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CONNECT

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2023

Throwback 2022
A Regulatory Perspective

2023 and Beyond
A Regulatory Heads-up

REGULATORY: INTELLIGENCE | AFFAIRS | LABELING | ARTWORK | SUBMISSIONS | COMPLIANCE AND AUDIT | MEDICAL WRITING | SOFTWARE | CONSULTING

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What's INSIDE?

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FOREWORD

Dear Patrons,

Greetings! Wish you and all your loved ones a **very happy new year!** Your continuous support has made **Freyr CONNECT one of the preferred Regulatory Intelligence assets.**

Thank you, and on that note, we are excited to bring you a brand-new Issue of

Freyr CONNECT Vol 10. Is 3.

2022 was all about tremendous growth and excitement at Freyr. We have:

- added **260+ new customers** to our portfolio
- started and doubled our **operations in numerous countries such as China, Japan, Australia, Mexico, and Brazil**

With that highlighted, we are stepping into 2023, furnishing the best of Regulatory Intelligence. We begin with a brief insight into the 2022 Regulatory landscape, followed by a roadmap of where it is going to be in 2023 (in terms of regulations and mandates to be followed). Later on, you can find insights on the most discussed industry topics like nanocosmeceuticals, eCTD 4.0, ICH Q12, AI in medical writing, child-resistant packaging, etc.

With all said and done, we hope that this latest Issue imparts a better Regulatory perspective to reevaluate your strategies. We intend to make it more insightful and tailored to your information requirements with every Issue. Help us make it one with your valuable feedback.

Happy reading, and once again, a **very happy new year** to you and your loved ones! Cheers to the good times ahead...

Best Regards,

Suren Dheenadayalan

CEO

Center of Excellence
Regulatory Intelligence

Lead Story

THROWBACK 2022
A REGULATORY PERSPECTIVE

The year 2022 has been all about getting back to normalcy and continuing to work tirelessly toward meeting our business goals with the help of technological advancements. As with any other industry, the Life Sciences sector has also adopted automated processes based on Machine Learning and Artificial Intelligence and implemented enhanced software solutions to ensure the best results in stringent timelines.

FREYR CONNECT

Whether medicinal products, medical devices, consumer goods, or food and food supplements, the Regulatory aspects of the Life Sciences industry have been dynamic in nature. Major global Health Authorities (HAs) modified the regulations and have released several guidelines, mandates, and deadlines for guiding the industry. Relooking at them might quickly give us what we have passed through and what kind of Regulatory best practices we should keep up with in 2023. Let us take a segment-wise look at some of those Regulatory updates from 2022.

PHARMACEUTICALS
REGULATORY UPDATES 2022

NMPA Announced the Use of Electronic Certificates of the Documentation for the Export of APIs to the EU and Certificate of a Pharmaceutical Product

Electronic certificates of the documentation for the export of APIs to the EU and the certificate of a pharmaceutical product have been enabled from December 01, 2022, while the National Medical Products Administration (NMPA) will still accept the paper version. The announcement was dated November 08, 2022, and it aims to streamline the business environment in China and enhance the administrative services for drug export companies.

China Patent Linkage System

In July 2022, the NMPA and the China National Intellectual Property Administration (CNIPA) released "Measures for the Implementation of Early Resolution Mechanisms for Drug Patent Disputes (Trial)." A patent registration platform for chemical and biological drugs and Chinese medicines, it is meant to increase the opportunities for market approvals of said products.

The patent registration system in China applies to both the Orange Book and the Purple Book, and there are specific exclusivity periods for each patent type.

DMA Revised 2022 Submission Deadline for MA and Clinical Trial Applications

As per the update from the Danish Medicines Agency (DMA) dated October 19, 2022, the deadline for submitting marketing authorization and clinical trial applications was December 20, 2022. The move came as the DMA was closed from December 24 to January 01, 2023, for the Holiday Season. Applicants had to abide by the new deadlines to get approvals for their applications on time.

ANVISA Approved Key Drugs and Vaccines in a Drive to Fight Against Monkeypox

Brazil was considered the Latin America region's Monkeypox hotspot as it had more cases than the other neighboring countries in 2022. Due to this, the National Health Surveillance Agency (ANVISA) approved the use of the vaccine Jynneos/Imvanex and the drug Tecovirimat for the treatment of Monkeypox in Brazil. The Agency reviewed and validated the data from the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) to grant the approvals.

Nitrosamine Impurity Confirmatory Testing by MAHs

As per the guidelines stated by the United States Food and Drug Administration (US FDA) to mitigate nitrosamine impurity, MAHs were obliged to submit the conclusions of the risk evaluations of all their product categories for chemically synthesized Active Pharmaceutical Ingredients (APIs) and biological APIs by the end of 2021. If the required documents weren't already submitted, the MAHs had to ensure the applications were submitted to the CMDh per the newly specified timelines.

The template released by the CMDh included two (02) case scenarios:

1. **If 'no risk is identified,'** MAHs must just submit step 1 only after reaching a conclusion about the products.
2. **If 'risk is identified'** in the product, the MAHs should go ahead and submit the step 1 response template and continue with step 2 confirmatory testing of the finished product.

The deadline for the completion of the confirmatory testing was **September 26, 2022.**

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).

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

- **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 health care data by increasing the scopes in terms of medicines, geography, etc.

US FDA's Final Guidance on Population Pharmacokinetics

After nearly two (02) decades of issuing the first draft guidance, the US FDA finalized the guidance on population Pharmacokinetics (PK) in February 2022. The latest draft explained the application of population PK in drug development and recommendations on therapeutic individualization. The guidance applies to Investigational New Drug (IND) applications, New Drug Applications (NDAs), Biologics License Applications (BLAs), and Abbreviated New Drug Applications (ANDAs).

EU Announced Clinical Trials Transformative Initiative

In mid-January 2022, the EC, the Heads of Medicines Agencies (HMA), and the EMA proposed a new initiative titled "Accelerating Clinical Trials in the EU (ACT EU)."

This initiative aims to strengthen the European environment for clinical trials and promote the development of high-quality, safe, and effective medicines. In addition, the initiative has priority actions for the year 2022-23.

TGA Guidance on Responsibilities of Medicines and Biologics Manufacturers

In early 2022, the TGA issued guidance describing the responsibilities of manufacturers of medicines and biologics. It is a step-by-step guide for:

- Australian manufacturers of therapeutic goods (medicines, Active Pharmaceutical Ingredients (APIs) and biologicals, human blood and blood components, and haematopoietic progenitor cells) applying for a manufacturing license for an Australian manufacturing site
- Australian sponsors of therapeutic goods manufactured overseas and applying for GMP certification of the overseas manufacturer
- Overseas manufacturers inspected by the TGA

MEDICAL DEVICES
REGULATORY UPDATES 2022

COFEPRIS' New Requirements for Online Submission of Medical Devices

In April 2022, COFEPRIS announced new rules for medical device submission. Until 2021, every application was printed, gathered, and submitted in physical copies in the submission window of COFEPRIS, including GMP certificate applications, modifications, renewals, warehouse licenses, etc.

COFEPRIS retained its digitalization processes through DIGIPRIS – a platform for procedures and Services of COFEPRIS. In early 2022, new modifications were included in the digital COFEPRIS submission system, which set new rules for registration, certification, post-approval changes, and renewals.

ANVISA's Updated Resolution for Brazilian Good Manufacturing Practices (BGMP)

The ANVISA came up with a new resolution, RDC 687/2022, for granting or renewing the Brazilian Good Manufacturing Practice (BGMP) certification for medical devices, and this has been in effect from June 01, 2022, annulling the RDC 183/2017.

According to RDC 687/2022, the criteria for certifications apply to manufacturers of Class III and Class IV medical devices and are as follows:

- Manufacturing site that manufactures the finished product in its name or for another company
- Manufacturing site performing the final release of the final product, related to at least one production stage, debarring design, distribution, sterilization, packaging, and labeling.
- Manufacturing site of Software as a Medical Device (SaMD)

Swixit - Regulatory Impact on Medical Devices & Med Tech Industry

The revised MedDO has been in effect since August 01, 2021, and it is compliant with the new EU Medical Device Regulation (MDR). All EU-based medical device manufacturers shall comply with the revised Medical Device Ordinance (MedDO). These companies shall appoint a Swiss Authorized Representative, and the representative must have access to a copy of the technical documentation or should be able to submit the documents within seven (07) days from the day as requested by Swissmedic.

The Swissmedic provided transitional timelines for various device categories for appointing a Swiss Authorized Representative (AR), including the corresponding labeling. All the EU-based manufacturers of Class IIb and IIa devices had to appoint a Swiss AR by March 31, 2022.

MDSAP and Device Registration in Japan

Japan's Ministry of Health, Labor, and Welfare (MHLW) updated its processes and procedures for accepting QMS audit reports from medical device market registrants under the MDSAP.

In the past, a document review and on-site audit were undertaken by the Japanese Regulatory Authority to receive a Medical Device registration certificate. With the official acceptance of MDSAP reports from April 01, 2022, the procedure has been streamlined because the Regulatory Authority will only be responsible for document review.

