions, labeling, market access strategy, publishing, artwork services, case processing, and other Regulatory or safety commitments.

4. Decision-making based on data

One of the foundations of the Regulatory arena in which Freyr specializes is in identifying and understanding 'actionable insights.' Our customers need quick access to very specific data and answers in order to achieve product, market, and safety compliance.

And the cornerstone of this work is Intelligence - competition, market, R&D, risk profiling, global and local insights, and more. I would argue that a significant advance in Intelligence gathering and processing, in turn leading to improved decision making, should be at the heart of any Digital Transformation program.

Short-listed solutions need to be data focussed. This may sound obvious but many of today's systems are founded on legacy document management architectures, objects, graphics, and other content. Today, patient records, clinical trials, financial, and drug information all boil down to pure data - binary 1s and 0s, metadata, etc. – and as such, solutions need to be based on the latest Cloud architectures that manage and manipulate data quickly and efficiently. This principle needs to be at the core of Digital Transformation solutions. Which means you should be looking at Big Data, analytics, web-crawling and other technologies: they are more than the latest buzzwords.

Working smarter, not harder

There is sometimes the dystopian view that AI technologies will put whole workforces out of work. This is simply not the case for several reasons. In Life Sciences, you will always need the Regulatory, clinical, data, and drug safety specialists to interpret and make decisions on the information with which they are working.

In the recent past, I came across a study that concluded that Data Scientists only spent 20% of their time doing their core work. The rest is spent 'data wrangling' including data cleaning and preparation (40%), labeling and feature engineering (10%), and even the overlooked pain of waiting for long running jobs to complete (also 10%).

What Digital Transformation enables, is for the expert workforce to focus on its core work. Web crawling, NLP, controlled dictionaries - they all support the sourcing of relevant information, screening out irrelevant content, and triaging data. These more mundane, repetitive, and manual tasks can be sped up significantly and delivered with much greater levels of accuracy. This provides two (02) things: the ability to handle ever more volumes of data, reports, etc. and of course, for data scientists and other specialists to focus on the jobs we are paying them to do.

Measured success from the outset

I am going to finish my guide at the beginning. Having discussed how Digital Transformation can deliver huge change and benefits to all types of organisations, and implementation can be small and incremental as well as enterprise wide, we should cover the first thing you need to do. Planning. At Freyr, this discovery or analysis phase is critical and can be as fundamental as deciding whether a program is worth starting...or not. We focus on three (03) key assessment criteria: Operational, Technological, and overall Business Improvement.

We refer to this process as 'Automation Use Case Identified and Index Scoring' or AiX Score. We work with customers to understand and measure their existing practices and processes, and generate a 'score'. This score helps determine the potential value an automation project can deliver, or not. To facilitate this study, we take our customers through detailed questions such as:

- Estimated time taken per transaction for traditional/ manual approach of the each of the operational steps - Total Time Taken (mins/hours/days).
- Is the Automation team able to 'visualize' the process?
- Direct Profitability Analysis (especially for unit-based billing. Is profitability improving significantly by investing in automation?)

These are just a very few examples. As well as underpinning the consulting effort during initial 'discovery' phases, it has also led us to develop industry indexing scores that provide comparative benchmarks.

My message is clear: think ground-up, structure this thinking (go into a lot of detail), identify immediate, exponential business benefits and automate as a means to an end (don't get carried away with all the jazzy tools out there). Realise incremental innovation now, and work into long term disruptive innovation. This is the essence of true Digital Automation.

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GLOBAL REGULATORY PUBLISHING TRENDS

Regulatory information is required to prepare the dossier of a drug product, which differs according to the regulations of the local Regulatory Authority. To get a harmonized system, the International Council for Harmonization (ICH) has developed a standard content format, the Common Technical Document (CTD), organized with consistent sections and headings. Apart from the US, Europe, and Japan, various countries like Australia, Switzerland, Canada, etc. have adopted the ICH guidelines and followed the standard content format. Most countries and their Regulatory Authorities have migrated to the electronic Common Technical Document (eCTD) submission format. The United States Food and Drug Administration (USFDA), the Medicines and Healthcare products Regulatory Agency (MHRA), and the European Medicines Agency (EMA) (majority of the European Union

regions) have started accepting only eCTD submissions for all the application types. The eCTD is a standard format for submitting applications, amendments, supplements, and reports to various Regulatory agencies. The Non-eCTD electronic Submissions (NeeS) format still exists in a few countries across the European Union and Gulf Cooperation Council.

Global Regulatory Publishing Process

The Regulatory requirements of various countries across the globe differ based on the local agencies. One of the primary challenges for authorities is to ensure that the pharmaceutical products are developed as per the Regulatory requirement of that specific country. A Regulatory submission includes data and information that need to be compiled and managed for thoroughness, accuracy, and integrity against agency requirements. Regulatory agencies require these to establish whether a product can progress to clinical testing and to confirm if the product is safe and efficient for marketing. A typical submission process flow includes Submission Management, Document-level Publishing, Submission-level Publishing, Validation and Verification, and Dispatch to Agency.

Submission Management - Source documents are received from the sponsors, and a submission planner is prepared based on the application and submission type.

Document-level Publishing – It includes PDF conversion, document formatting, bookmarking, hyperlinking, Table of Content (ToC) creation, pagination of the documents, document properties setting as per the agency, and ICH criteria and specifications.

Submission-level Publishing – This phase includes creating a submission outline in the publishing software, uploading the documents as per the CTD structure and submission planner, and compiling and generating the output of the published submission.

Verification and Validation – The published output is set to run in a validation tool to verify and validate the submission that fulfills the agency's need. Any errors or warnings must be fixed before proposing the submission to the Regulatory Authority.

Dispatch to Agency – Error-free and validated submissions are dispatched to the agency through CD/DVD for paper submissions and the respective gateways for NeeS/eCTD submissions.

Submission Formats

Non-eCTD electronic Submissions (NeeS)

A NeeS is a submission of electronic information sent by an applicant to an agency, and it is merely a collection of electronic files either as a "bunch" of files or organized in folders. The NeeS format was developed in Europe and was intended as a steppingstone to the eCTD. It uses the same files and folders as the eCTD but simplifies the navigation by using a PDF ToC with hyperlinks. NeeS is an electronic submission without XML and SPL. It does not have metadata and no life cycle of the documents is maintained. Even the EU and other RoW regions have started their transition from NeeS to eCTD. NeeS is still acceptable in the EU by a few member states for national, decentralized, and mutual recognition procedures. The US does not accept the NeeS format, whereas other RoW regions that do not accept eCTD versions and are getting transitioned from the paper version or previously submitted applications, the NeeS format is still accepted.

Electronic Common Technical Document (eCTD)

The eCTD is a specification for an electronic submission created by the ICH. The intention is to give a common format for the electronic version of the CTD dossier. This means there is a common dossier structure provided by the CTD and the regional content requirements. One of the key features of the eCTD is "Lifecycle Management," which provides information about the relationship of one document to another (represented by the "operation" attribute such as new, replace, append, and delete) and about the relationship of one submission to another (represented by "related sequence" attribute). An eCTD is the submission of mostly PDF documents stored in the eCTD directory structure, crucially accessed through the Extensible Markup Language (XML) backbone (index.xml), and with the file's integrity guaranteed. The eCTD is defined as an interface for the industry to transfer Regulatory information while considering the facilitation of the creation, review, lifecycle management, and archival of the electronic submission. It follows a common structure for Modules 2 to 5, and country or region-specific requirements for Module 1. It is submitted as a "Baseline Submission" when getting transitioned from the paper or NeeS format. The benefits of the eCTD are easy to distribute and review highly organized electronic ToC, more efficient use of resources, less cost and stress to the organization, cross submission integration, etc.

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eCTD is different from other formats in the following aspects:

- Overall ToC provided in Extensible Markup Language (XML)
- Utility files to enable technical conformance and viewing
- Submission folders, XML, and utility files are created automatically if an eCTD builder is used
- High level of granularity in documents
- More precise structure
- Easier lifecycle management of the submission

The eCTD is widely accepted by the US, EU, UK, a few GCC countries, Canada, and other RoW regions such as Australia, New Zealand, Russia, South Africa, and the Asia Pacific regions are getting transitioned from the paper and NeeS format.

Paper

The structure of a paper submission must be in accordance with the sequence of documents as referenced in either the XML backbone of the eCTD or the overall ToC of the NeeS. The location of each document in the paper submission dossier must be marked by a tab identifier. The name for the tab identifier should be the name of the document. The paper format is only accepted in countries where the NeeS and eCTD versions are not available.

Conclusion

Although there is a continuous process of harmonization across the globe, there are challenges to be overcome by the pharmaceutical industry due to the heterogeneity in the Regulatory Authorities of various countries. Initially, the submissions were processed in a paper format which transitioned to NeeS, and now, most of the countries are accepting eCTD submissions for the benefits therein. Irrespective of the format, the most common of all three (03) is a standard content format, the CTD, which is organized with consistent sections and headings that were developed by the ICH.

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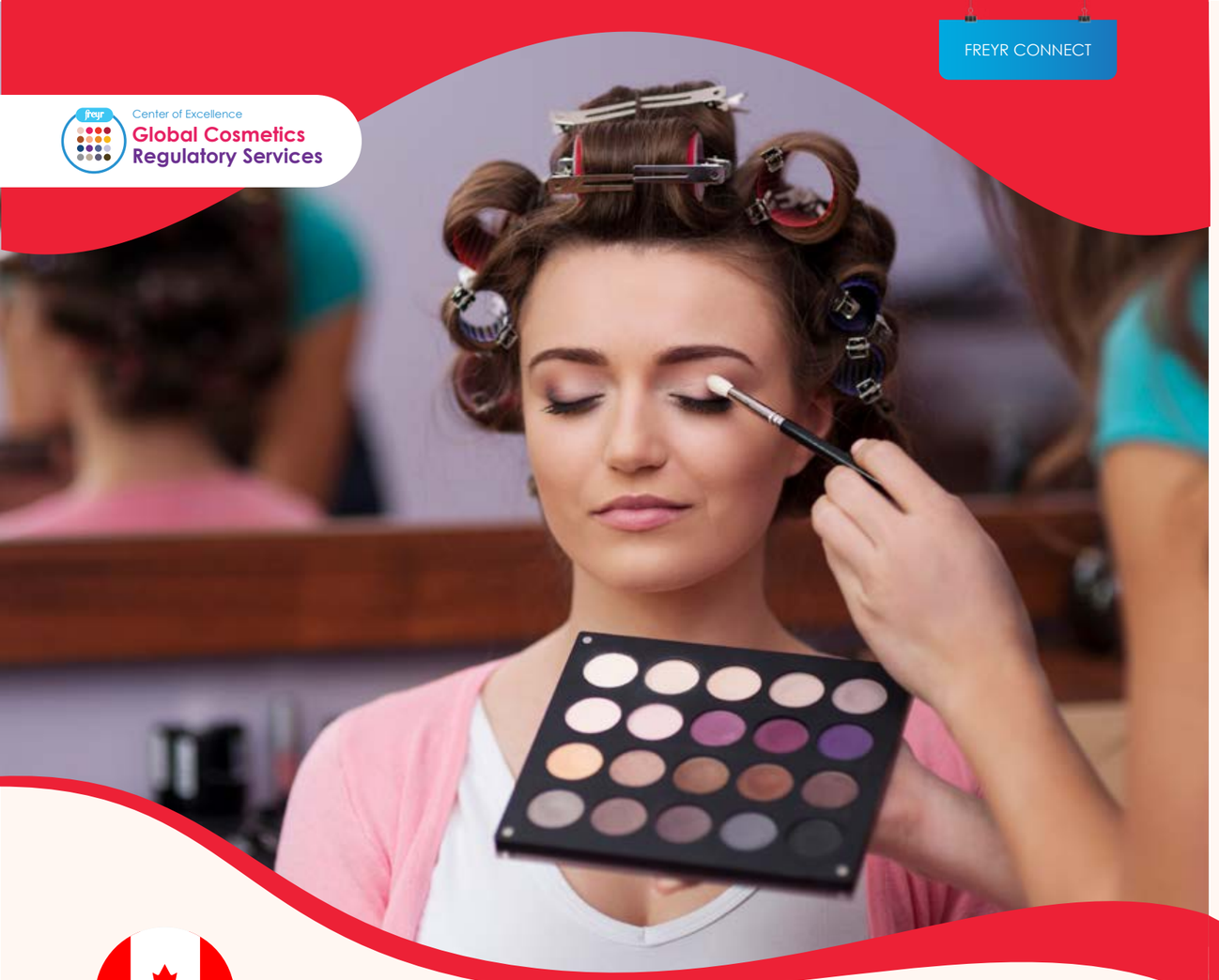
Applied Clinical Trials



PREREQUISITES FOR COSMETIC INGREDIENT LISTING IN HEALTH CANADA

Health Canada regulates cosmetics sold in Canada. Manufacturers selling cosmetic products in Canada must ensure that their product labels comply with the labeling requirements. Cosmetic labeling includes various information, but one of the most important parts of the labeling is ingredient listing, which informs the customers about product composition.

Writing a compliant ingredient list is not an easy task, so it is essential to understand the requirements on how to write it. Here are the prerequisites cosmetic manufacturers must adhere to market their products in Canada:

- **Descending Order of Predominance** - All ingredients must be listed on the label in the descending order of concentration by weight. It means the ingredients provided at the beginning of the list are present in a greater quantity than those at the end.
- **Ingredients with Concentration of 1% or Less** - Ingredients with a concentration of 1% or less may be listed in random order after the ingredients with a concentration of more than 1%.
- **Coloring Agents** - Regardless of the concentration, all coloring agents must be listed in random order after the ingredients that are present with a concentration of more than 1%. It is also acceptable to list coloring agents in the descending order of predominance.
- **Fragrance** - The word "parfum" must be used for fragrances to indicate that the ingredients have been added to the cosmetic to produce or mask a particular odor. It can be inserted at the end of the list or at the appropriate point in descending order of predominance. Manufacturers who do not wish to use the term "parfum" to indicate the presence of fragrance ingredients must list each fragrance ingredient individually.
- **Flavor** - The word "aroma" can be used for flavors to indicate that ingredients have been added to the cosmetic to produce or mask a particular flavor. It can be inserted at the end of the list of ingredients or at the appropriate point in descending order of predominance. Manufacturers who do not wish to use the term "aroma" to indicate the presence of flavor ingredients must list each flavor ingredient individually.
- **Make-up, Nail Polish, and Nail Enamel** - The coloring agents for make-up products (such as lipstick, blush, eyeshadow), nail polish, and nail enamel that are sold in a range of color shades, may be listed preceded by the phrase "may contain/peut contenir" or the symbol "±" or "+/-."
- **Cosmetics in Small Packages or Containers** - If the cosmetics are packed in small containers or packages, it would be difficult to see the list of the ingredients on the label. Therefore, the list of ingredients may appear on a tape, tag, or card affixed to the container.
- **Cosmetics in Ornamental Containers** - For cosmetics in an ornamental container with no outside package (e.g., a perfume bottle without packaging/box), the list of ingredients may appear on a tape, tag, or card affixed to the container.
- **Cosmetics in Odd-shaped Containers** - For cosmetics that have no outside package and whose shape, size, or texture makes it impractical for a tape, tag, or card to be affixed to the container (e.g., bath beads), the list of ingredients may appear in a leaflet that must accompany the cosmetic during the sale.

In a nutshell, manufacturers, to successfully sell their cosmetic products in Canada, must comply with the ingredient labeling requirements prescribed by Health Canada. Find out whether your cosmetic ingredients are accepted in Canada with Freyr iREADY, a ready-to-use cosmetics ingredient database. Request for a demo.

SCIENTIFIC WRITING: A LIFELINE COMMUNICATION BETWEEN THE CREATOR AND THE AUDIENCE

Abstract

Today, there is a need to disseminate scientific communications more efficiently than ever. The past decade has witnessed a tremendous transformation in how we collect, analyze, and transfer knowledge. Scientific Writing (SW) is the only technique through which creators, like researchers, scientists, investigators, etc., communicate their scholarly work to various audience groups such as the general public, healthcare professionals, Regulatory Authorities, scientists, etc. In such scenarios, customization of scientific content per the target audience is essential to meet the objective of scientific writing.

Aspects and Prospects

The term 'Scientific Writing' (SW) can be used in two (02) ways:

- specifically, to refer only to publications in peer-reviewed journals that report on original research, or
- generally, to include any form of written communication used by the scientists to disseminate information about their research findings to other science and non-science groups

In recent years, even for scientists, the publication of their research work has become crucial for various reasons, including career advancement. When conducting a research study, there are many obstacles to overcome such as selecting an appropriate study design, ensuring high-quality data collection, data storage and entry, and conducting appropriate statistical analyses.

However, after overcoming these obstacles, writing a research work for publication is another formidable task. It may be regarded as the culmination of the entire research conduction process. The essence of unpublished work is that it is incomplete or undone. Consequently, publishing research findings in a reputable and easily accessible journal is crucial. Writing a manuscript is comparable to giving shape to one's ideas.

By adhering to a few fundamental manuscript writing rules, one can acquire the skill of SW, which is vastly distinct from conducting a research study. Taking a systematic approach to writing for publication can make the task more manageable and efficient, even for a beginner. Planning, writing, submitting, revising, resubmitting, and proofreading are all the key components of the writing process for publication.

The perspectives behind the SW may vary from noble to base. First and foremost is altruism, which indicates the passion for writing for reasons other than one's own personal gain. SW includes the joy of expressing creatively through writing and the pleasure of discussing intellectual pursuits with others. Authors with this clarity use writing to express their gratification in scientific discovery. At the bottom of the list, writing can remain viewed by some individuals as an assignment and publication as a "necessary evil" to comply with particular prerequisites.

Concept and Context

The utterance "Publish and Flourish" appears to be as relevant as always in the minds of researchers globally. As a metric of scientists' eminence, the scientific community has consistently affirmed the quantity and quality of scientific papers.

One of the finest paradoxes in research is that regardless of the field, work must be written and published before it can be considered complete. Yet, writing instruction is uncommon in the curriculum for budding scientists.

A common proverb states, "if you haven't written it down, you haven't done it." Research is incomplete until it is communicated and the underlying scientific communication unit is published in a peer-reviewed journal. At the core of SW is the decision to write and make an effort to write well. Most people believe that sloppy SW indicates sloppy thinking, which is detrimental to research and research reporting.

The most technical phrases and jargons used in SW are unfamiliar to the general public. In the nineteenth century, experts used vocabulary and communication formats familiar to the educated non-experts from various disciplines and occupations. Subsequently, the communication techniques in scientific research have diverged from the general public's vocabulary customs regarding content and style.

Prevailing Perspectives

SW follows a rationale that, though familiar to other creators, it can be challenging for non-experts to understand, access, and use. Consequently, a communication gap has developed between the scientific community and the general public. The gap added more significant apprehension regarding scientific exploration conclusions and built skepticism on the experimental methods used in scientific research by scientists. Hence, the communication gap exists between scientists, the general public, and amongst scientists working in different study domains.

After World War II, investments in scientific research grew substantially, expanding the number of scientists, subdisciplines, and specified communications within respective subjects. Today, SW is so specialized that a "form as legible as the average newspaper has, in some fields, become a jungle of jargon that even those familiar with the territory may find difficult to comprehend." Since research articles and presentations are the primary means through which scientists disseminate their findings, and scientific research is becoming progressively interdisciplinary, this might constitute a barrier among researchers engaged in various scientific fields.

The writing is exceptionally resilient. A poorly written or prematurely published scientific paper can haunt a scientist indefinitely. Despite enormous technological advancements, there is no reason to believe that the value of SW has diminished in the twenty-first century.

Despite this, writing is one of the minor skills scientists use in their research. Let us briefly examine the statistics. As part of the scientific training, less than 5% of scientists have ever received formal instruction in scientific writing. Reading scientific literature is the only learning experience for most

scientists. About 10% of individuals find writing enjoyable, while 90% view it as a necessary chore.

Customization

The audience is the most crucial aspect to consider in customizing scientific communications. The response of the audience to communication is the parameter that determines whether the communication achieves its objective or not. It is essential to retain the audience's interest when creating writings and observe the communication output as much as possible through their eyes and ears.

Adapting scientific communications to an expert or non-expert audience necessitates numerous alterations to the content and approach. Important issues include selecting the appropriate level of detail and method for displaying evidence. Expert audiences would require the highest level of specificity and the most comprehensive presentation of facts to understand the research and its implications for the subject. In contrast, a non-specialist audience may be more receptive to a research summary that emphasizes relevance and impact but alludes to specificity. Using words familiar to the target audience is vital. An audience of professional scientists aid from the practice of specialized phrases and jargon, which serve as a shorthand contained by the subject; yet, these arguments alienate the general public and may be unfamiliar to scientists from other fields. Customizing the content and vocabulary to the requirements and interests of the audience prevents you from talking over the heads of lay people or talking down to specialists, both of which hinder audience engagement and your communication objective.

Final word

Effective scientific writing presents the fact of the research context and the capability to communicate the connotation of the investigation in a narrative fashion. By identifying the audience, intent, and framework of communications, one can modify their scientific writing style by accentuating the research's potential global significance. These approaches might indeed increase access to scientific research for a variety of audiences, including both experts and non-experts.

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Center of Excellence
Global Food and Food Supplements
Regulatory Services

NUTRACEUTICAL REGULATIONS:

A COUNTRY-BY-COUNTRY REVIEW OF GLOBAL REGULATORY REQUIREMENTS

How does the Regulatory process for supplements differ in emerging markets around the world? One expert reviews the differences.

Across the world, countries are recovering from the COVID-19 pandemic, with people still struggling with lockdowns, health status, job security, and income while coping with this new normal. In times like these, tools for boosting immunity and preventive health remain popular. This presents an ongoing opportunity to the food supplement industry as consumers around the world use supplements to maintain their health and wellbeing. Some countries also permit the use of supplements for medicinal purposes.

Indeed, there are more global opportunities for these products than before. But dietary supplement companies that develop, manufacture, sell, market, distribute, or import/export their products first need to ensure they meet the Regulatory requirements of each country's specific Health Authority (HA) and Ministry of Health (MoH). Failure to do so can result in significant penalties.

Compliance issues are complex, and gaining a comprehensive understanding of different countries' nutraceutical laws and regulations is often extremely challenging. This article aims to review Regulatory requirements across regions.

Demand Goes Global

The pandemic marked a significant growth in the usage of dietary supplements across the world. Consumers across regions have become more health-conscious, driving the growth of the dietary supplements market. Considering this growth, investors in the dietary supplement market are increasing. HAs have also framed the regulations accordingly to ensure the safety of products and their use.

The Asia-Pacific (APAC), Middle East/North Africa (MENA), Latin America (LATAM), and African markets have shown tremendous growth in dietary supplement demand compared to the already-mature U.S. and EU markets

- The APAC nutraceutical and functional food market is projected to witness 5-10% CAGR in the coming years
- The MENA dietary supplement market is projected to witness a CAGR of 8.2% during 2020-2025
- The African nutraceutical market is projected to register a CAGR of 6.05% during 2020- 2025
- The LATAM region is estimated to reach a CAGR of 7.3% by 2026

Health Authority/Ministry of Health

Dietary supplement companies that develop, manufacture, sell, market, distribute, or import/export their products in these markets should ensure they know who the country-specific HA and MoH are, as well as how these products are classified e.g., as dietary supplements, food supplements, or health supplements. A comparative table of product classification and respective HAs across regions is provided below (Tables 1-4).

Table 1. ASEAN

Country	Classification of Nutrition Products	Health Authority
Brunei	Health Supplements	Ministry of Health (MoH)
Cambodia	Health Supplements	MoH
Indonesia	Food Supplements	The National Agency of Drug and Food Control of Indonesia (BPOM)
Malaysia	Health Supplements	National Pharmaceutical Regulatory Agency (NPRA)
Philippines	Food Supplements	Philippines Food and Drug Administration (PFDA)
Singapore	Health Supplements	Health Sciences Authority (HSA)
Thailand	Health Supplements	Thailand Food and Drug Administration (TFDA)
Vietnam	Dietary Supplements	MoH/Drug Administration of Vietnam (DAV)

Table 2. Middle East

Country	Classification of Nutrition Products	Health Authority
Bahrain	Health Supplements	National Health Regulatory Authority (NHRA)
Egypt	Health Supplements	Egyptian Drug Authority (EDA)/Egyptian Ministry of Health (MoH)
Israel	Health Supplements	MoH
Jordan	Health Supplements	MoH
Kuwait	Health Supplements	MoH
Lebanon	Health Supplements	MoH

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Country	Classification of Nutrition Products	Health Authority
Oman	Food Supplements	MoH
Qatar	Health Supplements	National Health Authority (NHA)
Saudi Arabia	Food Supplements	Saudi Food and Drug Authority (SFDA)
Turkey	Health Supplements	MoH
United Arab Emirates (UAE)	Health Supplements	MoH

Table 3. Africa

Country	Classification of Nutrition Products	Health Authority
Nigeria	Dietary/Health Supplements	National Agency for Food and Drug Administration and Control (NAFDAC)
South Africa	Complementary Medicines	South African Health Products Regulatory Authority (SAHPRA)
Kenya	Health Supplements	MoH
SADC	Health Supplements	MoH

Table 4. LATAM

Country	Classification of Nutrition Products	Health Authority
Brazil	Dietary/Health Supplements	Brazilian Health Regulatory Agency (ANVISA)
Peru	Dietary/Health Supplements	Direccion General de Medicamentos, Insumos y Drogas (DIGEMID)
Colombia	Health Supplements	MoH
Mexico	Food Supplements	Comision Federal para la Proteccion contra Riesgos Sanitarios (COFEPRIS)
Argentina	Health Supplements	Administracion Nacional de Medicamentos, Alimentos y Tecnologia Medica (ANMAT)

Regional Regulations

Now, let's take a look at the regulations across various markets. Each market has its own requirements in terms of legalizing foreign/local products within its territory. Certain markets follow pathways of regulated countries while developing strong internal regulations.

In the APAC market, most countries require a product to be registered with the country-specific HA before it can be marketed. Certain countries like Singapore and Hong Kong are compliance-based markets - meaning once you are compliant with the local regulations, you can launch the products in the market. Certain markets like Thailand, Malaysia, Indonesia, the Philippines, Vietnam, and Taiwan require product registration with their respective HA. Countries like Japan, South Korea, and China have stringent rules and regulations for product registration. Documentation and testing details are required to be submitted based on the formula and claims of the product.

In the Middle Eastern countries, before placing a product in the respective market, companies need to ensure it meets the country-specific regulations along with GCC Standardization Organization regulations, and get the product registered with the assistance of a specified local agent. The case is similar in the African and LATAM markets.

Key Markets

Here's the list of a few key markets for dietary supplements (Table 5):

Table 5. Key Markets for Dietary Supplements

Country	Country	Country	Country
Brazil	Philippines	China	Malaysia
Peru	Singapore	South Korea	Indonesia
Colombia	Thailand	Japan	Sri Lanka
Mexico	Vietnam	South Africa	India
Argentina	Taiwan	Nigeria	Australia/New Zealand

Finding a Local Agent

Any foreign manufacturer/brand owner willing to enter these markets requires a local office or a local agent appointed by them to facilitate registration activities and to liaise with the respective HA to answer technical queries. Selecting this local agent is critical as most countries have certain prerequisites. This local agent is called by different names across countries, including Legal Representative/ Market Authorization Holder (MAH) and Responsible Person (RP). The local agent can be an entity or a person as well. Below is the list of the factors to consider when choosing the right local agent.
Certain parameters might vary across countries.

- Is the local agent a citizen of the country?
- Is the entity or representative person acting as local agent self-registered with the
- respective HA in the country?
- Will the local agent possess the company's licenses?
- The local agent should be authorized by the ministry to import food supplements.
- The local agent should possess a valid commercial registration.
- The local agent should be a science graduate or come from a pharmaceutical
- background or be a pharmacist.
- In certain countries, the local agent can be the distributor as well.

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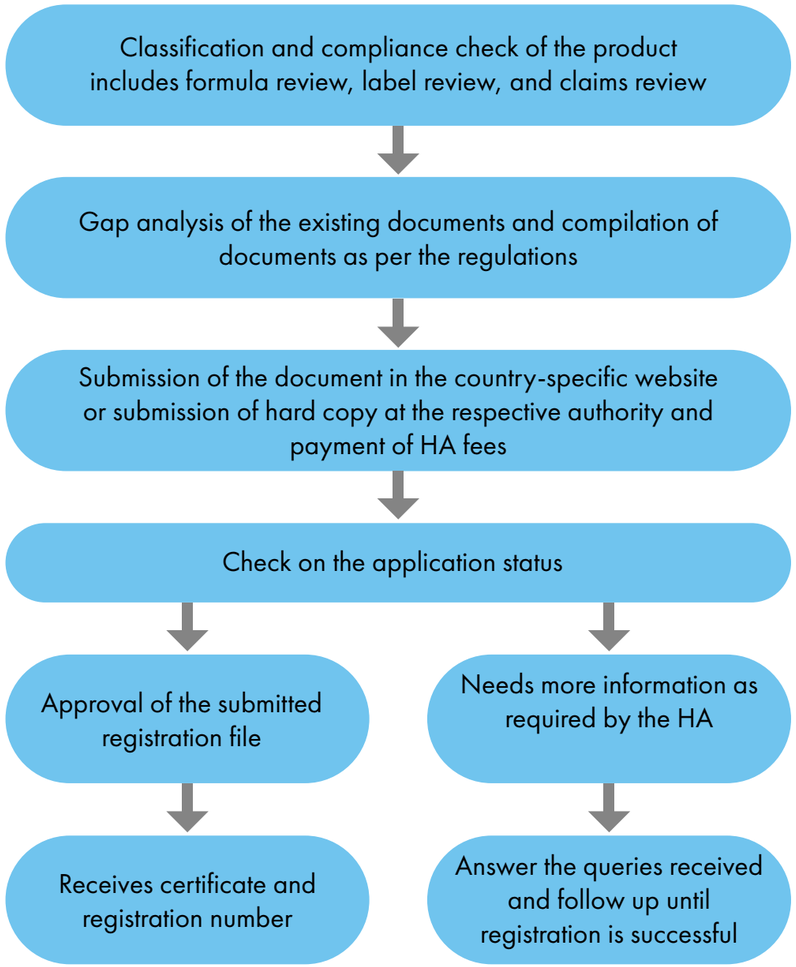
Product Registration

Once the local agent is selected, the next step is the process of getting the product registered
under the country's regulations. Below is a high-level list of documents required for registering a
product:

1. Cover letter from the local agent and respective license details
2. Application form
3. Valid Good Manufacturing Practice (GMP) certificate/ manufacturing license of the manufacturer (legalized)
4. FSC/product license from the country of origin (legalized)
5. Composition of the product
6. Finished-product specification
7. Mock-ups for the outer label, inner label, and package leaflet
8. Samples for laboratory test (as applicable)
9. HA fees payment proof

Also keep in mind that each country has its own checklist for registering a product. In certain countries like South Africa, the dossier must be submitted in the form of a CTD (common technical document) format.