Class C & D Medical Devices & IVDs Registration with the CDSCO

Effective April 1, 2020, the status of a medical device in India expanded beyond the twenty-three (23) previously notified medical devices, requiring that all medical devices be registered under the Drugs and Cosmetics Act of 1940.

Beginning October 01, 2022, all Class A and B medical devices must have import licenses before importation.

Indication of the Manufacturer and CH-REP

Any foreign manufacturer that places medical devices and IVDs on the Swiss market must officially appoint a Swiss Authorized Representative.

Manufacturers of Class D IVD devices have already appointed their Swiss Authorized Representative (CH-REP) under IVDR. The last date these products can be placed onto the market without a CH-REP was until December 31, 2022.

COSMETICS
REGULATORY UPDATES 2022

European Green Deal and its Impact on the Cosmetics Industry

To address the growing source of waste, the European Union Commission proposed new EU-wide rules on packaging on November 30, 2022. Currently, 40% of plastics and 50% of paper is used for packaging purposes. When the new rules are implemented, the Commission aims to boost Europe's recycling capacity and achieve climate neutrality by 2050.

FOOD AND FOOD SUPPLEMENTS
REGULATORY UPDATES 2022

FSSAI Mandates Registration and Inspection of Foreign Food Facilities Effective from June 01, 2022

The Food Safety and Standards Association of India (FSSAI) announced new regulations to amend the existing Food Safety and Standards (Import) Regulations, 2017. The regulations came into force on November 06, 2021, and all the Food Business Operators (FBOs) started complying with change to them from June 01, 2022.

The FSSAI has included a new chapter for the registration and inspection of Foreign Food manufacturing facilities, which includes:

- Registration of Foreign Food Manufacturing Facilities
- Application Processing for Registration of Foreign Food Manufacturing Facilities
- Inspection of Foreign Food Manufacturing Facilities
- Issuance of Registration
- Suspension or Cancellation of Registration

Therefore, all foreign food manufacturing facilities must be compliant with the FSSAI regulations and register with the Authority to market their food products in India.

Health Canada Nutritional Labeling Regulation & Implementation Phases

On December 14, 2016, Health Canada published revisions to nutrition labeling, food color requirements, and the list of ingredients of the Food and Drug Regulations. The revisions intended to help Canadians easily understand the nutritional facts and list of ingredients to make informed choices. The major revisions include the following:

- New requirements for legibility of the list of ingredients
- Changes to the information in the Nutrition Facts table (NFt)
- Grouping of sugars in the list of ingredients
- Removal of the certification requirement for synthetic colors
- New requirements for declaration of food colors
- Incorporation by reference of daily values, reference amounts, serving sizes, templates for the Nutrition Facts table (NFt) formats, and food color specifications

Organizations have started complying with the new nutritional labeling provisions from December 14, 2022. Products manufactured in Canada, imported from other countries, or packed at retail before this date can remain in the warehouse and continue to be sold on store shelves.

Front of Pack Labeling (FOPL) Key Highlights from the FSSAI's Recent Update

The FSSAI published a major update on the Front Pack of Labeling (FOPL) on February 22, 2022, after a meeting with the stakeholders to decide the remaining issues related to 'Front of Pack Labeling' under the Chairmanship of the CEO, FSSAI. The FSSAI commenced the meeting with a presentation on the development journey of FOPL in India and the decisions taken in the last meetings.

Health Star Rating (HSR) has come out as the recommended FOPL format for Indian consumers based on IIM-A's survey report. Consumer organizations and the representative from the WHO opined that the FOPL should be made mandatory right from the inception, considering the rising status of non-communicable diseases (NCDs) in the country. They also suggested that, at the most, three (03) years may be given for such a transition.

Decode the FSSAI's New Labeling & Display Regulations

The Food Safety and Standards Authority of India (FSSAI) has divided the 'Food Safety and Standards (Packaging and Labeling) Regulations, 2011' into two (02) separate regulations: Food Safety and Standards (Packaging) Regulations, 2018 and Food Safety and Standards (Labeling and Display) Regulations. On December 14, 2020, a new regulation, named 'Food Safety and Standards (Labeling and Display) Regulations, 2020' was published in the Official Gazette.

The regulations prescribe the labeling requirements for pre-packed foods and display essential information about premises where food is manufactured, processed, served, and stored.

Food Business Operators (FBOs) have started complying with all the provisions of these regulations. As for chapter 3, the FBOs have started complying from July 01, 2022.

FSSAI Amends Labeling & Display Regulation - Makes INR (Indian Nutrition Rating) Mandatory on FOPNL of Food Products

The Food Safety and Standards Authority of India (FSSAI) released a draft notification on September 14, 2022, amending the Food Safety and Standards (Labeling & Display) Regulations, 2020. These regulations may be called the Food Safety and Standards (Labeling & Display) Amendment Regulations, 2022. It shall come into force on the date of their final publication in the Official Gazette.

Compliance shall be voluntary until forty-eight (48) months from the date of final notification of these regulations and is expected to become mandatory thereafter.

Health Canada has Announced Amendments to Nutrition Labeling, List of Ingredients, and Food Colors

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Health Canada has amended the nutrition facts table and list of ingredients on food labels to make them easier to understand and help Canadian people make informed decisions. A five (05)-year transition period, which ended on December 14, 2021, was provided to allow sufficient time for the industry to make the necessary changes to its labels. As of December 15, 2022, the CFIA has started the enforcement discretion for non-compliance and showed detailed plans on how to meet the new requirements at the earliest.

CHEMICALS
REGULATORY UPDATES 2022

EU REACH Information Requirements

The European Commission (EC) has revised the information requirements for registering chemicals under REACH. The proposed changes were effective from October 2022. The new changes will also impact the International Uniform Chemical Information Database (IUCLID). The next major change to the IUCLID includes modifications to its validation assistant and is all set to release in April 2023.

European Commission (EC) Published the Omnibus Act V

The European Commission (EC) published the Omnibus Act V which bans fourteen (14) chemical substances. Moreover, the update restricted Methyl Salicylate per category. Omnibus Act V has been effective from December 17, 2022.

Conclusion

A précis of the major 2022 Regulatory updates shows that the year has been eventful, promising, and evolving. Whether it is the announcement of new HA regulations globally or the adoption of digitization in the workflows and growth strategies by Life Sciences companies, the industry has had quite a busy 2022.

Center of Excellence
Regulatory Intelligence

2023 AND BEYOND: A REGULATORY HEADS-UP

Innovation and the ability to adapt to technological advancement are the vital factors that drive an organization's success. The Life Sciences sector accomplished several milestones in 2022 by adopting automated workflows, which resulted in enhanced market penetration. As we enter 2023, the industry looks forward to renewed prospects by embracing digital transformation in every aspect of the business.

FREYR CONNECT

As a leading, global, Regulatory solutions and services provider helping our clients in devising the best business strategies, we have listed a few Regulatory updates that impact the approach to achieve compliance and faster market entry. Here we give you a Regulatory heads-up of what to expect in 2023:

PHARMACEUTICALS
REGULATORY UPDATES FOR 2023 AND FURTHER

Getting Ready for Adoption of eCTD 4.0

Based on the Health Level Seven (HL7) standard called RPS (Regulated Product Submission), eCTD 4.0 brings in major changes and introduces certain substantial updates. The eCTD 4.0 aims at streamlining the review process of Regulatory information, which will continue to develop with each iteration of the eCTD, thereby benefitting the Regulatory submissions and publishing space.

The table below provides more details on the pilot and implementation dates for eCTD 4.0 region-wise:

Region	Technical Pilot	Implementation Dates
ANVISA, Brazil	2Q 2023 (Planned)	3Q 2023 (Production Pilot) 2023 (Voluntary)
EC, Europe	2023 CAPs (Planned)	TBD
FDA, United States	2022	2023 (Voluntary) 2028 (Mandatory)
Health Canada, Canada	2023 (Planned)	2024 (Voluntary) 2027 (Mandatory)
MHLW/PMDA, Japan	2Q 2021 (Completed)	2022 (Voluntary) 2026 (Mandatory)
Swissmedic, Switzerland	2023 (Planned)	2024 (Voluntary) 2028 (Mandatory)
TGA, Australia	TBD	2023 (Voluntary)

Upcoming PSGs for Generic Drug Product Development

To support generic drug development and generic drug approval, the FDA issues new and revised Product-specific Guidances (PSGs) on a quarterly and as-needed basis. On November 17, 2022, the FDA published a list with the new and revised PSGs for 2023 regarding both complex and non-complex generic drugs, along with the dates for their respective planned publications.

NMPA Announces the Use of Electronic Certificates of the Documentation for Export of APIs to EU and Certificate of a Pharmaceutical Product

From December 01, 2022, the electronic certificates of the documentation for the export of APIs to the EU and the certificate of a pharmaceutical product have been enabled, while the NMPA will still accept the paper version. This announcement, dated October 27, 2022, aims to streamline the business environment in China and enhance the administrative services for drug export companies.
All provincial-level Regulatory Authorities are issuing the certificate of a pharmaceutical product based on the new template published by the NMPA. Applicants must first register and be authenticated with their real name in the Online Office Hall of the NMPA to take it further.

Medical Writing Trends: 2022-2030

Medical writing refers to writing scientific documents by specific healthcare professionals for various purposes, including Regulatory submissions. The global medical writing market was valued at USD 3.6 billion in 2021 and

is expected to reach USD 8.4 billion in 2030, growing at a CAGR of 10.41%.

Listed below are the key market trends to look out for, which will be relevant until 2030:

- Regulatory Medical Writing is Expected to Experience Significant Growth by 2030
- North America will Persist to Experience Substantial Growth in the Coming Years
- Asia Pacific to be the Fastest Growing Market over the Years
- Medical Journalism to Boost the Market in the Coming Years
- Clinical and Regulatory Writing to Dominate the Market

DMA Revises 2022 Submission Deadline for MA and Clinical Trial Applications

As per the update from the Danish Medicines Agency (DMA) dated October 19, 2022, the deadline for submitting marketing authorization and clinical trial applications was revised to December 20, 2022. The move came as the DMA was closed from December 24 to January 01, 2023, for the Holiday Season.

For the applications submitted past the deadline, the date of receipt of the applications is being considered as January 02, 2023. Applicants must be aware of a few other specifications, which are discussed below:

Clinical Trial Applications

Further to the deadline, applicants must know that the EU Clinical Trials Directive expires on January 31, 2023. The Directive applies to the clinical trials of medicinal products for human use. Post this date, all the applications must be applied through the Clinical Trial Information System (CTIS).

Marketing Authorizations

The latest guidelines are for marketing authorizations and include variations, extensions, and follow-up cases. For variation and response applications, applicants must use the right attributes while updating the dossier, e.g., new, replace, or delete.

Nitrosamine Impurity Confirmatory Testing by MAHs

Considering the severity of nitrosamine impurities, the Co-ordination group for Mutual recognition and Decentralized procedures – human (CMDh) - issued the following first three (03) steps a manufacturer must follow to mitigate the amount of impurity in the final drug product:

- Risk Evaluation
- Confirmatory Testing
- Update the Health Authorities (HAs)

Post the confirmatory testing, the manufacturers must submit the amended manufacturing process protocols to the HA. The revised protocol must include procedures that help bypass the nitrosamine impurity. In July 2022, the CHMP and CMDh extended the deadline for submitting documents with variations in applications for chemical medicines from September 26, 2022, to October 01, 2023.

MEDICAL DEVICES
REGULATORY UPDATES FOR 2023 AND FURTHER

EU Notified Bodies (NBs) Updates and MDR & IVDR Implementation Challenges

The European Notified Bodies (NBs) published a new position paper to address the concerns of MDR/IVDR-designated NBs. It has been effective from May 26, 2022, and is applicable until May 26, 2024. The MDR/IVDR regulations aim to improve patient safety by strengthening the requirements for manufacturers and NBs.

The NBs are facing challenging situations as the Directives certificates are to reach their expiry dates in 2023 and 2024. As per the latest polls performed by Team NB and the European Commission (EC), most of the valid AIMDD/MDD/IVDD certificates are expiring in the first five (05) months of 2024. Specifically, it should be noted that the MDR postponement resulted in the extension of MDD certificates and a delay in the MDR submissions. Furthermore, team NB illustrates the challenges where only:

- 25 NBs are Currently Designated for the MDR
- 6 NBs for the IVDR
- 51 for the MDD, and
- 21 for the AIMDD/IVDD

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Key Considerations for Successful Creation and Submission of a 510(k) eCopy

Certain technical standards are written into the FDA eCopy software coding for successful submission. If the detailed standards are not met, then the eCopy does not pass through the FDA's eCopy loading process.

The review of the submitted eCopy will be put on hold if errors are found. In case of formatting errors, the module will generate a report to resolve the errors before the final submission of the eCopy to the FDA [PKJ10] [RH11]. Starting October 01, 2023, all 510(k) submissions, unless exempted, must be submitted as electronic submissions using eSTAR.

Step-by-Step Process for Obtaining 510(k) Clearance for your Medical Device

510(k) is essentially the name of the process/pathway that medical device manufacturers intending to market their moderate to high-risk devices in the US, undergo to demonstrate that the product to be marketed is as safe and effective as a legally marketed device. Starting October 01, 2023, all 510(k) submissions, unless exempted according to the final guidance, must be submitted as electronic submissions using eSTAR.

After the 510(k) is submitted, a unique control number is assigned which is known as the "510(k) number" or "K number." FDA conducts two (02) verification checks, one to verify if the proper user fee has been paid, and the second to verify if a valid eCopy or eSTAR has been provided.

Understanding the UKCA and the Deadlines Therein

The UKCA Mark stands for United Kingdom Conformity Assessment (UKCA) Mark. It is a new product marking adopted by the UK and is applicable for goods placed in Great Britain. The UKCA is a requirement for most of the goods subjected to CE Marking before Brexit. Medical devices require UKCA marking and are also subject to some special rules.

The UKCA marking has been in use from January 01, 2021, and it is voluntary till June 30, 2023. Medical devices that conform to, and are CE marked under EU MDD, EU AIMDD, EU IVDD, EU MDR, and EU IVDR, will be accepted and marketed until this date. From July 01, 2023, the new devices placed in the Great Britain market will need to conform with the UKCA marking requirements.

Class C & D Medical Devices & IVDs Registration with the CDSCO

Effective April 1, 2020, the status of a medical device expanded beyond the twenty-three (23) previously notified Indian medicak devices, requiring that all medical devices be registered under the Drugs and Cosmetics Act of 1940.

From October 01, 2022, all Class A and B medical devices needed to have import licenses before importation. All the remaining non-notified Class C & D devices must have import licenses by October 01, 2023 (from October 01, 2023, Class C & D devices will constitute the licensing regime). Medical devices that do not currently require import licenses must still register their product(s) through the CDSCO's ePortal.

Indication of the Manufacturer and CH-REP

Any foreign manufacturer that places medical devices and IVDs on the Swiss market must officially appoint a Swiss Authorized Representative.

Manufacturers of Class D IVD devices have already appointed their Swiss Authorized Representative (CH-REP) under IVDR. The last date these products could be placed on the market without a CH-REP was December 31, 2022. The deadline for Class B and C IVDs is March 31, 2023, and the deadline for Class A devices is July 31, 2023.

Until July 31, 2023, identification details should be mentioned either on the label or in the document accompanying the device; but after July 31, 2023, it is mandated to be on the label.

FOOD AND FOOD SUPPLEMENTS
REGULATORY UPDATES FOR 2023 AND FURTHER

FSSAI Adopts ICMR's Revised

Nutritional Requirements

The ICMR revised the nutrient requirements for Indians and published new RDAs in 2020. The FSSAI has decided to adopt the same. A collated document w.r.t the new RDA values is provided for vitamins, minerals, and amino acids. The law comes into force on July 01, 2023.

Indonesia's BPJPH Mandated HALAL Labeling for Food and Cosmetic Products

On May 11, 2021, the government of Indonesia notified the WTO regarding the adoption of Government Regulation No. 39 of 2021 on the Organization of Halal Product Guarantees. This regulation sets a new legal framework for the mandatory certification of all halal products and updates provisions on the implementation of Halal product guarantees.

The compliance timelines are divided into different phases based on the product type, such as:

- **Food Products:** October 17, 2024
- **Cosmetic Products**: October 17, 2026

COSMETICS
REGULATORY UPDATES FOR 2023 AND FURTHER

China Finalizes Administrative Measures on Cosmetic Labeling

On June 3, 2021, China's National Medical Products Administration (NMPA) released the finalized Measures for the Administration of Cosmetic Labels. China's new cosmetic regulations discuss the requirements for the labeling and the prohibited claims of cosmetics.

The Measures have been implemented from May 1, 2022. The cosmetics that have been notified or registered but have not complied with the Measures before May 1, 2022, should update the product label by May 01, 2023.

The EC Publishes a New Glossary of Common Ingredient Names

On April 29, 2022, the European Commission (EC) published a new glossary of common ingredient names to be used in the labeling of cosmetic products, and these will apply from April 29, 2023.

CHEMICAL
SAFETY AND REGULATORY AFFAIRS REGULATORY UPDATES FOR 2023 AND FURTHER

EU Mandates Harmonized PCN Format for Hazardous Chemical Mixtures

Under the Classification, Labeling, and Packaging (CLP) of substances and mixtures regulation, chemical companies who wish to place hazardous chemical mixtures such as paints, coatings, detergents, solvents, etc. in the European market are required to provide notifications of the hazards in their products. Poison centers take the responsibility to collect relevant information about hazardous mixtures and provide medical advice during health emergencies.

With various notification systems and information requirements across different countries in the EU, ANNEX VIII of the CLP Regulation was implemented. It aims to harmonize the hazardous information and the format that must be submitted to poison centers to improve emergency responses.