Below is a flow chart that describes the registration process of various countries in detail:



Product Classification

Classification is one of the key steps to be performed before launching a product in any market. The definition of a dietary supplement varies a bit across countries; for example, in South Africa, dietary supplements are classified as Complementary Medicines; in Nigeria, they are classified as Herbal Medicine and Related Products; in Malaysia, they are classified as Health Supplements; and in Thailand, there is an option to reach out to the FDA for classification inputs. In Indonesia, a Health Supplement is a product that is meant to complement the nutritional need; maintain, increase, and improve health function; contain one or more ingredients in the form of a vitamin, mineral, amino acid, or other ingredient (originating from plant or non-plant sources) that have nutritional value and/or physiological effect; and not be intended as food.

Each country has its own definitions and classification criteria; hence, it is important to ensure your product is classified correctly before proceeding ahead with the registration/notification process, because classification will provide a clear pathway.

Compliance Check

Once classification is complete, the next step is to check the product for Regulatory compliance, including formula review, label review, and claims review. Looking at every parameter gives a complete picture of whether the product is compliant with the country's regulations. At times, regulations for certain ingredients accepted across countries might differ by country in terms of limits on usage. Also keep in mind that certain additives might be new to a country, or the main ingredient itself might be a new/novel ingredient for that country. In that case, it is necessary to take the further steps of getting the new/novel ingredients registered first, followed by product registration.

In a nutshell, the process mentioned above is a common process across countries. Now, let's see the overall picture for certain countries in the table below (Table 6):

Table 6. Registration Details Across Countries

Country	Health Authority	Registration Process	Registration Valid For:	Local Agent/LR/ MAH Required
Brazil	ANVISA	Sanitary Registration	5 years	Yes
Peru	DIGEMED	Sanitary Registration	5 years	Yes
Colombia	INVIMA	Sanitary Registration	10 years	Yes
Mexico	COFEPRIS	Notice of Operation	-	Yes
Argentina	RNPA	Sanitary Registration	5 years	Yes
Philippines	PFDA	Certificate of Product Registration	3 or 5 years	Yes
Singapore	HSA	Compliance-Bases Market	-	-
Thailand	TFDA	Registration Certificate	5 years	Yes
Vietnam	DAV/MOH	Registration Certificate	5 years	Yes
Taiwan	TAIWAN FDA	Registration Certificate	5 years	Yes

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Country	Health Authority	Registration Process	Registration Valid For:	Local Agent/LR/ MAH Required
China	CFDA	Registration Certificate	5 years	Yes
South Korea	MFDS	Registration Certificate	5 years	Yes
Japan	MHLW	Registration Certificate	5 years	Yes
South Africa	SAHPRA	Registration Certificate	5 years	Yes
Nigeria	NAFDAC	Registration Certificate	5 years	Yes
Malaysia	NPRA	Registration Certificate	5 years	Yes
Indonesia	BPOM	Registration Certificate	5 years	Yes
Sir Lanka	NMRA	Registration Certificate	5 years	Yes

Overall, most countries currently have a good demand for food supplements, and most of them have been updating their existing rules and regulations to boost the market. Some country regulations share certain similarities but are vastly different in their approach. Manufacturers and brand owners need to navigate a narrow pathway in this ever-changing Regulatory landscape to ensure compliance with the local regulations so that they do not miss any opportunities.

Meher Bhattip rolu is manager of global Regulatory services, food products, at Freyr (https://www.freyrsolutions.com/). Freyr is one of the largest global, Regulatory-focused solutions and services companies for the Life Sciences industry, supporting large, medium, and small global life sciences companies, including pharmaceutical, medical device, biotechnology, consumer healthcare, cosmetics, and food and food supplements. The company's Regulatory expertise ranges from Regulatory strategy, intelligence, dossiers, and submissions to post-approval/legacy product maintenance, labeling, artwork change management, and more. Bhattiprolu is a Regulatory and quality assurance professional with eight (08) years of experience in the food, nutraceuticals, pharmaceuticals, cosmetics, and personal care industry. A pharmacist by profession, Bhattiprolu's expertise includes Regulatory strategy and solutions, Regulatory support for global projects, quality assurance and compliance, new product development, and product registrations across markets

This article was first published by

Nutritional OUTLOOK

REVOLUTIONIZE REGULATORY PUBLISHING & SUBMISSION WITH AUTOMATION

For years, Regulatory publishing was done by manual tasks. Publishers used to work for hours formatting documents, generating agency-compliant PDFs, performing quality checks, compiling documents for submissions, and troubleshooting issues related to submissions.

Moreover, pharmaceutical companies are under immense pressure to submit error-free documents within stringent timelines. The inability to meet the timelines delay the product launch.

Current Challenges for Publishing and Submissions

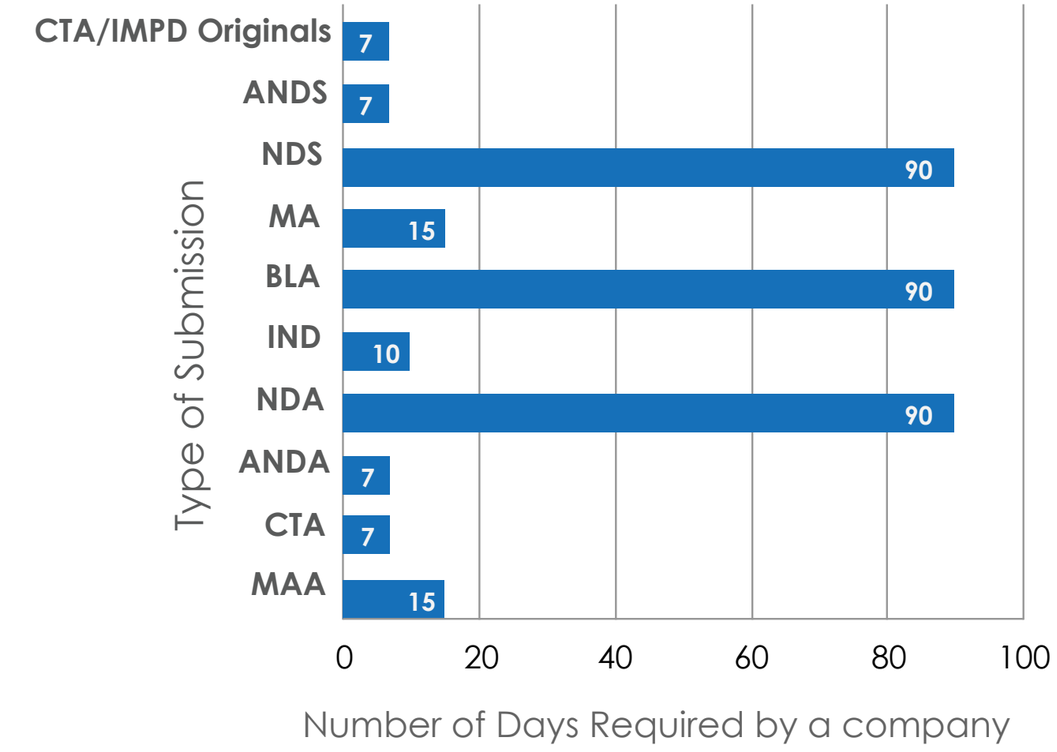
- **Time-consuming:** Manual bookmarking, hyperlinking, checking PDF properties, and page-by-page quality checking of the documents leads to time consumption. In such scenarios, re-work is a significant cause of submission delays.
- **Training:** To maintain standardization across the submission process, organizations are required to train their teams on the SOPs.
- **Multiple Tools:** Multiple licenses for tools and technologies are required for each resource working on the document. Large submissions take extensive energy and focus on manually uploading hundreds of documents to the eCTD publishing software.
- **Correct Version:** Multiple versions of the same document can be presented on the publisher's desktop. The publisher must identify the correct version of the document before uploading it.
- **eCTD Structure:** Correct sequence and eCTD structure must be created for every submission request.
- **Manual Errors:** There are high chances of mistakes while providing metadata or file naming during document submission.

Although there is an increase in the adoption of Artificial Intelligence (AI) and automation in every industry, it is rare to find its impact in Regulatory Affairs Therefore, to overcome the challenges of manual, repetitive, and contextual document processes, organizations must step into the possibilities of the world using automation at the submission level and the whole process of compilation, validation, and document finalizing.

Automation offers a chance to enhance processes and workflow when preparing eCTD submissions in existing markets and expanding into newer markets. As enterprises consider automation for eCTD requests, it's essential to consider the capabilities that will benefit and drive efficiency. Currently, some organizations have stepped into developing automation tools by using databases, but this is a time-consuming and manual activity.

The graph below demonstrates the number of days required for a company to file various applications using the manual process.

eCTD submissions for different applications



As we can see, it usually takes ninety (90) days for companies to file a New Drug Application (NDA), and fifteen (15) days to file a Market Authorization Application (MAA). By automating a few repetitive steps, it is observed that an NDA Submission that usually takes ninety (90) days can now be submitted within thirty (30) days, approximately. Thus, this could significantly reduce the publishing efforts by 57% every year and improve productivity by saving 60% time for publishers.

Hence, to eliminate time-consuming steps and drive efficiency in completing regular and repetitive tasks, the implementation of automated publishing tools for document-level and submission-level processes is the need of the hour.

Artificial Intelligence can transform and have the power to revolutionize the end-to-end process of document management and submissions. With a massive experience of executing 100000+ global submissions – eCTD, NeeS and Paper formats – for large and small-to-medium BioPharma companies, Freyr has established the industry's first publishing automation innovation toolkit.

With a fresh and innovative method of evaluating day-to-day publishing activities from a simplified version, Freyr's Digital Publishing Automation is built using an array of RPA & NLP modules that automate document-level and submission-level publishing. It works on all Regulatory PDFs with the main header and sub-header, bookmarking and hyperlinking, keyword-based search, particular keyword highlights with colored font presentation, and internal and external hyperlinking between multiple documents. It works both on text-based PDFs and image-based PDFs. Publishing Automation tool is a REST API, cloud-based solution that is scalable and designed to work on all kinds of Regulatory PDFs from Health Authorities like the US FDA, EMA, HEALTH CANADA, SWISSMEDIC, SFDA, SAHPRA/MCCZA, TGA, and EAEU. To learn more about how you can automate your Regulatory publishing and submissions, reach out to Freyr.

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Center of Excellence
Chemicals Safety and Regulatory Affairs

CIRCULAR ECONOMY: A NEW ERA IN THE POLYMER WORLD

Plastics are the products of human innovation, and they are stable, durable, lightweight, and most importantly, inexpensive. They are a type of polymer, composed of a chain of polymers. The life we currently live is not possible without these amazing polymers. Unfortunately, our appetite for plastic shows no sign of back-pedal. Plastic pollution has become a global concern as our planet is drowning in plastic microplastic litter. In developed countries like the EU, it is reported that in 2018, over 80% of virgin plastic was produced and accumulated in landfills and the natural environment. This paved the way to take up actions in reducing plastic waste in the EU. The European Commission published the European Strategy for Plastics in a Circular Economy (2018), which aims to protect the environment, reduce the pollution caused by plastics and transform the design, production, consumption, and recycling of plastics in Europe.

Chemical recycling is used for processing wastes, including concrete and biomass. The technologies of chemical recycling have attracted industrial sectors and scientists. Firstly, because of the rapid increase in waste generation and environmental pollution, and secondly, due to the exhaustion of natural resources that dramatically affect the future of humankind. Hence, to tackle this challenge, a "Circular Economy" was developed, which follows a 'closed-loop' system to reduce the consumption of natural resources and safe and continuous use of materials and products with less waste.

In March 2020, the European Commission launched the Circular Economic Action Plan (CEAP) to help accelerate the transformational change required by the European Green Deal. The plan offers several interrelated initiatives to establish a coherent and robust product policy framework

that will help sustainable products, services, and business models to become the norm and transform the current consumption patterns so that no waste is produced in the first place. The proposed measures for plastics in the CEAP mainly cover waste reduction and uptake of recycled waste, focusing on the most significant streams of plastic waste – packaging, construction materials, and end-of-life vehicles. The objectives and targets relevant to the recycling of plastic waste were provided in several EU policy documents: the Waste Framework Directive (WFD) 2008/98/EC, Packaging and Packaging Waste Directive 94/62/EC (PPWD), and End-of-Life Vehicle Directive 2000/53/EC (ELVD).

A survey related to post-consumer plastic waste revealed that around 61% of the waste is attributed to packaging. Choosing a type of chemical recycling mainly depends on the output of the plastic. i.e., Plastic-to-Plastic (P2P) and Plastic-to-Fuel (P2F). The main contribution to the circular economy is P2P chemical recycling products. P2F products are much less desirable as they do not result in recyclable resources. In the EU, waste recycling is subject to various regulations. In turn, the role of recycling is two-fold: it is a means for achieving both the circular economy goals and efficient waste management. Historically, the EU policies on waste and chemicals management did not contain the circular economy dimension and were mainly oriented towards creating a non-toxic environment and efficient waste management.

The European Commission (EC) recognized the need to consolidate the circular economy and waste management objectives, and develop effective means for their implementation in communication on the circular economy package options to address the interface between chemical, product, and waste legislation.

The EU's strategy for plastic takes us one step closer to sustainably tackling the global plastics crisis. With this sustainable approach, the EU aims to achieve the recyclable target of 50% by 2025 and 55% by 2030.

Freyr, a global Regulatory solutions company, provides services in maintaining the compliance of packaging material of food, cosmetics, and consumer products. Apart from the requirements and Regulatory updates, Freyr also supports voluntary certification and standards for packaging material. Contact us today for Regulatory packaging services in the EU.

Center of Excellence
Global Pharmaceutical Regulatory Services

COMPARATIVE ANALYSIS OF DOSSIER SUBMISSIONS - EU & US

Over the past ten (10) years, the cost of bringing a drug into the market has increased by 140 percent. Globally, the top twenty (20) pharmaceutical organizations spend nearly sixty (60) billion dollars every year to bring a drug into the market and the average cost is estimated to be $2.6 billion, including drug failures. With the increased demand for rare/life-saving drugs, the Market Authorization Application (MAA) filings are also increasing. A disparity between supply-chain operations and manufacturing processes has led to disconnected systems. Lack of coordination within various departments (clinical science, Chemistry, Manufacturing, and Controls (CMC), nonclinical, pharmacokinetics, pharmacodynamics, medical writing, and clinical operations) has compromised the quality of product information, escalating the risk of non-compliance in submissions. Hence, it is essential to understand dossier submissions and the product's potential value in the marketplace. Pharmaceutical organizations must scrutinize the submission working method via monitoring the timelines and critical path implementation. Let us now take a look at the US - EU submission comparison.

Comparison of Information Submitted

A standard format of how the applicants must submit the data is set up in the files transmitted to the regulators for application submission. Metadata is the fulcrum of all the data required for eCTD submissions. It gives information about other data and is contained in the eCTD backbone files. Metadata is divided into structural metadata, i.e., how data is organized, and descriptive metadata, which provides information about the content.

The US Market

The United States Food and Drug Administration (USFDA) is the first Health Authority to adopt the eCTD format introduced by the International Council for Harmonization (ICH). The applicants need to submit an application form depending on the type of drug proposed, i.e., Investigational New Drug (IND), New Drug Application (NDA), Abbreviated New Drug Application (ANDA), Over-The-Counter drugs (OTC), Biological License Application (BLA), Drug Master Files (DMFs), etc., along with a cover letter to the USFDA.

The following table explains the details of various submissions and the respective applications in the US:

Submission Type	Submission Sub-Type	Supplement Effective Date Type (If applicable and submission-sub-type "application")	Valid For Application Types
Original Application	Presubmission Application Amendment Resubmission		IND, NDA, ANDA, BLA, DMF, EUA
Efficacy Supplement	Presubmission		NDA, BLA
	Application	Prior Approval Supplement(PAS)	
	Amendment Resubmission		
Chemistry Manufacturing Controls Supplement	Presubmission		NDA, ANDA, BLA
	Application	Prior Approval Supplement (PAS), Changes Being Effected (CBE-0), or Changes Being Effected 30 (CBE-30),	
	Amendment Resubmission		
Labeling Supplement	Presubmission		NDA, ANDA, BLA
	Application	Prior Approval Supplement (PAS), or Changes Being Effected (CBE-0)	
	Amendment Resubmission		
Annual Report	Report Amendment		IND, NDA, ANDA, BLA, DMF
Postmarketing Requirements or Postmarketing Commitments	Original Amendment		NDA, BLA
Promotional Labeling Advertising	Original Resubmission Amendment		NDA, ANDA, BLA
IND Safety Reports	Report Amendment		IND
Periodic Safety Reports (Periodic Adverse Drug Experience Report (PADER) or Periodic Safety Update Report (PSUR)	Report Amendment		NDA, ANDA, BLA

Source: www.fda.gov

The most critical element for a successful submission is to have the eCTD modules filled properly and stored in the metadata. The format in which the submissions are to be made is explained as follows:

Module 1 Specifications

The type of submission establishes, defines, and identifies the Regulatory activity. An application can comprise one (01) or more Regulatory activities, each of which can consist of one (01) or more submissions. The first submission of this kind demonstrates the submission ID that will be used in subsequent submissions for the same Regulatory activity in an application. Using the same submission ID number for an activity facilitates submissions to be grouped for that specific activity. This is achieved by using the submission ID number, which is governed by the sequence number of the first submission to each Regulatory activity.

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Grouped Submissions

A grouped submission is a single sequence comprising us-regional.xml, index.xml, and any applicable files concerning more than one (01) application. Such a submission terminates the need to submit multiple, identical submissions to different authorities.

Applicants are required to submit all the reports (clinical and non-clinical) for a particular study in modules 4 and 5 in the form of a Study Tagging File (STF) as per the USFDA.

The EU Market

In the EU, applicants need to submit all information in the form of metadata which will be covered as envelope information. Based on the requirement of the applicant, there are four (04) different procedures for the MAA respectively - Centralised Procedure (CP), Decentralised Procedure (DCP), Mutual Recognition Procedure (MRP), and National Procedure (NP).

eCTD Specifications

- 'Single' (variation)
- 'Grouping' (variations of the same type influencing the same marketing authorization)
- 'Grouping' (variations of different types influencing the same marketing authorization)
- 'Grouping' (one (01) or more Type IA variations, influencing multiple marketing authorizations of the same Marketing Authorization Holder (MAH). A high-level submission number is also required for these submissions)
- 'Work sharing' (one (01) or more Type IB and/or Type II variation(s) affecting multiple marketing authorizations of the same MAH. A high-level submission number is also required for these submissions)

Module 4/5

Applicants are not required to re-organize the reports for submission to the European Medicines Agency (EMA) or the National Competent Authority (NCAs). To maintain a compatible eCTD lifecycle and table of contents (via index.xml), applicants are advised to use node extensions for all clinical study reports, regardless of the granularity of the content (i.e., even reports that consist of only one (01) document must also be presented in node extensions).

Conclusion

	US	EU
Application Submission	Application form + Cover letter	Cover letter + EU eCTD envelope
Information Submission	Applicants are required to submit all the information as reports (clinical and non-clinical) for a particular study in modules 4 and 5 in the form of a Study Tagging File (STF) as per the USFDA.	The "EU-envelope" element is designed to be used for all types of submissions (MAAs, variations, renewals, etc.) for a given medicinal product and will mainly be used for the first, simple processing at the Agency level. The envelope provides meta-data at the eCTD application and sequence level.
MAA Submission Deadline	Can be submitted anytime	Specific windows, depending on whether your product qualifies for standard review or accelerated.

Attainment of high-quality, timely submission that aligns with Regulatory requirements, stakeholders' interests, and company expectations demands excellent strategic and tactical planning and the focus of a dedicated and experienced Regulatory submissions Project Manager. Based on the Agency requirements, Freyr's regional experts, with proven capabilities in the Publishing and Submissions (P&S) space, bestow tailor-made services required to meet the application specifications. The experts review each dossier submission, put forth any gaps identified during the review along with the suggestions, and assist in the compilation of the MAA P&S, which includes resubmissions within an industry-leading industry turn-around-time at competitive pricing. Contact Freyr for details.

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Global Pharmaceutical Regulatory Services

WHO CONSIDERATIONS FOR REGULATING CELL AND GENE THERAPY PRODUCTS (CGTPs)

To promote global convergence among the Health Authorities and encourage the Member States to strengthen their Regulatory system on CGTPs regulations, the World Health Organization (WHO) proposed a risk-based framework for regulating CGTPs. The WHO white paper outlines the fundamental principles that are important for providing adequate Regulatory oversight for different types of CGTPs and should be reviewed in that context. Let's decode them.

WHO Considerations

The Regulatory framework should be based on scientific and ethical principles, and a comprehensive evaluation of risks vs benefits for different categories of CGTPs. For low-risk Human Cells and Tissues (HCTs), the regulations must concentrate on controlling possible contaminations and disease transmission, whereas the Regulatory expectations for Advanced Therapy Medical Products (ATMPs) are higher in order to address the risks of highly manipulated products. The key elements of this framework include:

- Clear definition of the categories of products that constitute CGTPs
- Risk stratification of the products defined as CGTPs
- Aligning the level of Regulatory control based on different risk categories
- Consideration of the maturity level, expertise, and resources of the Regulatory Authority for providing oversight of CGTPs in different risk categories

The document is the first step in responding to the 2018 International Conference of Drug Regulatory Authorities (ICDRA) recommendation and outlines the priorities and next steps as identified by regulators from both developed and developing countries, for advancing global convergence on the regulation of CGTPs, including ATMPs. The priorities are to:

- Clearly describe what the CGTPs are, describe how the subsets of HCTs and ATMPs are defined from this larger class, and provide definitions of key terminology relevant in this area.
- Summarize the existing state of ATMPs that are approved or under development, including examples of challenges in the development and where solutions have been identified. These examples should cover non-clinical development, clinical development, and product manufacturing & quality.
- Provide the key elements of a Regulatory framework that supports the safety and effectiveness of CGTPs, including suggested Regulatory controls for different risk categories of products. The products cover key elements for adequate oversight spanning the entire product lifecycle from the investigational phase through post-market surveillance.
- Develop a proposal for how the Regulatory framework for the risk categories could be implemented in countries with different levels of Regulatory maturity.

Different Frameworks for HCTs and ATMPs

As per the document, the WHO proposes different Regulatory classifications for HCTs and ATMPs. HCTs are minimally manipulated or intended for homologous use when compared to ATMPs, which are derived from human or animal cells and involve more extensive manipulation. Therefore, ATMPs require more comprehensive regulation and demonstration of safety and efficacy, along with:

- More stringent manufacturing and quality controls, including process changes and comparability assessments for clinical trials and commercial production under Good Manufacturing Practice (GMP)
- Non-clinical studies to generate pharmacodynamic (PD), pharmacokinetic (PK), biodistribution, and safety data for the products to ensure the risks are known and mitigated before human exposure (Good Laboratory Practice (GLP) required for pivotal safety studies)
- Clinical studies with proper design and control to collect robust and reliable safety and efficacy data for the products and long-term follow-up of the patients (Good Clinical Practice (GCP) required for conducting the studies)

It is hopeful that, through various initiatives for Regulatory reliance regionally and internationally, the Regulatory convergence will ultimately lead to Regulatory harmonization. Aligning with these Regulatory requirements for HCTs and ATMPs would benefit public health by making potentially transformative, safe, and efficacious medical products available for unmet medical needs. Would you like to know more about the WHO considerations for regulating CGTPs? Contact Freyr – a trusted Regulatory partner for a decade. Stay informed. Stay compliant.

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Global Cosmetics
Regulatory Services

SUNSCREENS IN AUSTRALIA: A REGULATORY OVERVIEW

Sunscreen is an important component of an effective sun protection regime. They must be safe, effective, and of good quality. For this reason, the TGA regulates sunscreens as therapeutic goods in Australia under the Therapeutic Goods Act 1989. The Australian Regulatory Guidelines for Sunscreens (ARGS) describe the Regulatory requirements and standards for sunscreens and their ingredients. As per the ARGS, sunscreens regulated under the Act are referred to as therapeutic sunscreens.

Sunscreens that fall under therapeutic goods are classified into:

- **Primary Sunscreen**s - Products primarily used for protection from UV radiation
- **Some Secondary Sunscreens** - Products with a primary purpose other than sun protection but contain sun screening agents, e.g., moisturizers containing sunscreen with Sun Protection Factor (SPF) greater than 15

Manufacturers must include only approved ingredients in sunscreens, and all these approved ingredients are assessed for safety. Therapeutic sunscreens must be listed in the Australian Register of Therapeutic Goods (ARTG) before they can be legally marketed in Australia. To market a sunscreen in Australia, manufacturers must have:

- an ARTG entry for that therapeutic sunscreen; or
- retail arrangements with a sponsor who has an ARTG entry for that therapeutic sunscreen

TGA requires the efficacy of each product to be tested to determine the SPF printed on the label. Sunscreen labels may carry company logos, symbols, and consumer information as per the current Labeling Order and Advertising Code. The advertising and labeling of therapeutic sunscreens must comply with the following:

- the current version of the Advertising Code
- the current version of the Labeling Order
- the Australian Sunscreen Standard

In a nutshell, manufacturers of therapeutic sunscreens must comply with the TGA ARGS standard for market entry in Australia. Partnering with a Regulatory expert is always a flexible option for hassle-free market entry of sunscreens in Australia. Contact Freyr today!

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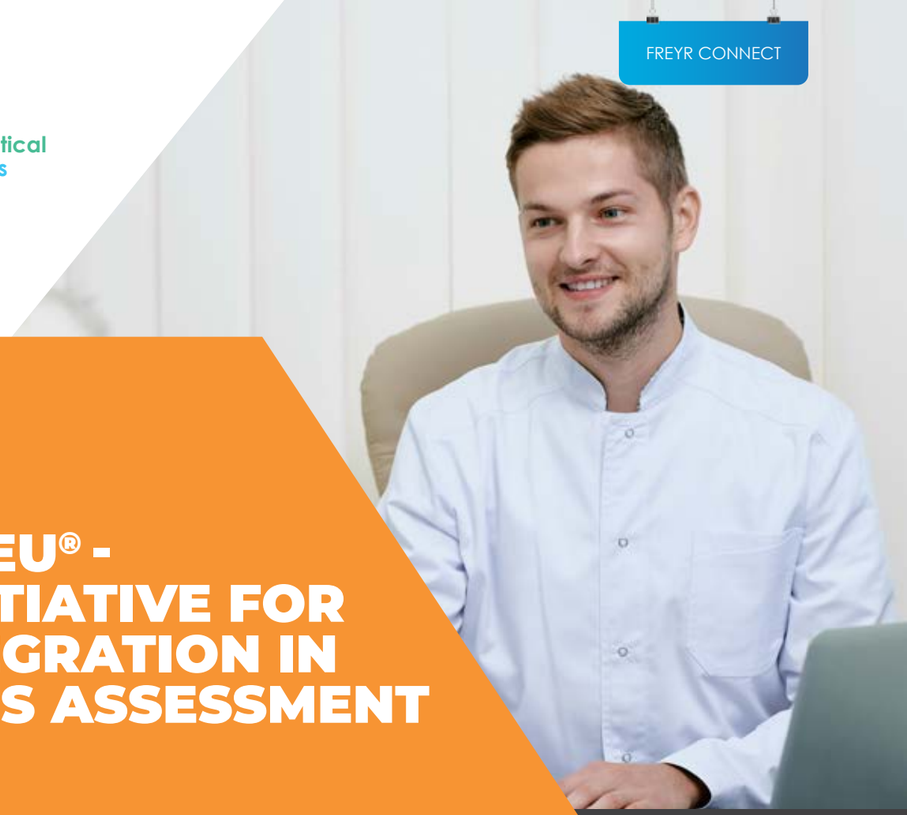
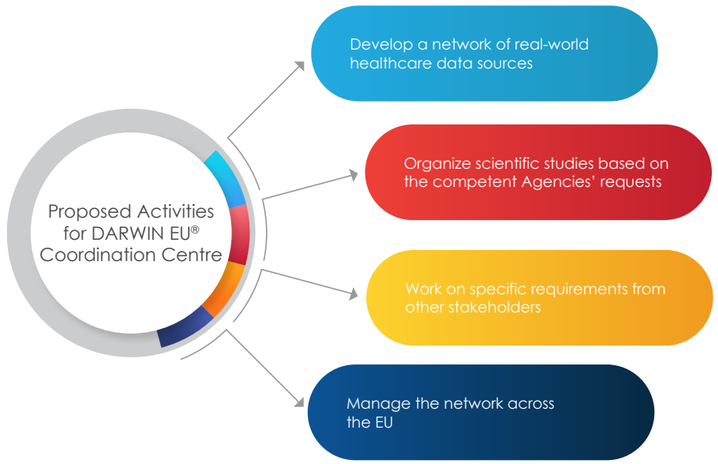


DARWIN EU® - EMA'S INITIATIVE FOR RWE INTEGRATION IN MEDICINES ASSESSMENT

On February 09, 2022, the European Medicines Agency (EMA) commenced the establishment of a Coordination Centre for Data Analysis and Real-World Integration Network (DARWIN EU®). It is the first step towards integrating Real-World Evidence (RWE) into assessing medicines across the European Union (EU).