Notification Deadlines

- Mixtures intended for industrial use must comply from January 01, 2024.
- Mixtures that are already placed in the market and notified under the national legislation must comply from January 01, 2025.

Expiry Dates and Renewal of PPP Active Substances

Since Brexit, the Health and Safety Executive (HSE) has operated a Plant Protection Product (PPP) active substance renewal program for Great Britain, that is independent of the EU.

All active substances that were approved in the EU on December 31, 2020, remained approved in Great Britain. However, the transitional provisions of the plant protection products (Miscellaneous Amendments) (EU Exit) Regulations 2019 allowed the extension of expiry dates for active substances, as approved in Great Britain, to allow an orderly transition to the national regime. This means that all active substances with an expiry date before December 31, 2023, are extended by three (03) years.

France to Ban Mineral Oil Usage in Packaging and Printed Matter

To fulfill the requirements of the French AGEC law, the Ministry of Ecological Transition initiated a public call for the draft Decree titled "Prohibition of the use of mineral oils in packaging and printed matter." The draft includes specific restrictions on mineral oils and prohibits MOAH containing 1 – 7 aromatic rings and MOSH containing 16 - 35 carbon atoms. The law has been effective since January 01, 2023, and the requirements will be reinforced as of January 01, 2025.

EC's Revised Information Requirements for EU REACH

The European Commission (EC) has revised information requirements for registering chemicals under REACH. The proposed changes were effective from October 2022. These new changes will also impact the International Uniform Chemical Information Database (IUCLID). The next major change to the IUCLID includes changes to its validation assistant, and it is all set to release in April 2023.

Conclusion

2023 promises to be a year of renewed opportunities. Thus, Life Sciences companies must abide by all the latest regulations and mandates to be successful in their business strategies and tap the growing market. The global pharma, medical devices, food and food supplements, chemicals, and cosmetics sectors must brace themselves for the impending Regulatory updates and always ensure compliance. Stay ahead of your competition by partnering with us, and have a fruitful year ahead!

GETTING READY FOR ADOPTION OF eCTD 4.0

Since 2003, eCTD has been accepted by several Health Authorities around the world. Its standard has evolved incrementally over time. Based on the Health Level Seven (HL7) standard called RPS (Regulated Product Submission), eCTD 4.0 brings in major changes and introduces certain substantial updates. The updates focus on addressing a few key constraints that both Agencies and sponsors have discovered over the last two (02) decades. The eCTD 4.0 aims at streamlining the review process of Regulatory information, which will continue to develop with each iteration of the eCTD, thereby highly benefitting the Regulatory Publishing and Submissions space.

Considerations for Adoption of eCTD 4.0

As we adapt to any system, it is essential to understand and consider the practical nuances which need to be considered to ensure that the adoption of eCTD 4.0 goes smoothly for the applications at different stages with Health Authorities.

- No stylesheet is available in eCTD 4.0 version which will make it difficult to view the submission TOC and content in the browser
- Lifecycle management is challenging between eCTD v3.2.2 and v4.0
- Requires cutting-edge technology and seasoned staff
- When submitting the first eCTD v4.0 sequence to an eCTD v3.2.2 dossier, the next available sequence number is submitted as a whole number. For example, if the last eCTD v3.2.2 message has a sequence number "0003", the first eCTD v4.0 submission unit will be sequence number "4"
- When the submission is a continuation of an open Regulatory activity, the initial sequence number is needed to link the submission to the v3.2.2 Regulatory activity. The v3.2.2 sequence number should only be submitted to the first eCTD v4.0 submission for the open Regulatory activity
- Once a v4.0 submission unit has been received for an application, all future sequences must be sent in v4.0 – i.e., if a v3.2.2 message is received after the initial v4.0 message, the latter will be rejected
- All v3.2.2 applications included in an eCTD v4.0 grouped submission will be converted to v4.0 messages
- When submitting v4.0 content that should be grouped with v3.2.2 content, the keyword codes and values must match

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Timelines for Regions Adopting eCTD 4.0

The implementation guide for eCTD 4.0 was published by ICH in 2018 with minimal updates in June 2021. This will be adopted by Regulatory authorities throughout the world.

- Japan finished its pilot in 2021 and will be the first to start implementing the new version in this year, 2022.
- Brazil will commence with their pilot for the version 4.0 specification from 2023 onwards.
- The pilot for Europe will also be for year 2023, post when the actual implementation dates will be decided.
- By end of 2023, Australia and the US will start with the implementations for the new version, with Switzerland beginning the following year.
- The pilot for Canada is planned for year 2023, and its implementation has been scheduled for the year 2024.

Initially, the use of eCTD 4.0 will not be mandatory in all regions. An overlap period is anticipated when both eCTD 4.0 and 3.2.2 submissions will run in parallel, with each country defining its own grace period between two (02) - five (05) years before mandating the new version's use. Find the table below for more details on the pilot and implementation dates for eCTD 4.0 region wise:

Region	Technical Pilot	Implementation Dates
ANVISA, Brazil	2Q 2023 (Planned)	3Q 2023 (Production Pilot) 2023 (Voluntary)
EC, Europe	2023 CAPs (Planned)	TBD
FDA, United States	2022	2023 (Voluntary) 2028 (Mandatory)
Health Canada, Canada	2023 (Planned)	2024 (Voluntary) 2027 (Mandatory)
MHLW/PMDA, Japan	2Q 2021 (Completed)	2022 (Voluntary) 2026 (Mandatory)
Swissmedic, Switzerland	2023 (Planned)	2024 (Voluntary) 2028 (Mandatory)
TGA, Australia	TBD	2023 (Voluntary)

In a nutshell, the primary goals of eCTD 4.0 are to implement changes that speed up the Regulatory submission process, enhance how Agencies and sponsors communicate, and improve global harmonization of the format.

With this thought, we at Freyr, being at the forefront of driving innovation through advanced tech-enabled products, will be geared towards supporting our customers by adopting eCTD 4.0 in our Regulatory Publishing and Submissions software - Freyr SUBMIT PRO.

We recently conducted a webinar on eCTD 4.0, which elaborates more about the change and Freyr's readiness for eCTD 4.0. Please click here to download the archived webinar session.

Are you having quick queries related to the eCTD submissions? Consult us today!

SIGNIFICANCE OF ICSRs IN PHARMACOVIGILANCE: THE EU PERSPECTIVE

Developing novel and essential medicinal products has significantly increased the burden of monitoring and tracking the Adverse Drug Reactions (ADRs) and Adverse Events (AEs) of drug products. An Individual Case Study Report (ICSR) is collected at an individual level, which leads to causality assessment or a tilt in the risk-benefit ratio of a medicinal product to be determined distinctly. In the European Union (EU), the enhanced EudraVigilance system was launched in 2017. Consequently, reporting the ICSR in an ISO-based format per the Pharmacovigilance Risk Assessment Committee's (PRAC's) recommendations to the European Medicines Agency's (EMA's) management board has become mandatory from June 30, 2022.

ICSR reporting criteria directed towards Health Authorities:

1. An identifiable patient - Any identifiable patient information such as the initials, age, gender, birth date, and a medical record number
2. An identifiable reporter (Verbatim) - Any identifiable reporter information such as the name, initials, qualifications, and address
3. A suspect drug - The brand or generic name of at least the single suspect drug/medicinal product
4. An adverse event - Information of any AE and/or ADR with a suspicious causal association with the medicinal product

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Through the Spectacle of the European Medicines Regulatory Network (EMRN)

Understanding Expedited and Spontaneous ICSRs

Based on the reporters' information and healthcare professionals' assessments, ICSRs can be categorized as expedited and spontaneous. Expedited reports involve a direct relationship between ADR and drugs. After the necessary follow-ups, these reports subsequently move into a fifteen (15) calendar-days timeframe for EudraVigilance database submission. On the other hand, spontaneous reporting can be from either solicited or unsolicited sources.

The labor-intensive process of spontaneous reporting leads to under-reporting of the ADR with varying country-wise patterns. This results in reporting only 5% of all AE cases. The safety of the population is a significant concern alongside the safety of drugs from a Regulatory standpoint. The systems presently report the ICSR of vulnerable populations in a mandated format. The manual process of ICSR reporting and case handling seems time-consuming, considering the drug approvals rate. Moreover, fast-tracking the conventional systems can pose a greater risk to vulnerable populations than the non-vulnerable ones. Technology thus makes the ICSR reporting more seamless and Regulatory-compliant.

Automation in ICSR Processing

Artificial Intelligence (AI), automation, and data analytics have revolutionized the functioning of organizations by aiding drug approvals and multiple drug product market authorizations. On the contrary, with an increasing number of drugs in the market, patient-centricity approach, healthcare, and well-being awareness are some factors responsible for increased ADR/AE reporting.

ICSR forms the source of pharmacovigilance data and needs a right-first-time approach. Manual case-processing and relevant literature search define the causality or cause of the ADR. However, it becomes an exorbitant cost affair. The new guide developed for standardizing ICSR by the EMA and Heads of Medicines Agencies (HMA) focuses mainly on eCTD formats and processing. This may indicate developing all-around, fool-proof innovative solutions for IT services and solutions firms.