Ensuring the safety and efficacy of medicines is the prime activity of any Regulatory Agency, and RWE is proving to be a reliable source for gathering real-time evidence from global healthcare databases. Therefore, this move by the EMA is meant to enhance the quality of drugs in the EU region and make them available faster.

Major Activities Planned for the Coordination Centre for DARWIN EU®



How is the DARWIN EU® Going to Help EMA and Relevant Authorities in the Regulatory Space?

Innovative drugs that are readily available to patients are the need of the hour. The Regulatory processes for the development, approval, marketing, and post-marketing surveillance take a substantial amount of time, making the demand for novel drugs unmet. Reducing the time-to-market while ensuring innovative drugs' safety, efficacy, and quality is the way forward. Several global Health Authorities are identifying the benefits of integrating RWE in their Regulatory approvals, and DARWIN EU® is the EMA's initiative.

The EMA plans to connect the European medicines Regulatory network to the European Health Data Space (EHDS) for better data exchange and enhanced access to various health data types under this program. It will also set standards for scientific evaluations and Regulatory decision-making.

Here are a few activities that the DARWIN EU® aims to achieve:

- Usage of RWE in decision-making activities for the regulation of new drugs, vaccines, etc.
- Integrating RWE in the entire lifecycle of a drug such as development, authorization, and post-market surveillance
- Prepare for any future medical emergencies such as pandemics
- Benefit the pharmaceutical industry with insightful and reliable RWE on patients, diseases, and usage of drugs
- Make informed Regulatory decisions based on RWE for the safe and effective use of medicines
- Improved accessibility of life-saving drugs to patients in need, owing to accurate and timely data analysis

Proposed Timelines for DARWIN EU® to be a Fully Functional Network in the EU

The EMA also specifies the timelines for DARWIN EU® to be fully operational, and they look like this:

- **2021** – Initiation of the project
- **2022** – Establishment of DARWIN EU®
- **2023** – Development of DARWIN EU® and defining its usages
- **2024** – Making DARWIN EU® fully operational
- **2025** – Enhance the Regulatory uses of healthcare data by increasing the scopes in terms of medicines, geography, etc.

The EMA is collaborating with the Erasmus University Medical Center Rotterdam for the establishment of DARWIN EU®. The goal of this partnership is the establishment of the Coordination Centre to create a distributed data network. Both of them have also taken up the tasks of conducting scientific studies, supporting Regulatory decision-making processes, and managing a catalog of real-world data sources.

What Does the Initiation of DARWIN EU® Mean for the Future?

The EMA and the Head of Medicines Agencies (HMA) have always worked together to identify the challenges, set time-bound goals, and define priorities in their five (05)-year strategy documents. It is meant to provide strategic direction to the activities carried out by the European medicines Regulatory network.

The initiation of DARWIN EU® is a major step towards the delivery of the EMA's Network Strategy. Conducting scientific studies to answer research questions, supporting the evaluation of medicines in the EU, and maintaining metadata for medicine Regulatory activities are the main objectives. DARWIN EU® is foreseen as a major player in medicines regulation in Europe, and the pilot studies are proposed to be ready by the end of 2022.

If you are a drug manufacturer and wish to know more about RWE and how it is shaping the future of Regulatory decision-making, contact the Regulatory Affairs experts at Freyr.

PHARMACEUTICAL PROMOTION MATERIAL

GLOBAL LAWS OVERVIEW

Pharmaceutical advertising or prescription/non-prescription drug promotion will remain a widely debated topic, perhaps until a global understanding of regulations surrounding it is established. When it comes to promoting prescription and non-prescription drugs, evolving laws and regulations bring about a complexity like none other in pharmaceutical Regulatory Affairs. In multiple countries, the primary source of educating the end users/prescribers is a unidirectional promotional material flow. For a company aiming to launch a molecule in multiple markets, insight into the regulations in that market and drawing a comparison to regulated/semi-regulated/unregulated markets may help understand and navigate precedents and complexities. This piece consolidates the current thought process behind promotional material globally and the author's opinion on pharmaceutical advertising utopia.

One of the most important tasks of any Regulatory body is to ensure that pharmaceutical products are developed in accordance with the local/regional Regulatory requirements. It not only includes the process of regulating and monitoring the manufacturing of medicines but also the processes of their distribution and promotion.

Therefore, for any global pharmaceutical marketer, it is important to analyze the differences and commonalities of Regulatory requirements and pharmaceutical legislation around the world.

Over the last few years, pharmaceutical companies have faced several challenges when it comes to their ad campaigns

The reasons why the recent news is focused on pharmaceutical advertising and promotions is the changing regulations and stricter laws surrounding promotions put into place by Health Authorities (HAs) to keep in check pharmaceutical manufacturers from often unknowingly making flawed, misleading, and unlawful statements about their products. Rising fines, notices of violation, and cease and desist letters cost pharma a lot, and as an industry-wide movement, pharmaceutical companies are now moving towards performing a medico-legal-regulatory review that they should have taken up before beginning to market their products.

With about US$ 1.6 billion spent by pharma in print advertising, approximately US$ 565 million in programmatic ad spend between January 2020 and August 2021, and an expected US$ 15 billion expenditure on influencer marketing by the end of 2022, it's no doubt that people are talking about pharmaceutical advertising and promotions. The way promotions are done is changing, and it's time that the laws governing promotion are decoded and communicated to marketeers in a manner that aids compliance.

Where exactly is the problem?

Based on the analysis of an independent survey of over

one thousand (1000) recent healthcare advertisements, it was found that:

- About nine (09) per cent of the advertisements contained false or misleading claims
- Fourteen (14) per cent of the ads contained "unsolicited, inappropriate, deceptive, unsupported, or irrelevant advertising"
- Forty-four (44) per cent of the ads included language that would mislead a consumer who did not understand the medical condition and what the product or treatment could do
- Twelve (12) per cent of the ads misrepresented facts about a specific product or service, and fifteen (15) per cent were redundant or inappropriate

Those are Alarming Numbers

One may ask why they are even observed with the current set of laws in place. What is the root cause for these misleading advertisements and promotions? The answer to this question is rather simple.

Each country and its regional laws - the existing, the adapted and/or translated - and the deep grey chasms in between, and the inconsistencies in understanding, consolidating differences, and similarities in said laws are the pain points in creating globally compliant promotional material.

Logic demands universally applicable laws, albeit slurred with a slight variation to suit regional nuances often referred to as regional contextualization.

Therefore, when a comparison was drawn between developed and regulated markets and semi/unregulated ones on promotional material for pharmaceuticals, it was found that almost every country follows the developed nations and regulated markets with slight deviations. However, here the deviations seemed to arise from the ability, or lack thereof, of a statutory body to be able to regulate, legislate, and govern while keeping a watchful eye over what's happening. Or it stemmed from the lack of confidence in developing self-regulation parameters.

Another reason could be that the pharmaceutical manufacturers aren't looking at specific markets as potential earners and are yet to start heavy promotions there. But we can only speculate.

Let's Take a Few Examples

Globally, the mandates are rather similar - barring certain small deviations:

- Direct-to-Consumer (DTC) is risky, so do it with care in a mannerism of education
- Self-regulate, and we trust you to not mislead the consumers
- Do not claim that which is untrue

Some examples of country-specific deviations are as follows:

- Larger regulated markets like the US and Europe have multiple Regulatory Authorities, while semi-regulated have a single, or sometimes no specific authority to monitor the promotions.
- Countries like Ethiopia, Fiji, Zimbabwe, Uganda, Tanzania, Ghana, Venezuela, and Estonia don't have recent updates and don't adopt newer methods (especially digital/social) of medical promotions.
- In countries like Portugal, Estonia, Belarus, Denmark, Ireland, Belgium, and Norway, the definition of advertisement is perceived as being informative rather than communication-focussed, as compared to others.
- Finland, Belarus, Czech Republic, Iceland, Portugal, etc. have specifically called out that they do not allow direct comparison with competitor products directed to the general public as compared to other countries. Prescription advertisement is prohibited in all countries except New Zealand and the US. Google Ads allows manufacturers to advertise digitally in Canada with certain restrictions.
- Pharmaceutical manufacturers promote over-the-counter medicines in countries like Australia, Austria, Brazil, Canada, China, Czech Republic, France, Germany, Hungary, Hong Kong, India, Italy, Japan, Kenya, Mexico, Netherlands, New Zealand, Norway, the Philippines, Poland, Portugal, Russia, Slovakia, South Korea, Spain, Sweden, United Kingdom, and the US.
- The US, UK, North Macedonia, Venezuela, etc., actively monitor promotional material before it is broadcasted to the public and health professionals. However, in a few countries, advertisers do not require pre-approval of their promotional material before being broadcasted.

Advertisers, in terms of copy or creatives, are under immense pressure to follow global mandates and guidelines and are sometimes forced to sacrifice creativity in the pursuit of compliance. This frenzy, clutter in tracking, memorizing, and complying with individual country laws have often resulted in global pharma marketers losing track or sometimes completely forgetting submissions, resulting in fines and notices of violations.

Now, what can one do to avoid this confusion? What is the ideal solution for this?

The Role of a RAP Specialist

At a pharmaceutical company, the Regulatory Advertising and Promotion (RAP) team or the Promotional Review Committee (PRC) is responsible for understanding and interpreting the laws, rules, codes, and guidelines governing prescription drugs' advertising and promotion.

It is imperative that all statements made in advertising, whether express or implied, can be fully substantiated. This is due to the level of accuracy, quality, and honesty required by pharmaceutical and biotechnology companies to support the promotion of medicines and products. This is exactly where the RAP specialist plays a crucial role. The RAP specialist provides advice on strategic adjustment before and after marketing activities, when risk-based cross-functional decision-making is critical. When providing strategic advice on drug advertising and promotion, the ability to think broadly and paying attention to detail ensures compliance with the local HA rules and guidelines.

Those working as RAP specialists (usually medical, legal, and Regulatory professionals; a.k.a. MLR committee at times) need a deep understanding of the Regulatory framework to ensure business compliance. They should provide strategic Regulatory guidance to businesses throughout the pharmaceutical product lifecycle. It is critical that the legal, Regulatory, and medical teams take the time to understand business goals and support achieving those goals within legal and Regulatory constraints. Equally important is that the business groups value the role of external auditors and specialized promotional material consultants in ensuring that products are properly marketed.

In the Advertising Review Committee, friction can often arise between the marketing team and members representing the medical, legal, and Regulatory issues. Integrating content with the medical, legal, and Regulatory review processes delivers more value to patients and consumers, reduces the cost of producing content, and helps an organization become a more efficient company. The costs associated with setting up, training, and sustaining a RAP committee can often run into hundreds and thousands of dollars. Hence, smaller companies, and often even large multinationals, are choosing to outsource this function to specialized medico-Regulatory consultants and auditors, while keeping only legal teams in-house.

On the Future of Pharmaceutical Advertising

The drive to be rational has led people to trust and conjure laws and regulations bound tightly by universal applicability and generalization.

But context, on how people think, behave and act, is perhaps missing when it comes to pharmaceutical advertising. One of the guiding factors that need to be incorporated in promotional material regulations is the fact that considerations need to be made to susceptibility and the potential influenceability of the intended audience by drawing up certain measures of maturity and self-decision-making capabilities with regards to health by the nation's populace. When added to self-regulation norms, it makes for better content. A touch of personalization as a mandate would also generally benefit the sector. For example, if a group values prevention and community medicine, pharmaceutical companies should develop approaches for that group, knowing that traditional pharmaceutical marketing won't work. Instead, they need to understand the social, cultural, economic, and ethical impact of their medicines, and use this knowledge to personalize their approach towards consumers. They can no longer focus solely on the positive or negative health effects of drug usage.

Despite limited cost controls, Regulatory constraints, and global competition, the drug-marketing space will have to focus on users, taking a patient-first, and not pill-first approach in the future. One thing is for sure, interesting promotions lie ahead.

This article was first published by

PHARMA FOCUS ASIA

Center of Excellence
Global Pharmaceutical Regulatory Services

ALERT SIGNAL – THE VITAL TRIGGER FOR PHARMACOVIGILANCE ACTIVITIES (EMA)

The journey of a drug product doesn't end with its post-market authorization. The drug's performance is now openly evaluated by the general population. To safe guard the population against any undesirable outcomes post the consumption of a drug, a pharmacovigilance alert system is in place. A risk management committee of experts monitors drug safety and evaluates every alert signal issued by the people to address the concern.

The science and activities related to the initial detection, understanding, and prevention of Adverse Drug Reactions (ADRs) or any other drug-related problems are known as pharmacovigilance. It is an initiative taken by the Health Authorities (HAs) to prioritize patient safety by studying the drug behavior while it is being consumed by the patient population and the ADR profiles.

The trigger for the pharmacovigilance system in place is identifying an alert signal. An alert signal regarding a drug product can be raised by a physician or a health practitioner to the Marketing Authorization Holder (MAH) or the National Competent Authority (NCA). Spontaneous reports can also be received by the patients directly. However, in cases of spontaneous reporting, the credibility of the data received can be compromised due to a lack of medical proficiency in the reporting document. Once the alert signal is compiled and consolidated as an Individual Case Safety Report (ICSR), it contributes to the EudraVigilance database maintained by the European Medicines Agency (EMA) to predict probable drug interactions, adverse effects, etc., based on the past repository of information.

Stringent compliance protocols ensure that drug safety is paramount. However, with the changing nature of drug delivery, advanced therapy medicinal products are gaining momentum. The drug development cycle and post-authorization monitoring of novel medicines can cater to the decade-old challenges identified in the treatment of rare diseases. The Committee for Human Medicinal product (CHMP) is the preceding committee in association with the Pharmacovigilance Risk Assessment Committee (PRAC) and the other NCAs, which work towards forming a formal opinion about a drug product. The Committee relies heavily on research findings, case studies, reports, etc., while evaluating the suitability of the drug. The post-authorization stage can seem overwhelming with GxP compliance mandates. Our experts at Freyr are familiar with the ICSR, signal detection, and literature monitoring, and understand your aggregate reports' needs, including the Periodic Benefit-Risk Evaluation Report (PBRER), Periodic Safety Update Reports (PSUR), Periodic Adverse Drug Experience Report (PADER), and the Clinical Study Report (CASR). To know more about the challenges associated with the EU market entry and the pharmacovigilance activities therein, tune in to Regulatory Radio today!

Center of Excellence
Global Medical Device Regulatory Services

US AGENT AND TOP 15 FREQUENTLY ASKED QUESTIONS (FAQs)

The United States (US) is the largest medical device market worth USD 180 billion (2021) and is expected to reach USD 670 billion at a CAGR of 5.2% from 2022 to 2027. Global medical device manufacturers find it promising to get their devices approved by the US Food and Drug Administration (FDA) and subsequently export them to the US.

One critical need for non-US device manufacturers who intend to market their products in the US is to appoint a US agent. Manufacturers may either choose to appoint a reliable US agent service provider or their importer/distributor to represent their devices in the US. Foreign device manufacturers may have certain questions about US agents such as their role and their responsibilities. Here is the list of the top fifteen (15) questions that medical device manufacturers frequently pose:

1. Is it mandatory to appoint a US agent?

Yes! As per the USFDA, all foreign medical device manufacturers seeking to market their products in the US are required to designate a US agent.

2. What are the prerequisites for a US agent?

The US agent can be a person or an entity and must reside in the United States. The entity must be registered in the US and must have an active Data Universal Numbering System (DUNS) number. The agent should have a physical premise as an address to contact. The appointed entity or person should be available to assist with any communication during normal business hours.

3. What is the difference between a US agent and an official correspondent?

An official correspondent is the point of contact for device submissions such as 510(k), Premarket Approval (PMA), etc., and can be an employee of the sponsor or a third-party agency. The official correspondent is required for any submission, irrespective of whether it is a domestic or foreign manufacturer. The official correspondent need not be in the US and can be from any country. On the other hand, the US agent is not involved in the device submissions and approvals. However, foreign manufacturers can choose to appoint the same person as both the US agent and the official correspondent. In such cases, the entity shall fulfill the roles and responsibilities of both.

4. What are the responsibilities of a US agent?

The US agent will primarily be responsible for assisting any bilateral communication between the FDA and the manufacturer, and scheduling an FDA inspection.

US agents will respond to questions concerning the foreign establishment's devices that are imported or offered for import into the United States.

Suppose the FDA is unable to contact the foreign establishment directly or expeditiously. In that case, the FDA may provide information or documents to the US agent, and such an action shall be considered to be equivalent to providing the same information or documents to the foreign establishment.

5. Do the responsibilities of a US agent vary with the risk class of the device?

No, the roles and responsibilities of a US agent remain the same irrespective of the Class of a device manufactured in a given foreign establishment.

6. As a US agent, what information about the device and its manufacturing should one be informed about?

As per the US FDA, "The US agent has no responsibility related to reporting of adverse events (21 CFR Part 803), or submitting 510(k) Premarket Notifications (21 CFR Part 807, Subpart E)." The manufacturer should keep their US agents informed about any post-approval changes, revisions in the device version, changes in manufacturing sites, labeling and packaging, and/or any change concerning the registration and listing of medical devices. The official respondent would be key to any post-approval change notifications submitted to the US FDA.

7. Is it mandatory to notify the US FDA about the US agent details?

Yes, the foreign manufacturer is required to update the US agent's details in the FDA Unified Registration and Listing Systems (FURLS). Information such as name, title, business name, address, phone, fax, DUNS number, and email of the US agent is required to be submitted.

8. When should a foreign medical device manufacturer appoint a US agent?

Foreign manufacturers must designate a US agent to carry out the establishment registration, device listing, and other activities, which must be completed before importing the device to the US. In the case of the 510(k) exempted Class I and II devices, the US agent can be appointed right away, followed by an establishment registration, device listing, and importation into the US.

For Class I and II devices without 510(k) exemption and a few Class III devices subject to premarket notification, they shall be 510(k) cleared before appointing the US agent and carrying out the establishment registration and device listing activities. Likewise, a few Class II and III devices are subject to premarket approval and must secure the PMA, post which they can appoint an agent. The same would apply to other devices opting for the De-Novo, IDE, and HDE submissions.

9. Can a foreign manufacturer appoint their distributor or importer as a US agent?

Yes, a foreign manufacturer can choose to appoint their distributor or importer as a US agent. The manufacturer shall evaluate potential conflict of interest or biases on their role as distributor or importer and their Regulatory obligations as a US agent. Alternatively, independent third parties such as Regulatory service providers can be appointed as US Agents. Though there is an additional cost involved, they ensure confidentiality and offer dedicated and professional US agent services without any bias or conflict of interest.

10. Is it possible to change my US agent at any given point in time?

Yes, the foreign manufacturer can change their US agent at any time. Change of the US agent will not affect the registration or business.

Even if the device is being actively imported and marketed in the USA, the manufacturer can choose to change their US agent. Details of the newly appointed US agent like the name, location, contact information, business name, address, etc., must be updated in the FURLS system, followed by a confirmation via email verification.

11. How to change US agent information in the FDA registration?

- Login to your account
- Update information in the US agent section
- Submit the registration
- The US agent will receive notice from the FDA for confirmation

12. Is it possible for a manufacturer to appoint different US agents for different products?

As per the US FDA, for each foreign establishment, only one (01) US agent can be designated. However, If two (02) products are being manufactured in different establishments (one (01) in each), the manufacturer can appoint different US agents. If the products are manufactured in the same establishment, only one (01) US agent should be appointed. On the flip side, if one (01) product is manufactured in two (02) different establishments, the manufacturer can appoint two (02) different US agents (one (01) for each establishment) for the same medical device.

13. My device is GMP-exempted. Do I need to appoint a US agent?

Most Class I and some Class II devices are GMP-exempted while others must comply with GMP. However, the exempted devices are subjected to general requirements, and appointing a US agent is one of the requirements. Hence, irrespective of whether a device is GMP-exempted or not, all foreign manufacturers must appoint a US agent.

14. I am a medical device component manufacturer. My products are imported by a re-packager for assembling the final finished device. Do I have to appoint a US agent?

Yes, as per the FDA's definition, any foreign establishment which is involved in manufacturing, preparing, propagating, compounding, or processing a medical device is required to appoint a US agent. Thus, even if you are selling the component of the medical device (which will fall under compounding) in the US, it is mandatory to appoint a US agent.

15. I am a medical device specification developer and not engaged in manufacturing activities. The products are manufactured at a CMO site and exported to the US. Do I have to appoint a US agent?

Yes, the specification developer is also subjected to establishment registration and is required to appoint a US agent as well as an official correspondent.

As per the FDA, any person who initiates or develops specifications for a device that is to be manufactured by a second party requires establishment registration and listing. The FDA requires the specification developer of the foreign establishment to register with the FDA before doing business in the US. Therefore, the specification developer is also subjected to appointing a US agent.

Global device manufacturers can tap the US medical device market, but only after all the US FDA requirements are duly fulfilled. One may obtain quotes from various service providers for US agent services. The quotes may vary significantly across different service providers as few may account for the initial establishment registration and device listing, and subsequent annual registrations, whereas others may account for just being appointed as a US agent. The foreign manufacturers, while appointing the US agent, must diligently discuss and negotiate the scope of the US agent's services and ensure that a comprehensive agreement is in place.

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CSV OR CSA? A COST-SAVING APPROACH IN 2022

Do you know? One can save up to a million in the coming three (03) years by introducing Computer Software Assurance (CSA) in place of the existing Computer System Validation (CSV) model!

Over the years, pharmaceutical organizations have incorporated CSV, a risk-based validation approach to ensure computer operating systems are at par with Regulatory requirements.

As the industry is now getting ready for the next transformation (next to a risk-based approach), that is CSA, the United States Food and Drug Administration (USFDA) is planning to release new guidance on CSA in 2022 to help organizations understand product quality and Regulatory compliance. The guidance is expected to give a clear understanding of how, where, and what measures need to be undertaken to conduct a successful Software Risk Assessment.

Let's now broadly discuss the comparison between CSV and CSA from a process, people, and technology perspective; and how a successful implementation of CSA can provide tangible benefits to an organization.

Process

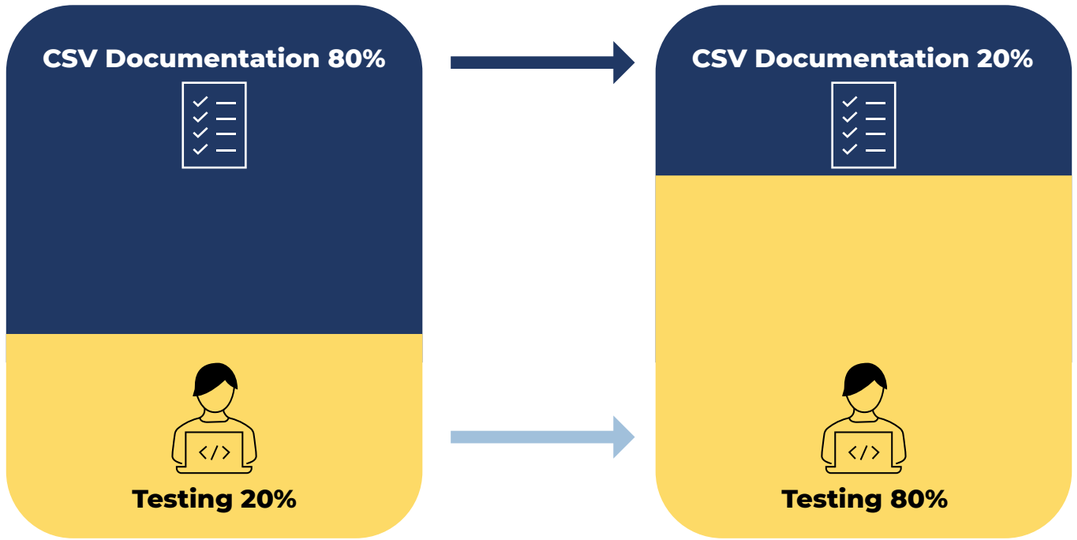
CSV is a compliance-centric documented approach that acts as evidence, ensuring the system is fit for the intended purpose.

An organization invests 80% of its effort into the documentation of the validation process and 20% in testing. Any discrepancies in the CSV testing in association with the expected results need documentation and corrective action plan implementation.

CSA is a quality-centric approach that emphasizes the impact software system has on patients' safety, product quality, and data integrity.

The main objective is to focus on validating and documenting safety-risk activities based on software complexity. Such an approach encourages the usage of digitization and automation, thereby improving product quality. The reduction in the documentation process helps organizations react to critical software issues and comply with the Health Authority (HA) guidance. CSA leverages the vendor quality systems for unscripted testing for validating low-risk systems, allowing organizations to invest their 80% efforts into testing and 20% effort into documentation. Hence, processes should be tweaked (amended) to reflect the CSA approach at different stages of SDLC, which can be achieved by:

- **Quality by Design (QbD)** - Prioritizing patient safety and product quality ensure the primary goal of the software system installed is to fulfill the user requirements to optimize product quality.
- **Risk-based validation strategy** requires vigilant testing and documentation for systems prone to failures/defects for direct risk cases and less for indirect or no risk cases.
- **Re-thinking on document versus testing** ratio enables the sponsors to redefine their validation process by asking them to spend 80% effort on testing and 20% effort on documentation.
- **Providing tangible benefits** by relaxing the documentation pressure.



People

The differentiating factor between CSV and CSA is in the hierarchy of strategy. CSV observes documentation followed by testing and critical thinking, while CSA observes critical thinking as the first step, followed by testing and documentation. CSV demonstrates documented evidence providing efficiency and effectiveness that a computerized system conducts activities according to pre-agreed specifications and quality attributes. On the other hand, CSA recommends the sponsor's trace process improvements to mitigate risk and possible errors.

At the leadership level, widen the scope of critical thinking by having multiple ways to deal with uncertain situations as there's no "one" right way of getting anything accomplished. Critical thinking will open doors for innovation to develop reliable products.
At the practicing and application level, train people and prepare them to transform and adapt to CSA via effective collaboration and effective training programs.

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Technology Perspective

Comprehensive guidance on CSV is already in place as per Regulatory Authorities like the USFDA, EMA, MHRA, and many more. So, do we need CSA? The answer is yes. CSA will put the objective of validation into perspective and will clear the disparity between sponsors and HAs. There are adequate regulations and industry guidance arrangements that pharmaceutical organizations need to understand to get business benefits by simplifying the approach of the validation process. Transitioning from traditional CSV to CSA shifts the organization's priority from fulfilling the Regulatory compliance needs to product quality and safety. Such a shift maximizes the effect of the validation process by reducing the extensive documentation burden, project timeline, and costs on Life Science companies.

At the strategic as well as operational levels, this can be achieved by encouraging digitization and automation, and mitigating all the possible risks and human errors.

Conclusion

As the US FDA's guidance on CSA is yet to be published, pharmaceutical organizations should proactively start thinking and chalking out protocols for transitioning from CSV to CSA. The organizations must:

- Re-evaluate and identify systems having a direct and indirect impact on patient safety, product quality, and data integrity
- Allocate resources capable of ensuring a smooth shift in the validation process
- Conduct gap analysis assessment against the existing system to identify any discrepancies

Assessment of the validation approach tells what an organization can do to effect change when they encounter any system issue. Proper execution of the CSV process requires an in-depth understanding of the system and insights into the ways to utilize it.

The need of the hour for organizations is to partner with CSV experts in moderating simple to complex projects and who can aid in a smooth transition from CSV to CSA. A quality review framework minimizes re-work in the product and vendor validation process to ensure total compliance and validation at any stage during deployment, maintenance, and decommissioning at an extremely competitive price. Reach out to Freyr for compliance.

REGULATORY INTELLIGENCE (RI): THE FOCAL POINT OF YOUR BUSINESS

Introducing innovative products across global marketplaces is imperative for Life Sciences companies to ensure profitability and maintain their presence in the market. Regulatory compliance and authorizations being the key factors behind any winning launch, inadequate Regulatory information can trigger an increase in costs and time-to-market.

With well-managed compliance data management, the Life Sciences industry can handle the initial risk, but it is required to be governed continuously with evolving regulations. A comprehensive Regulatory Intelligence (RI) role by harnessing the power of data is an apt approach for your future business decisions.

Current Challenges in the Industry

Regulatory Intelligence offers strategic excellence to address the current challenges in the industry, such as unstructured free text, inconsistent data quality, inefficient processes, constantly growing data volume, multiple translations, and information sources.

With the change in the world and so much emphasis on data, it is becoming essential for Regulatory-based organizations to focus on monitoring data intelligence and analyzing any product in detail.