Conventional ICSR Reporting	Automation-enabled ICSR Reporting
• Manual-process/limited technology • Chances of under-reporting in case of spontaneous ICSR reporting • Challenging, fast-track drug approval PV process • Time-consuming • Capital-intensive • Limited scope for literature meta-analysis	• Technology-driven automated process • Detailed ICSR case processing • Fast-track PV-based submission • Time-saving • Cost-effective • Wide scope for literature meta-analysis

Conclusion

In conclusion, to circumvent the issues of under-reporting and tedious manual intervention in reporting processes, a strong, compliant, and time-saving mechanism must be integrated right from case intake to AE reconciliation. These robust and HA-compliant technologies can indicate any Regulatory department to count on the use of software and Machine Learning tools to manage the ICSR.

Smart innovation and software solutions developed in the ICSR reporting process can be anticipated to exhibit a significant improvement. At Freyr, we have developed an end-to-end approach that can resolve the Regulatory business requirements of our customers. Consult Freyr.

GLOBAL HEAVY METAL LIMITS FOR COSMETICS - AN OVERVIEW

Heavy metals are ubiquitously present in the environment surrounding us. Heavy metals containing ingredients such as thimerosal (mercury) and lead acetate were used as cosmetic ingredients in the past. They were also used as reaction catalysts during chemical synthesis and for manufacturing industrial equipment, containers, or closures.

These heavy metals can be found as impurities (commonly called elemental impurities) in cosmetic raw materials and/or finished cosmetic products. Health Canada acknowledges that heavy metal impurities in cosmetic products are unavoidable due to the ubiquitous nature of these elements but should be removed wherever technically feasible.

Some elements, such as iron, zinc, cobalt, etc., are essential for the human body at trace levels. Some of them are relatively non-toxic like silver, indium, etc. Contrarily, some heavy metals are not essential for the body and pose health hazards independent of the route of exposure. They also present environmental hazards due to their bioaccumulation potential. Among the heavy metal impurities, lead, cadmium, mercury, arsenic, antimony, and nickel are exceptionally toxic (carcinogenic, reproductive/developmental toxicants, and/or sensitizers).

Thus, the levels of these heavy metals must be controlled for the safety of the consumer. These toxic metals are controlled in cosmetics by various Regulatory bodies. The table below reflects heavy metal limits for finished cosmetics in the major global markets.

Table: Heavy Metal Limits for Cosmetics in the Major Global Markets

Heavy metals	German (EU)	GCC	ASEAN	Thailand	China	India (BIS)*	Canada	Korea	Taiwan	US FDA
Lead	2 ppm	10 ppm	20 ppm	20 ppm	10 ppm	20 ppm	10 ppm	20 ppm	10 ppm	20 ppm (Colorants) 10 ppm (Lip care products)
Cadmium	0.1 ppm	3 ppm	5 ppm	3 ppm	5 ppm	-	3 ppm	5 ppm	5 ppm	-
Mercury	0.1 ppm	1 ppm	1 ppm	1 ppm	1 ppm	-	1 ppm	1 ppm	1 ppm	1 ppm (Colorants)
Arsenic	0.5 ppm	3 ppm	5 ppm	5 ppm	2 ppm	2 ppm	3 ppm	10 ppm	3 ppm	3 ppm (Colorants)
Antimony	0.5 ppm	5 ppm	-	-	-	-	5 ppm	10 ppm	-	-
Nickel	10 ppm	-	-	-	-	-	-	10 ppm	-	-

*Cosmetic colorants limits; GCC - Gulf Cooperation Council; ASEAN - Association of Southeast Asian Nations; BIS - Bureau of Indian Standards

Currently, the heavy metal limits in cosmetics are largely established based on levels that could be technically avoided. To exemplify, we can consider the limits set by Germany's Federal Office of Consumer Protection and Food Safety (BVL) and Health Canada.

In a nutshell, cosmetics manufacturers must comply with the heavy metal limits to expand their global footprint. For Cosmetics Regulatory support and hassle-free global market entry, reach out to Freyr.

PERSPECTIVES AND STATE-OF-THE-ART APPROACHES FOR DESIGNING NANOCOSMECEUTICALS

Abstract

For personal care products, when it comes to cosmeceutical formulations, businesses around the world are making significant progress. Nanotechnology is becoming increasingly prevalent in cosmeceuticals to overcome traditional products' inadequacies. Nanotechnology provides considerable opportunities for cosmetic formulations to produce novel treatment approaches that are environment-compatible and degrade over time. Nanocarriers, such as liposomes, niosomes, nanoemulsions, microemulsions, solid lipid nanoparticles, nanospheres, and nanostructured lipid carriers, have replaced traditional delivery systems. Nanocosmeceuticals utilized for skin, hair, nail, and lip care to treat disorders such as wrinkles, photoaging, hyperpigmentation, dandruff, and hair damage, have gained popularity. Nanocosmeceuticals significantly affect the bioavailability of a product, aesthetics, and delivery efficiency, and pave the way for several future developments in the industry. This analysis considers a wide range of nanotechnology-based cosmeceuticals that are commercially available everywhere.

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Introduction

For some formulations such as cosmeceuticals, nanotechnology has been employed for improved safety and efficacy for decades. Many organizations use this innovation to optimize their products while limiting negative effects resulting from the standard formulation. This technique, known as cosmeceutical nanotechnology, improves several traditional topical delivery systems' drawbacks. The Food and Drug Administration (FDA) defines cosmetics as "particles intended for application to human bodies or any part thereof for the purposes of cleansing, beautifying, boosting attractiveness, or altering the appearance." Cosmeceuticals are a niche between cosmetics and pharmaceuticals. The products contain bioactive components with quantifiable therapeutic efficacies, and their formulations are diversified from skin to body to hair for a variety of therapies. Cosmeceuticals are the personal care business sector with the highest growth rate, and the market for personal care is expanding rapidly.

This article examines the many nanocarrier classes such as liposomes, niosomes, solid lipid nanoparticles (SLNPs), nanoemulsions, etc., that are employed for the transport of nanocosmeceuticals. Significant advantages of nanocosmeceuticals include prolonged action, increased bioavailability, enhanced visual appeal, drug, polymer, additives composition, ratio, and manufacturing process. These products are efficient adjuvants in cosmeceuticals due to their tiny size and high surface-to-volume ratio compared to conventionally utilized cosmeceuticals. In addition, using nanoparticles in cosmetic formulas does not alter cosmeceuticals' qualities but improves their look, coverage, and skin adhesion.
Cosmeceuticals are viewed as the sector of the personal care business with the highest growth rate. Numerous nanocosmeceuticals are incorporated into nail, hair, lip, and skin care products.

Nanocosmeceutical Classification

Skin Care: Cosmeceuticals for skin care products improve the skin's texture and function by promoting collagen production and preventing the damage caused by free radicals. They make the skin healthier by maintaining the integrity of the keratin structure. In sunscreen products, zinc oxide and titanium dioxide nanoparticles are the most efficient minerals that protect the skin by entering the deep layers of the skin and making the product less oily, odorous, and translucent. SLNPs, nanoemulsions, liposomes, and niosomes are widely employed in moisturising formulations because they form a thin coating of humectants and retain moisture for an extended period.

Hair Care: Included among hair nanocosmeceutical goods are shampoos, conditioning agents, hair growth accelerators, colouring, and style treatments. Nanoparticles' intrinsic features and unique sizes enable them to target the hair follicle, shaft, and increase the quantity of active chemicals. Submerging nanoparticles in shampoos lock moisture within the cuticles by maximizing resident contact time with the scalp and hair follicles through the formation of a protective film. The purpose of conditioning nanocosmeceuticals is to add softness, sheen, silkiness, and gloss, and to facilitate detangling of hair. Novel carriers such as niosomes, microemulsions, nanoemulsions, nanospheres, and liposomes play an essential role in mending damaged cuticles, restoring texture and gloss, and rendering hair nongreasy, lustrous, and less brittle.

Lip Care: Nanocosmeceutical lip care products include lipstick, lip balm, lip gloss, and lip volumizer. Various nanoparticles can be included in lip gloss and lipstick to soften the lips by inhibiting transepidermal water loss, preventing pigments from migrating off the lips, and preserving colour for an extended time. A lip volumizer with liposomes improves lip volume, hydrates, outlines lips, and fills in lip wrinkles.

Nail Care: The benefits of nanocosmeceutical-based nail care solutions are more significant than those of conventional products. The nanotechnology-based nail paints have improved toughness, quick drying, durability, chip resistance, and application ease due to flexibility. To treat infected toenails, nail polishes containing antifungal ingredients, such as silver and metal oxide nanoparticles, have been developed.

Nanocosmeceutical Carriers

Carrier-based technology is utilized for the delivery of nanocosmeceuticals, which offers an intellectual approach

for the delivery of active constituents.