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Regulatory Intelligence Competency Maturity (RICM) helps in measuring the competency of RI in the current scenario. Let us look at some of the Regulatory Intelligence competence parameters:

Competency Parameters	Initial	Evolving	Mature
Data Collection	S, M	L	
Data Repository	S	M, L	
Data Monitoring	S	M, L	
Up-down Integration	S, M, L		
Data-Driven Decision making	S, M, L		

S- Small companies M-Mid-size companies L- Large Companies

1. **Data Collection:** Data collection is often manual in small-medium level companies with slight evolution in large companies. There is no specific benchmarking on data quality, and the content is often not curated & limited to key products/markets. For large organizations currently lying in the evolving stage, there are certain bot-driven data scraping defining the QC process.
2. **Data Repository:** Data repository is properly maintained for medium and large organizations. However, for small companies, no single repository exists. For small organizations, the data repository is maintained in regular spreadsheets or local databases, and for medium and large, it is managed in a centralized spreadsheet with a limited key to markets and Health Authority (HA)-issued regulations.
3. **Data Monitoring:** Data monitoring is often passive and asynchronous in small-size companies, whereas there is some level of automation in medium and large-size companies. The frequency of data monitoring is set to pre-set rules and is initiated by internal teams manually.
4. **Upstream & Downstream Integration:** Most of the product information in the small, medium, and large-size Life Science companies exists in standalone systems. Access to integrated information is often manual and time-consuming.
5. **Data-driven Decision-making:** In all industries, the current capability lies in decision-making capability for basic data translation, often limited due to the lack of integrated information available. Dashboarding & visualization of key information are often manual for small, medium, and large organizations.

For systematic data collection, monitoring, and data-driven decisions, automation with AI/ML is required to be integrated within the system. Integration of Regulatory Intelligence solutions is required for holistic decision-making, and the great promise of RI in technology and Life Sciences brings modernization with the improvement of relevant data.

The key results of RI in the Regulatory industry lie in timely submissions, efficient approval, better decision-making for turnaround time, compliance, and proactive marketing strategy. Freyr enables the Regulatory industry to adhere to the HA regulations and leverage data by accelerating advancement through interactive dashboards and reports. Freyr IMPACT – an in-house Regulatory Intelligence platform infused with automation and Machine Learning - brings innovation in the Regulatory world with hidden insights into data and advanced intelligent solutions.

To know more about how Freyr IMPACT can accelerate intelligence-driven decisions in your business, contact our digital transformation experts.

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LABELING CLAIMS FOR FOOD AND FOOD SUPPLEMENTS IN THE USA

Food labeling claims in the USA can differ based on factors like types of claims, the product of interest, and usage. They are also different for animal food, human food, and dietary supplements. The regulations and scientific standards ensure the labeling claims for Food and Food Supplements (FDS) are mentioned correctly and substantiated scientifically.

Understanding the Regulatory framework behind these claims helps take better steps toward FDS.

Types of Claims

The labeling claims for food products are categorized into three (03) groups as per the FDA regulations. These can be used on food, food components, and dietary products.

Health Claims

All the diseases or health conditions related to food, food components, and dietary ingredients are categorized under these claims. Health claims must be supported by the "Significant Scientific Agreement (SSA)," proposed by the experts in Food and Drug Administration (FDA).

Health claims are further sub-categorized into three (03) types as listed below.

- NLEA-authorized Health Claims
- Health Claims Based on Authoritative Statements
- Qualified Health Claims

Nutrient Content Claims

Nutrient content claims include the level of nutrients present in food products and dietary supplements. These claims are also used to compare the level of nutrients in the food

Structure/Function and Related Dietary Claims

This category of claims focuses on the nutritive and non-nutritive effects of food components and dietary supplements. The effect of any food product on the body is mentioned clearly and tested under these claims. The FDA usually doesn't require the manufacturers to notify about these claims.

Are you willing to market your food products in the USA? Ensure understanding of the compliance best practices for labeling claims. Reach out to Freyr for a cost-effective claims review for all categories of FDS in the USA.

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WHAT IS SFDA/ CFDA/NMPA?

The pharmaceutical sector is one of the most highly regulated sectors globally. The industry directly deals with human lives, making it even more crucial and sensitive. Therefore, every country has its own rules and regulations to protect the health of its citizens. National governing bodies establish national Health Authorities (HA) indigenous to that country for quality assurance and regulation of drugs.

At present, China's Regulatory Authority is the National Medical Products Administration (NMPA). But the NMPA has a significant history.

China's first Health Authority formed in 1998 was State Food and Drug Administration (SFDA), founded based on State Drug Administration. The SFDA majorly regulated food items, cosmetics, and drugs. It was under the legislation of the State Council.

Later in 2013, restructuring and rebranding of the SFDA were done, leading to the formation of the China Food and Drug Administration (CFDA). The CFDA was a ministerial-level agency that supervised food, drugs, medical devices, cosmetics, and health food.

In 2018, CFDA was reorganized and renamed National Medical Products Administration (NMPA). The NMPA comes under the legislation of the State Administration. The NMPA focuses on drafting laws and regulations for drugs, medical devices, and cosmetics.

The NMPA has stringent requirements for a drug to register in China. Along with this, the procedure is lengthy and slow.

However, we can help you overcome the drug registration challenges in China. If you are experiencing a tough time juggling the terminology and challenges, please reach out to Freyr.

SERIALIZATION - A KEY TENET

With serialization legislation introduced in two (02) major drug markets, namely, the USA and the EU, the pharma industry is being forced to take action on a large scale. On the other side, people are slowly realizing the benefits that serialization could bring in terms of patient safety and supply chain management. The mandates to serialize drugs are driven in large part by a need to secure supply chains. In response to increasing concerns about drug integrity, over forty (40) countries have introduced laws that require the serialization and tracking of drug products when they cross supply chains. In addition to making products easier to track, pharmaceutical serialization allows officials to identify illicit products more effectively across the supply chain.

Serialization is intended to counteract illegal activities by tracking the prescription drugs' journey throughout the supply chain, from manufacturing to dispensing. As of November 2017, all drug companies selling prescription drugs in the US were asked to serialize every single, individually sold drug unit to facilitate tracking from the manufacturers to the pharmacies or doctors' offices, according to the 2013 Drug Supply Chain Security Act (DSCSA). Pharmaceutical manufacturers are required to include the unique product ID on the packaging and cases of prescribed drugs. The unique identifier includes a product's batch number, shelf life, the National Drug Code, and serial number, making it easy to identify over its entire shelf life.

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To fight counterfeit along with other issues related to pharmaceutical supplies, governments across the globe have laid out regulations which say that boxes containing drugs must be coded with a unique serialized barcode for tracking capabilities. Pharmaceutical companies that are gearing up to comply with package serialization requirements are investing in technology that marks the package lines. Serialization devices and number-management systems must be installed and verified at the packaging lines.

Marking and vision systems are critical ingredients in the efforts to comply with the world's serialization requirements. But as companies begin (or continue) producing serialized products, several other areas also require attention. Serialization presents the transformative opportunity to revisit and where appropriate, update data flows and applications of the enterprise processes that run from manufacturing to supply chains, contributing to process interoperability. This requires IT facilities capable of creating, storing, capturing, and communicating millions of serial numbers across multiple supply chains and updated analytics, supporting tracking and recall. Consequently, the quality of the master data will only grow in importance.

The regulations provide a major source of concern to drug companies in adherence to a central principle of regulation - which is of full confidence that the supply chain has the best possible code, as well as the possibility of detecting through rejection, damage, or some other classification, that which is not fit to use for commercialization. In the identification of optimal serialization architectures at both the networking and packaging line levels, a key tenet has been the notion - that all codes are issued on a line-level.

With serialization, the focus has evolved to producing identical units, identifying each unit with unique data, communicating that data to supply chain partners, and then, depending on your supply chain role, potentially accounting for that data for several years.

It is time for drug companies, and if they still haven't, and their supply chain partners, including their contract manufacturing and packaging partners, to set expectations and start the process for serialization projects. In many ways, working with more partners will make serialization more difficult for pharmaceutical companies and their contract partners alike.

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DOES THE PRIME PATHWAY BENEFIT YOUR NEW CHEMICAL ENTITY (NCE)?

Unmet Medical Need (UMN) is one of the most pressing priorities of health systems. Constantly evolving science and technology around healthcare have harbored the potential to explore various therapeutic options. Health Authorities (HAs) encourage innovative therapies that promise significant benefits to patients' quality of life. Building upon prioritizing innovation and targeting unmet patient needs for drug development, the European Medicines Agency (EMA) introduced the PRIority MEdicines (PRIME) pathway in 2016. Since then, the PRIME pathway has been a method for granting approvals for innovative therapies on an accelerated timeline. This type of facilitated pathway can be explored by any company, ranging from start-ups to mid-sized biotech to large multinational organizations. However, qualification for the pathway is limited to products under development and yet to apply for marketing authorization through the centralized procedure. The qualifying criteria are applied rigorously. Between March 2016 and April 2022, only 24% of the applications received the endorsement, whereas 72% of PRIME applications were rejected. Of the 24% that were selected for the PRIME pathway, the majority belonged to the oncology therapeutic area.

Innovators pursuing market authorizations of rare diseases or orphan drugs may often have limited datasets available by way of evidence to support their novel drug applications, as required by regulators. Applications for Advanced Therapy Medicinal Products (ATMPs) and orphan drugs usually face such challenges. Due to limited patient population data, constant interaction with regulators is encouraged to enable better insights for scientific review and approval requirements. The PRIME pathway can be useful for such therapies due to the early involvement of regulators in providing proactive support and guidance for data gathering and benefit-risk assessment.

Merits of Following the PRIME Pathway

- Helps innovators to develop a well-drafted development plan.
- Benefits innovators by engaging the HAs at the early development stage; this contributes to drafting high-quality market authorization applications.
- Speeds up overall evaluation by reducing the average

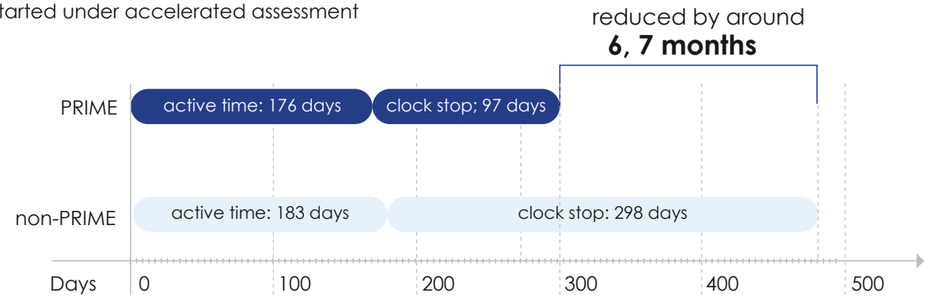
evaluation time so that medicines can reach patients more quickly.

- Supports innovators to focus their attention on the development of medication to improve patient outcomes and address unmet patient needs.

Evaluation Time in Detail

Average evaluation time

Evaluation time for SME products
Which started under accelerated assessment



257 days
average evaluation time for **PRIME medicines**, which started under accelerated assessment

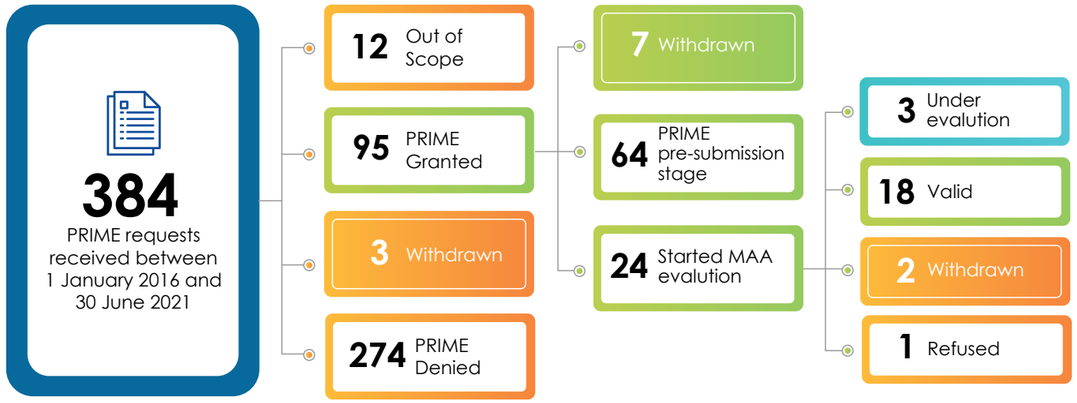
310 days
average evaluation time for **PRIME advanced therapies**

333 days
average evaluation time for all **new actice subtances** (in 2020)

For the Five (05)-year report on PRIME, visit the EMA website

Applications for PRIME Pathway

The PRIME pathway prioritizes unmet medical needs. Out of three hundred and eighty-four (384) PRIME requests received since March 2016, only eighteen (18) made it all the way through to marketing authorization by June 2021.



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Are you PRIME-ready?

The existence of the PRIME pathway is due to significant unmet medical needs and the focus on bridging the gaps by the European Medicines Regulatory Network (EMRN). To evaluate a product's suitability for the PRIME pathway, one must consider the following:

- **Findings:** Applicants must state the unmet medical need and provide a convincing argument on how their product will address the issue.
- **Potential:** Applicants must demonstrate the beneficial potential of the therapy in the unmet medical need criteria.
- **Pre-clinical data:** Applicants must present some data on the efficacy or performance of the therapy in the human biological system. Non-clinical models, however accurate, do not provide an exact overview of its behavior in the human biological system.
- **Stage of development:** Applicant must identify the right stage to enter the PRIME pathway to gain optimum guidance from the regulators and proceed further with the application.

Post the PRIME Grant

Once an applicant has been granted the opportunity to enter the facilitated route, the EMA will:

- Assign a rapporteur from the Committee for Medicinal Products for Human Use (CHMP) or the Committee on Advanced Therapies (CAT) in the case of advanced therapies.
- Organize a kick-off meeting with the CHMP/CAT rapporteur and a multidisciplinary group of experts to provide guidance on the overall development plan and Regulatory strategy.
- Assign a single point of contact for the applicant.
- Provide scientific advice at every key development milestone, involving an additional set of stakeholders such as health-technology-assessment bodies to fast-track access for patients to the new medicine.
- Confirm potential for accelerated assessment at the time of an application while considering marketing authorization.

Is your application for the Priority MEdicine pathway ready (PRIME-ready)? Contact Freyr today and evaluate. Learn more about how we can help with your Regulatory strategy and PRIME pathway designation. Stay informed. Stay compliant.

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ePI LABELING - AN OVERVIEW

In 1999, the European Medicines Assessment Agency (EMAA) and the European Federation of Pharmaceutical Industries and Associations (EFPIA) set out to design a new system to share product information electronically to support the submission of new products or variations post-approval. This was called Product Information Management (PIM), which was withdrawn in 2011.

We have come a long way in the journey of Product Information (PI) and Quality Review Documents (QRD) since then.