Liposomes: Colloids with a spherical or oval-shaped particle that can carry drugs of lipophilic and lipophobic carrier, and self-assembled & double-layered phospholipid drug carriers used in many pharmaceutical dosage forms are liposomes. Typically, the size of liposomes ranges between 20nm and too few microns. Liposomes are compatible, degradable in biological systems, entrap both hydrophobic and hydrophilic drug molecules, and are non-irritant and safe to use. Good encapsulation efficiency of liposomes makes the delivery system a drug of choice for the delivery of oil soluble vitamins such as tocopherol, retinol, and phylloquinone; and anti-oxidants like ß-carotene and lycopene. Liposomal delivery of these ingredients increases the product's stability and makes the component disperse in water. Many skincare and hair products in cosmeceuticals are phosphatidylcholine derivatives. The first nanoliposomal anti-ageing formulation, "CAPTURE," was introduced by Dior in 1986, typically the formulation. Compared to normal liposomes, nanoliposomes contain 10 to 20% of phosphatidylcholine as the phospholipid, which seizes mammalian characteristics with more incredible antigenic properties. Multi lamellar liposomes obtained by conventional preparations were converted to nanoliposomes at high-pressure ultrasonication. Companies like L'Oreal invested 3.53% of their total revenue to patent dozens of products developed on a nano-scale.

Niosomes: Vesicular nanoparticles which can encapsulate aqueous drugs within their bilayer, non-ionic surfactants and are useful as a transporter for the delivery of drugs and cosmeceutical formulations are niosomes. Stability of the particle, %EE [Entrapment Efficiency], penetration, and low production cost make these vesicles more reliable than liposomes. These vesicular systems are proven effective in topical delivery because of high residence time at the application site and abridged systemic absorption. These targeted delivery systems show their availability at the site of action. Between 1970 and 1980, L'Oreal patented many products on niosomal nanoparticles. Niosomal encapsulated oestradiol formulation was developed and evaluated by Van Hal et al. and proved their greater penetration ability through skin stratum. "Bola surfactant" niosomes were efficient for delivery through hypodermis. These vesicular particles are safe and effective for drug delivery through the skin stratum or hypodermis.

Solid lipid nanoparticles: Solid lipid nanoparticles (SLNPs) are carrier-mediated systems that are sub-micrometer in size, extend between 50 nm and 1000 nm, and are made from physiological lipids suspended in surfactant. In cosmeceuticals, SLNPs are mainstream because of their broad scope of uses; small-size SLNPs guarantee close contact with the layer cornea and improved entrance of dynamic fixings through the skin, are less poisonous considering physiological and biodegradable polymers, and have occlusion properties that outcome in expanded membrane hydration. SLNPs are valuable for advancing progressively compelling sunscreen frameworks with decreased reactions as they have physical UV blocker qualities on their own. Adding 4% SLNPs to an ordinary cream improves skin hydration to 31% following a month in an in vivo examination.

Nanoemulsions: Nanoemulsions are tiny droplet (20-300 nm) size emulsions. Nanoemulsions with droplet size above 100 nm appear white, and for dispersions, it is around 70-100 nm which appears opaque, and below that becomes transparent. The product's shelf life with nanoemulsion can be increased by stabilizing it to increase the time before creaming. In the high concentration range, shearing can accelerate the physical deterioration of nanoemulsions. Multiple nanoemulsions allow the application of non-compatible material at a time. Fratter and Semenzato developed a melatonin Nano emulsifying system for cosmetics, describing this system's analytical and developing characterization. Designing a matrix, formulating a nanoemulsion with omega-3-rich products like gel and lotion, and evaluating their physic-chemical properties like particle size, movement in electrophoresis, turbines, crystallization, and melting temperature confirmed change in visual appearance, skin sense, and brilliance. Korres' Red Vine hair sunscreen nanoemulsions are cosmetic products available on the market. Sinerga (Nanocream) and Kemira (Nanogel) are used as self-emulsifiers for emulsion stabilization.

Nanocrystals: Nanocrystals are sub-micrometer range particles. The size range varies between 10 and 400 nm, and thousands of atoms form cumulative particles. The first cosmeceutical nanocrystals, Rutin-nanocrystals, were launched by Juvena in 2000. These formulations showed 500 folds greater biological activity compared to hydrophilic rutin glycoside. Skin integrity products to protect from photo light were evaluated in human skin with a water-soluble derivative of 5% rutin and 5% equivalent rutin composition of rutin nanosuspension. The best results are obtained with nanoformulation.

Nanocapsules: In the year 1995, the first nanocapsules were propelled to improve L'Oreal's impact on their products and further evaluated their dermatological efficacy. Nanocapsules are polymer-coated, liquid-entrapped formulations with sizes ranging between 10 and 1000 nm. Nanocapsules act as reservoirs for delivering the lipophilic drug through the stratum cornea. This reservoir delivers the drug in a controlled manner throughout its availability at the application site. Titanium dioxide nanocapsules are one formulated cosmeceuticals of sunscreen nanocapsules available in the market. Adhesion to the skin surface increases during contact duration.

Gold and silver nanoparticles: Silver and gold nanoparticles are known for their strong bactericidal and fungicidal properties. These nanoparticles are extensively used in face masks, non-ageing, and body deodorizers. The silver ointment is extensively used in medical conditions such as skin burns or infection to provide a bactericidal effect. Research from scientist Dr. Philipee Walter confirmed that applying a gold nanoparticle dye in solution form to white hair follicles turned to golden color, which then changed to dark brown color as the nanoparticles were centred in the core cortex of the hair follicles and remained entrapped even after repeated washing. Vemuri et al. synthesized and biologically evaluated novel biosynthesised gold nanoparticles for breast cancer treatment.

Chitin nanofibril: These are very thin fibres, needle-shaped with a mean size range of 240 × 7 × 5 nm and with a very large surface area of 400 m2/1 g fibre. Chitin nanofibril can trigger the propagation of keratinocytes and fibroblasts, which regulate collagens, macrophage activity, and cytokine secretion. The exclusion of carbohydrates and polypeptides from the exoskeleton of crustaceans produces this natural saccharide, a form of nanocrystals. These hyaluronan backbones metabolize body enzymes efficiently; hence, their usage increased in cosmetics and textiles as they are safe to use, biodegradable, metabolized in body enzymes, and eco-friendly. These fibrils activate proliferating keratinocytes and fibroblasts and regulate collagens, macrophages, and cytokine secretions.

Cubosomes: One type of nano design particles with sub-micrometre, crystalline, continuous bilayered phases extensively used in the formulation of cosmeceutical products such as deodorizers and skin and hair integrity products, are cubosomes. These nanoparticles have been trying to stabilize the emulsions (o/w) and adsorb pollutants by top cosmeceuticals such as L'Oreal and Nivea.

Dendrimers: Dendrimers are very fine particles whose size varies between 2 to 10 nm. Chemically, they are organic and are partial polymeric rooted like structure. Twigs of these terminals are well-off functional nanoparticles. Cosmeceutical companies like Dow, L'Oreal, and Unilever claimed several patents related to their hair, nails, and skin integrity products. One such patented product with a good confrontation over water and sebum, good tactile sensation, and better appealing and binding properties over skin and hair is carbosiloxane dendrimer. For the effective functioning of topical skin integrity products, researchers developed a low viscosity polymer formed by combining film former polymers with these dendrimers for their ease of use. One such combined formulation which is proven effective in sunscreen products is a copolymer of butadiene-amine and dendrimeric-amine for UV absorbing capacity developed as low viscosity gel base, which minimizes side effects like skin ailment and provocative reactions due to high molecular weight and its ease of use.

Hydrogels: Hydrogels are 3D structured hydrophilic polymeric networks that are chemically and physically cross-linked. Hydrogels swell in aqueous and body fluids without dissolving. To prevent damage, they can change their properties and predict future changes accordingly.

Fullerene: Carbon fullerene or "Buckyballs" is a nano-scale material structurally comprised of carbon rings in odd numbers, such as a pentagon or heptagon carbon ring confined to spherical shape in a three-dimensional network. They display anti-oxidant properties in cosmetic products. As they are oxygen-free radical scavengers, they are used for the formulation of cosmetic products which can revive the skin. These lipophilic nanoparticles confined to lipophilic derivatives can solubilize with emulsifiers in aqueous solvents. The purpose of using it in its highest capability is to explore its free radical scavenger activity.

Conclusion

The utilization of nanotechnology in the cosmetics sector is becoming more prevalent in various formulation fields. In diverse cosmeceuticals, liposomes, niosomes, solid lipid nanoparticles, gold nanoparticles, and nanoemulsions, nanosomes are utilized as novel nanocarriers. As previously stated, formulations created using nanotechnology will exhibit enhanced stability, permeability, and availability at the site of action. In addition, their appearance will be more aesthetically appealing. When the particle size is decreased, there is an increase in surface area and a reduction in toxicity. Moreover, the finished product is both cost-effective and economically viable. As technology advances, researchers will access a more acceptable and convenient approach. In addition, clinical trials of cosmeceuticals, like those conducted for pharmaceuticals, should be undertaken to ensure the formulations' human

safety. The regulation and safety of cosmeceuticals and nanoparticles utilized in them should be governed by strict legislation.