Inspired by the projects conducted in Belgium and Luxembourg to assess the efficacy of electronic patient information leaflets, as well as by key principles created by the European Medicines Agency (EMA) and Heads of Medicines Agencies (HMA), the European Association of Hospital Pharmacists (EAHP) conducted a survey about ePI usage in the European hospitals. For the EAHP, therefore, it was highly relevant to know more about the use of the electronic patient leaflet and about the future potential of electronic Product Information (ePI). The development of the ePI is intended to enhance the availability of relevant product information about medicines, whenever and wherever needed.

European regulators announced in February 2022 that they had adopted a generic ePI standard for human medicines, which users and providers can access.

The ePI is advantageous in that it can be updated immediately and shared with stakeholders, rather than having to wait for the formatting and printing of the new information, officials from the EMA said in a statement.

The EMA, competent national authorities, and the European Commission (EC) are conducting a pilot project for ePI in order to pilot the use of the common EU ePI standard in Regulatory procedures.

The common standard on the ePI of the EU will support the harmonized provision of ePI on medicines across the EU, and according to the EMA, it is a step toward improving information delivery for patients, consumers, and health professionals.

According to the EMA, the standard will also allow the wider distribution of impartial, up-to-date information about all medicines available to patients within the EU via an expanded array of electronic channels. This electronic format of information about approved medicines is the first step toward more effective and accessible sources of medical information. Its purpose is to develop and implement an electronic source for scientifically verified information about authorized medicinal products in the EU. With that goal in mind, developing ePI is an excellent opportunity to look more closely at medicinal product packaging, with a particular emphasis on harmonization throughout Europe.

For instance, Spain's Agency of Medicines and Healthcare Products (AEMPS) has already made ePIs available for a number of its national-authorized products. The recent European strategy for pharmaceuticals highlighted how better the use of ePI could ease drug information provision for health professionals and patients within a polyglot EU context and supports wider drug availability in the member states.

Here is where ePI gets really interesting...

Information on packages to patients is being moved to an electronic format, eliminating the need for paper inserts. Digital patient inserts can save weeks in packaging because packaging can happen as regulators are reviewing the final information on a package rather than later.
Electronic information could provide patients and healthcare professionals with enhanced information that goes beyond the data currently listed in paper versions.

Scan triggered, automated medicine reminders, guiding videos on how to take medicines, visual experiences on health coupled with the pill, and all the information available in any language at your fingertips, are just some of the few benefits that come to mind when you think of ePIs.

An ePI, although currently only regional, opens up a huge opportunity in patient engagement and thus brings in better patient education on safe and fair use of medication as it takes over Europe.

Are you currently in plans to adopt the ePI format for your products? Contact Freyr for the best compliance practices.

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WHAT IS JPAL?

JPAL stands for Japanese Pharmaceutical Affair's Law. The JPAL establishes regulations covering the manufacturing and distribution of medical devices and pharmaceutical products in Japan.

Compliance with local laws can be one of the most challenging aspects when doing business in a foreign country. The JPAL intends to harmonize requirements and reduce conflicting demands by incorporating the guidance documents of the Global Harmonization Task Force (GHTF).

Benefits of the JPAL at a Glance:

- Compliance with various safety measures and post-marketing safety measures such as Good Clinical Practices (GCP), Good Quality Practices (GQP), and Good Vigilance Practices (GVP)
- Compliance with the ISO 13485:2003
- Access to global markets
- Meeting the requirements of set standards and regulations
- Procuring leads against the competition for lead audits
- Minimized risk of company liability with formulated safety standards
- Compliance with the local government and legal requirements

What are the Components of the JPAL Regulations?

The two (02) components of the JPAL regulations that are quintessential to doing business in Japan are "Kyoka" and "Shonin":

- Kyoka - The Marketing Authorization Holders (MAH), manufacturers, repairers, and distributors are required to submit a business license. In case the manufacturing facilities are located outside of Japan, the foreign manufacturing facilities are required to produce a Foreign Manufacturer Accreditation (FMA) instead of a Manufacturer License.
- Shonin - To market medical devices in Japan, the MAH is required to register the device through the following procedures:
- Pre-market submission (Todokede) – Class I medical devices
- Pre-market certification (Ninsho) – Class II medical devices
- Pre-market approval (Shonin) – Class II, III, and IV medical devices

Understanding the JPAL is fundamental to having an aligned presence in the Japanese market and providing manufacturing services to its pharmaceutical industry in collaboration with the local laws and regulations.

Having a blueprint of the local laws before entering the market influences the market-entry strategy heavily.

With Freyr's expertise, you can have a one-stop service to overcome all these challenges in the Japanese market. Consult Freyr's experts and get a clear understanding of the pharmaceutical laws in Japan for a better transition in the marketplace.

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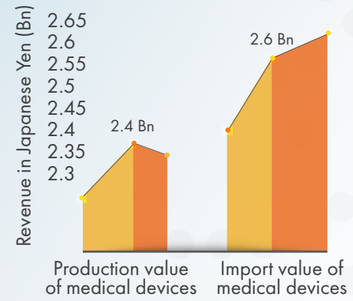
Infographic 1

Medical Device Risk-classification and Registration in Japan

DYK? Japan is considered as the third-largest market for medical device industry followed by USA and China. It is home to eight (08) out of the ten (10) biggest APAC-based medical device manufacturing companies.

Quick facts



Japan is highly dependent on imports with 49% of the total revenue being generated by sophisticated devices imported from global companies.

Device risk-classification in Japan

Japan follows a risk-based classification system for medical devices depending on the severity of the risk to the patient.

Class I	Class II	Class III	Class IV
Extremely low risk	Low risk	Medium risk	High risk
E.g., scalpel, X-ray films, etc.	**E.g., MRI, ultrasonic devices, etc.**	**E.g., dialyzers, etc.**	**E.g., pacemaker, stent graft, etc.**
Registration pathway- Notification/ Self-declaration	Registration pathway- Third Party Certification & Approval by MHLW	Registration pathway- Third Party Certification & Approval by MHLW	Registration pathway- Approval by MHLW

Device registration pathway in Japan

Pre-market Submission *(Todokede)* 届出

- Registration of low-risk Class I general devices
- Pre-market submission to the PMDA
- Timeline for approval: 1 month
- Agency for approval: NA

Pre-market Certification *(Ninsho)* 認証

- Registration of low/medium-risk Class I specified controlled devices
- Devices with certification standard (JIS), are subject to pre-market certification
- Timeline for approval: 3-5 months
- Agency for approval: Notified Body

Pre-market Approval *(Shonin)* 承認

- Registration of Class II controlled medium-risk devices, Class III highly controlled medium/high-risk devices and Class IV highly controlled high-risk devices
- Devices without certification standard (JIS), are subject to pre-market approval
- Timeline for approval: 9-16 months
- Agency for approval: PMDA

The device registration process in Japan is tedious, costly, and time-consuming.
The main factor determining the duration of device registration is the classification of the device.

To know more about Japan's medical device registration process

Talk to our Regulatory experts now!

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Infographic 2

Food Notification Process in Japan - An Overview

HERE IS A QUICK OUTLINE OF THE FOOD NOTIFICATION PROCESS IN JAPAN

1. **Appoint Responsible Person in Japan**
2. **Check Food Formula and Ingredients**
3. **Compile Product Information**
4. **Ensure Label Compliance**
5. **Submit Food Notification to Quarantine Officer/MHLW**
6. **Launch Your Product**

Decode Japan's notification process in detail. Contact Freyr today.

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Global Cosmetics Regulatory Services

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Infographic 3

NOTIFICATION PROCESS OF COSMETIC PRODUCTS IN JAPAN

As one of the leading economies of Asia, Japan is a preferred market by Cosmetic manufacturers across the globe. The Ministry of Health, Labour, and Welfare (MHLW) under the PMD Act, is responsible for regulating Cosmetics in the country.

IN JAPAN, COSMETICS ARE CLASSIFIED AS

COSMETICS

- **GENERAL COSMETICS** (haircare and skincare products)
- **QUASI DRUGS** (products used for skin whitening and acne treatment)

HERE IS A DETAILED PROCESS FOR COSMETICS NOTIFICATION IN JAPAN

1. Appoint a Responsible Person in Japan
2. Check Cosmetic Formula and Ingredients
3. Compile Product Information and Manufacturer Information
4. Ensure Label Compliance
5. Submit Cosmetic Marketing Notification Application Form to the Local Officer
6. Launch your product

To decode the notification process in detail, and for compliance best practices

Consult More

Center of Excellence
Global Pharmaceutical Regulatory Services

SUCCESSFUL ANDA AND PADER SUBMISSIONS WITH ZERO DEFECTS

Client
USA-based Global Leader in the Generics Industry

Health Authority
USFDA

Freyr CoE/Products
Publishing & Submissions

Service Offering
ANDA and PADER Submissions

Industry
Pharmaceuticals

Service Region
USA

Client Location
USA

Therapeutic Area/Indication
Bacterial Infections

BENEFIT HIGHLIGHTS

- Successful Original ANDAs and Supplements
- PADER Submission with Zero-deficiency Comments from the Client
- Increase in Cost Benefits by 70%

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Business Imperatives

- Original ANDAs, supplements, and PADER applications were to be filed and sent to the Agency
- Client was looking for quality submissions to be delivered in swift timelines

Challenges

- Reviewing of all the study documents as per the FDA PDF specifications, including content issues and getting revised versions of all the eCTD-incompatible documents
- Taking care of end-to-end publishing activity, from coordinating with the CRO for study documents to the final ESG submission
- Last-minute document changes

Freyr Solutions & Services

Freyr also provided a diverse set of services that included:

- Granular Document Level Publishing (DLP)
- Detailed tracker creation to track all the version changes made throughout the publishing cycle
- Validation using appropriate industry-accepted/Agency-recommended tools
- Rigorous quality checks performed at every step of the process

Client Benefits

- Provided valid submissions compliant with the Agency requirements, with zero errors and warnings
- Reducing overall turnaround time
- Cost benefits upwards of 70%

Case Study 2

RIMS SUPPORT FOR A JAPAN-BASED HEALTHCARE ORGANIZATION

Client
Japan-based Global Healthcare Organization

Health Authority
Health Authority of Targeted Region/country or Multiple

Freyr CoE/Products
Freyr SPAR

Service Offering
eLearning Modules for RIMS application

Industry
Pharma/Biologics/ Medical Devices/F&FS/ Chemicals and Biocides/OTC/Innovators

Service Region
Global

Client Location
Japan

Therapeutic Area/Indication
Oncology, Cardiovascular, Infectious, Diagnostics, etc.

BENEFIT HIGHLIGHTS

- Efficient time management
- Effective training material for ease and comfort of the user
- Real-time examples for ease of understanding.

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Business Imperatives

- The scope of the project included creation of eLearning modules as training material for RIMS

Challenges

- Organization is spread across multiple time zones making it difficult to arrange sessions for all the employees
- Organizing trainings and refresher trainings for employees in multiple times
- Difficulty to include large number of employees in such trainings at a time as availability of all the employees can be an issue
- Non availability of a product expert to provide demonstrations of the RIMS after the trainings are over
- Even after attending trainings, employees may still have doubts while handling the real-time scenarios

Freyr Solutions & Services

- With eLearning modules, employees can train themselves about the RIMS as many times as they need
- There will not be any issues of organizing trainings to include large number of employees. All the employees can get self-trained as per their availability
- As eLearning modules will be readily available with employees, they can go back to the relevant section anytime they have doubts

Client Benefits

- Efficient time management for trainings
- Effective training material divided into multiple modules for ease and comfort of the user
- Readily available audio-video demonstrations with real-time examples for ease of understanding
- These eLearning modules provide complete and clear demonstrations of all the activities to be carried out while handling the RIMS

Client **Testimonials**

I just wanted to send you a quick note to let you know that Freyr's resources have really stepped up this week. They are working on a submission that is taking an incredibly long time to prepare. They worked late last night and continued to plug away at it this morning. They have kept a positive attitude and have displayed true professionalism. I appreciate all that the publishers do for us, but I wanted to let you know how they have gone above and beyond this week.

Director, Regulatory Affairs Operations
A US-based Pharmaceutical Company

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I am highly satisfied with everyone I interacted with. Everyone supported us even when they had to go out of the way. I can define the Freyr organization as the symbol of professionalism and work ethics. It is my pleasure to work with Freyr, and I hope to continue working and build a stronger relationship. Thank you, Freyr and everyone. We will definitely continue to work with Freyr.

Sole Member
New Jersey-based Supplier

Thank you very much for the report. It is very clear and helpful. I have received the information I was looking for and am now able to address our challenges!

Regulatory Affairs Specialist
A Denmark-based Food Ingredient Manufacturing Company

We want to thank the entire Freyr's team for presentation, explanation, and dedication. We very much appreciate having a partner to address our questions, inquiries, and most of all, getting answers. Thank you so very much!

Quality Manager
A Romanian Food Manufacturing Company

I just wanted to say how pleased we are with Freyr and one of their team member's works. They have quickly come up to speed and doing a great job. Thank you for listening to our needs and finding such a great match.

Senior Director,
Specialty Regulatory Affairs
US-based, Global, Pharma Company

Thank you for sharing the FSSAI's updated information regarding Vegan certification. Very much satisfied with the services and the whole team working on our project. Also, I would appreciate it if Freyr could share FSSAI's updates specific to alcoholic beverages.

Co-founder
India-based, Leading Food & Beverages Company

I'll add my personal thanks and appreciation for all the good work and the extra efforts you have put in to support the NDA submissions. I really appreciate your expertise and accountability.

Thank you for a job well done.

CEO & President
US-based, Leading Innovator Pharmaceuticals Manufacturing Company

Webinars

Freyr
Webinar Series

In a view to make the industry understand the most recent updates of the Health Authorities and to ensure they follow the best practices for compliance, Freyr has conducted on-demand webinar sessions on following topics:

Decode the Cosmetic Regulatory Landscape of the UK

November 10, 2022

eCTD 4.0 - Preparing for the future of submissions with Freyr SUBMIT PRO

November 17, 2022

Regulatory Outlook on Food and Food Supplements in the EU

October 17, 2022

Abbreviated SmPC: A New Take on Promotional Materials in the EU

October 28, 2022

Know More

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Kindly note that the Regulatory scenarios and mandatory deadlines discussed in this Issue may be altered in the near future. It might be due to the current Pandemic outbreak or the periodic health authority updates. Hence, it is probable to find different perspectives/opinions in comparison. Kindly be aware.

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About Freyr

Freyr is one of the largest, global, Regulatory-focused solutions and services companies for the Life Sciences industry, supporting Large, Medium, and Small size global Life Sciences companies (Pharmaceutical | Generics | Medical Device | Biotechnology | Biosimilar | Consumer Healthcare: Cosmetics | Food Supplements | Chemicals) in their entire Regulatory value-chain, ranging from Regulatory Strategy, Intelligence, Dossiers, Submissions, etc. to Post-approval/ Legacy Product Maintenance, Labeling, Artwork Change Management, and other related functions. Freyr is also expanding its footprints into other key areas like Pharmacovigilance.

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