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FSSAI AMENDS LABELING & DISPLAY REGULATION

MAKES INR (INDIAN NUTRITION RATING) MANDATORY ON FOPNL OF FOOD PRODUCTS

The Food Safety and Standards Authority of India (FSSAI) released a Draft Notification on September 14, 2022, amending the Food Safety and Standards (Labeling & Display) Regulations, 2020. These regulations may be called the Food Safety and Standards (Labeling & Display) Amendment Regulations, 2022. It shall come into force on the date of their final publication in the Official Gazette. Compliance shall be voluntary until forty-eight (48) months from the date of the final notification of these regulations and expected to become mandatory thereafter.

Below are the highlights of the amendment

- The definition of Front-of-Pack Nutrition Labeling (FOPNL) and High Fat, Sugar, Salt (HFSS) food is added to the amended regulation.
- The name of ingredients used in the product shall be listed in the descending order of their composition by weight or volume at the time of its manufacture; provided that the percentage of fruits, vegetables, nuts, legumes & millets, if present in the food product, shall be declared.
- Dietary fiber (g) shall also be declared for nutritional information per 100g or 100ml or per single consumption pack of the product.
- Indian Nutrition Rating (INR) declaration on FOPNL forms a major part of this amendment.
  Below categories explains further how to display the INR
  - Baseline reference values and categories
    - For the purpose of Front-Of-Pack Nutritional Labeling (FOPNL), the baseline reference values for four (04) health risk increasing factors, i.e., energy, total sugars, saturated fat, and sodium per 100 g or 100 ml of the product; and the minimum percentage of positive nutrients viz., Fruit & Vegetable (FV); Nuts, Legumes & Millets (NLM), fiber, and protein are considered in the calculation for the rating of specific solid foods or liquid foods.
    - Further, all processed and packaged food products covered under the extant FSS regulations are classified into three (03) categories:
      - Category-I (Solid foods),
      - Category-II (Liquid foods)
      - Category-III (Exempted from FOPNL)
    - The system of pictorial display format shall be referred to as Indian Nutrition Rating (INR).
  - Pictorial Display Format
    - Every packaged food except those exempted from nutritional information under these regulations shall display the prescribed format (INR) on the front-of-pack calculated based on the contribution of energy (in kilo calories; kcal), saturated fat (g), total sugar (g), sodium (mg), and positive nutrients per 100 g of solid food or 100 ml of liquid food using the below formula:

Final INR score = (INR baseline points) – [(INR FV* points) + (INR NLM* points) + (INR P* points) + (INR F* points)]

    - Baseline points, FV points, NLM points, P points, and F points are further elaborated in the draft notification and have to be chosen based on the respective product category.

The INR system rates the overall nutritional profile for packaged food by assigning it a rating from half (½) star (least healthy) to five (05) stars (healthiest). More stars indicate that the food product is better positioned to provide for the daily human need for nutrients.

The format of the logo for INR is as indicated below:

  - Generation of INR logo
    - The FBO shall submit their product's relevant nutrient profile in the FoSCoS system for generating the respective INR score and the logo, with or without the optional interpretive information.
  - Food products with a milk logo, as specified under Food Safety and Standards (Food Products Standards and Food Additives) Regulation, 2011, shall be exempted from the purview of the HFSS definition.
  - FSSAI has further introduced Schedule III and IV guidance on proper INR rating calculation and exempted foods lists.

In a nutshell, Food Business Operators (FBOs) must be prepared to adhere to these regulations for a compliant entry into the Indian market. To know more and talk to our experts, please reach out to Freyr.

Center of Excellence
Compliance, Audit and Valida

TOP FAQs ABOUT MEDICAL DEVICE SINGLE AUDIT PROGRAM (MDSAP)

The Medical Device Single Audit Program (MDSAP) allows a recognized Auditing Organization (AO) to conduct a single audit of a medical device manufacturer's Quality Management System (QMS). It furnishes relevant Regulatory requirements for five countries, i.e., Brazil (ANVISA), USA (FDA), Japan (PMDA), Canada (Health Canada), and Australia (TGA). Aside from the participating Regulatory Authorities, several other international partners (the official observers and affiliate members) are involved in the MDSAP.

MDSAP certification is mandated by Health Canada for Class II, III, and IV devices but is voluntary for the other four countries. It has promoted transparency and Regulatory alignment between participating authorities and minimized the need for multiple audits, thus saving time and resources of the medical device manufacturers. To give you a better perspective on the MDSAP program, here we tried addressing the fifteen (15) most frequently asked questions.

1. **Why was MDSAP Program developed when a globally accepted ISO 13485 certification exists?**

   MDSAP was developed to reduce the burden of Regulatory audits for medical device manufacturers and to promote greater alignment of Regulatory approaches and technical requirements based on international standards and best practices. It focuses on bringing consistency, predictability, and transparency to Regulatory programs by standardizing procedures and practices of regulators and third-party auditing organizations.

   The audit is based on QMS requirements under ISO 13485 and Regulatory requirements of the

participating country where the medical devices will be marketed.

2. What are the eligibility criteria for undergoing an MDSAP audit?

Any medical device manufacturer intending to market their device in the participating countries can undergo an MDSAP audit. However, each Regulatory Authority may establish exclusion criteria for certain conditions if necessary.

For example, in Japan, the exceptions for eligibility are:

- A Registered Manufacturing Site (RMS) that manufactures medical devices made of human/animal tissues
- An RMS which manufactures radioactive IVDs
- An establishment of a Marketing Authorization Holder (MAH)

3. Does the MDSAP audit include combination products?

Medical devices that include drugs (medicinal substances) or biologics (e.g., materials of animal origin that have been rendered non-viable, or tissues, cells, or substances of microbial or recombinant origin, human blood or extracts of human blood or blood products, etc.) are considered as combination products, and may be included in the scope of an MDSAP audit.

However, due to differences in how these products are regulated in the jurisdictions of the participating Regulatory Authorities, MDSAP audit reports and certification documents may not be considered an alternative to the inspection and assessment requirements in some jurisdictions.

Australia - Combination products are subject to an off-site examination of the TGA under the Australian Conformity Assessment. But an effective MDSAP audit may reduce inspections for these devices.

Brazil, Japan - Combination products considered medical devices are included in MDSAP, as there are no specific requirements regarding QMS.

Canada - MDSAP model covers the QMS requirements for combination products considered medical devices.

USA - MDSAP audits are not considered alternatives to FDA inspections for combination products.

4. Can I select the country in scope for the MDSAP audit?

Yes, the audit is performed according to the scope declared in the application for certification services. Medical device manufacturers are expected to be compliant with regulations only in jurisdictions where their products are to be marketed.

5. I am a medical device manufacturer from the US, intending to market my device only in Japan. I am about to undergo an MDSAP audit. Do I need to comply with the requirements of other countries as well?

No, medical device manufacturers are only expected to be compliant with ISO 13485 requirements and regulations in jurisdictions where their products are to be marketed.

6. My Auditing Organization (AO) and European Notified Body are the same. Can I be audited for both at the same time?

If your AO and European Notified Body are the same, the conformity assessment can be performed after conducting the MDSAP audit, not simultaneously. European Notified Bodies are observers for MDSAP, and the conformity assessment is conducted as per the EU MDR 2017/745. For MDSAP, the assessment is performed as per the requirements of ISO 13485 and the Regulatory requirements of the participating countries in scope.

7. What is the difference between Stage I and II assessments?

The MDSAP initial audit process involves two (02) stages. The initial audit, also called the Initial Certification audit, consists of Stage I and Stage II audits.

Stage I audit includes documentation review and evaluation of the readiness of the medical device manufacturer to undergo a Stage II audit.

Stage II audit is performed to verify if all applicable requirements of ISO 13485 and other Regulatory requirements of the Regulatory Authority in scope are implemented.

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8. How many auditors can I expect for an MDSAP audit?

Audit Time Determination specifies how to determine the on-site audit duration in man-days. The AO decides how many auditors will compose the audit team. For example, a (06) man-day audit can be completed in

MDSAP Process	MDSAP Tasks per Process		Number of Applicable Tasks to be Audited	Minutes per Audit Task	Total Number of Minutes per Process	Audit Hours per Process	MDSAP On-site Auditor Days
			A	**B**	AXB	AXB ÷ 60	AXB ÷ 60 ÷ 8
Management	11			**28.8**			
DMA&FR	3			**28.0**			
MA&I	16			**30.4**			
MDAE&ANR	2			**30.4**			
D&D	17			**16.8**			
P&SC	29			**35.2**			
Purchasing	16	12*		**12.0**			
Total	94	90*					

*To be used with MDSAP AU P0002 Audit Model (reflecting ISO 13485:2016)
Management = Management Process
DMA&FR = Device Marketing Authorization and Facility Registration Process
MAI = Measurement, Analysis, and Improvement Process
MDAE&ANR = Medical Device Adverse Events and Advisory Notices Reporting Process
D&D = Design and Development Process
P&SC = Process and Service Controls Process
Purchasing = Purchasing Process

9. How is the MDSAP audit timed?

The Audit Time Determination Procedure, issued by the FDA, summarizes the process for determining the duration of audit calculation in the following table.

The calculation of the duration of the audit is primarily based on the number of applicable audit tasks associated with the type of audit to be conducted and the organization's specific activities to be audited.

For detailed information about the same, you can refer to MDSAP P0008007.

10. Is there a guide or a checklist that I can access to ensure compliance with an MDSAP audit?

Yes, you can access the MDSAP Audit Approach document. It is a well-organized guide issued by the USFDA that cross-references specific sections of ISO 13485:2016 and relevant regulations issued by Australia's TGA, Brazil's ANVISA, Canada's Health Canada, Japan's MHLW/PMDA, and the US FDA.

11. What is the role of an observer in an MDSAP audit?

An MDSAP observer is a Regulatory Authority who is permitted to attend meetings, assessments, and other activities but does not utilize the MDSAP deliverables. The observers are represented on the MDSAP Regulatory Authority Council (RAC) by one senior-level manager.

12. What are the next steps to take if I have received a grade score of 4 or above?

The grading system is given to non-conformances observed during the audit by AO. A grade score of 4 or 5 indicates a high risk for intervention. You must

provide a remediation plan for every recorded non-conformity within fifteen (15) calendar days of the date the non-conformity report was issued. The remediation plan must include outcomes of the investigation of non-conformity, its causes, and planned corrective actions to prevent any recurrence. The evidence of the implementation of the remediation plan/action should be provided within thirty (30) calendar days of the end date of the audit.

12. Is there a difference in the process of approaching the audit by an internal auditor vs. AO?

MDSAP follows a process approach. The AO is likely to look at linkages and threads, whereas an internal auditor might look more into one (01) functional aspect at a time. Therefore, the AO might find a non-conformity in one (01) functional area and seek answers in a different functional area. However, following the process approach might be disruptive during an internal audit.

13. Can I appeal to the AO if I can prove that a recorded non-conformity is not valid?

AO has an appeal or dispute process which you can use if you can demonstrate that a recorded nonconformance is invalid. However, grades assigned to nonconformities cannot be changed because of corrective actions. They can only be amended based on evidence to show that they weren't valid.

14. How long is the MDSAP certificate valid?

Medical device manufacturers certified under the MDSAP program will be audited annually, according to a three (03)-year certification cycle. The initial audit is a complete audit of the medical device manufacturer's QMS. It is followed by surveillance audits conducted yearly for two (02) consecutive years. The cycle re-commences with a re-certification audit in the third year.

To learn about our MDSAP services, schedule a call with our Experts.

Press Release

Otsuka

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CHILD-RESISTANT PACKAGING AND DETERMINATION OF 'F-VALUE'

Child-resistant Packaging (CRP) is a type of packaging that is difficult for young children to open (or gain access to the contents) as opposed to adults. CRP reduces child mortality/adverse effects from the unintentional ingestion of oral prescription drugs. They are usually manufactured by changing the foil material, blister material, adhesive, the orientation of blister pockets, and using different wadding materials in container closures.

Background

The Consumer Product Safety Commission (CPSC) declared the Poison Prevention Packaging Act in 1970 to establish standards for the special packaging of any household substances to protect children from serious personal injuries, or serious illnesses resulting from the handling, using, or ingesting such substances. In 2001, the CPSC extended the CRP requirements to oral drugs approved by the United States Food and Drug Administration (USFDA) for their sale as Over-the-Counter (OTC) drugs.

CRP testing is required to demonstrate that the packaging is safe. Formal tests are usually conducted to demonstrate that children cannot open the package, but adults/elderly can do so. However, there is no formal guidance

available for this assessment. Limited guidance/support documents from the CPSC or the industry provide some basis for this assessment. Therefore, this evaluation is generally performed based on the scientific principles of risk assessment.

‘F-Value’

“F” value, aka Failure Value, is defined as the number of individual dose units of a drug that can cause serious illness or injury in a 25lb (11.4kg) child. For highly toxic or harmful drugs, the “F” value is usually set at F1, indicating that the child’s access to a single unit is considered a failure.

Less toxic or less harmful products have a higher “F” value (for example, F8). When a child acquires access to a 9th unit in the US, a default restriction of F8 is typically adopted. The “F” value is typically calculated from F1 to F8.

‘Fail Test or Test Failure’

As per 16 CFR § 1700.20 on the testing procedure for special packaging, a test failure shall be any child who opens the special packaging or gains access to its contents. In the case of unit packaging, a test failure shall be any child who opens or gains access to the number of individual units, or for the complete ten (10) minutes of testing, accesses more than eight (08) distinct units, whichever is lower.

Role of a Toxicologist in ‘Child Resistant Packing’

Toxicologists can characterize substance-specific hazards (Carcinogenic, Mutagenic, and Reprotoxic (CMR)) and possible acute health effects (both systemic and local effects) in children.

Based on the acute data, repeated dose non-clinical toxicity data, acute human data, overdosage information, and various case studies (both adults and children), the Maximum Tolerated Dose (MTD) is identified and based on the allometric scaling, a Point of Departure (POD) needs to be determined for F-Value calculation after which the ‘F’ value is calculated.

Data Used for Determining the ‘F-value’

Overdose data in children and MTD in humans, clinical trial and post-marketing data in adults, Pharmacokinetic (PK) and Pharmacodynamics (PD) data, acute and repeat-dose toxicity data in animals, read across approach using surrogate molecules if needed, etc., is the main data used to determine the ‘F-value.’

Conclusion

Determination of the ‘F-value’ guides the requirement of CRP for a final formulation. If the ‘F-value’ is near one (01), it indicates that it requires special CRP, and if it is near eight (08), it indicates that the final formulation does not possess any significant safety concerns for children.

Therefore, it is of utmost importance that manufacturers consider the determination of the F-value to make the packaging child-resistant. A team of experienced toxicologists can support in determining the correct F-value, making it simple and compliant for the manufacturers. At Freyr, our expert toxicologists can help you with all your drug packaging needs. Consult Freyr for compliance.

FREYR CONNECT

The pharmaceutical and Life Sciences sectors have seen a steady increase in the need for Medical Writing. Patents have been expiring, Regulatory standards have changed quickly, and spending on research and development has been rising constantly. Because of this, the necessity to continuously adapt, produce, maintain, and update medical material has evolved.

Medical Writing is a highly specialized field that encompasses the art and science of content writing and clinical research. It involves the production of well-structured scientific resources including clinical research papers, web content for the healthcare industry, periodicals, journals, etc. These texts can be read by anyone from a layperson to a highly qualified medical professional.

As there is a steady shift toward accepting automation in various industries, the medical writing industry is also trying to adapt to this situation and is moving towards using innovative solutions which can ease the process.

Next-generation Solutions for Medical Writing

Medical Writing Automation (MWA) is a framework that leverages the techniques and algorithms of Natural Language Processing (NLP) and Natural Language Generation (NLG) to generate content. Artificial Intelligence (AI) has made major strides in producing, processing, and mining text. These AI-powered engines can understand the context and suggest appropriate terminology. The said technology is also helpful when creating intuitive material. If programmed properly, a computer displays no bias. Based on its training, it offers its predictions and recommendations. Medical writers can use computer innovation and the rise of AI in the fields of NLP and NLG to their advantage while producing medical documentation.

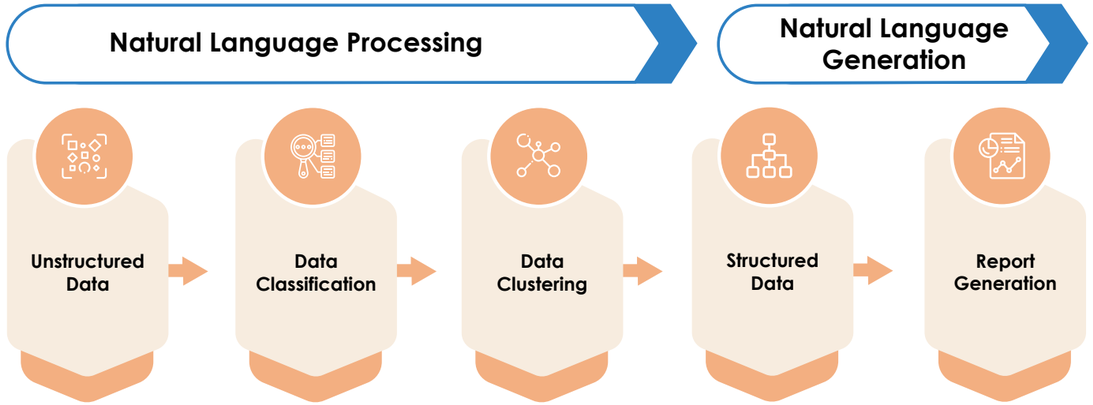
How Does this Work?

NLP is a five (05)-step process starting from identifying and analyzing the structure of words, checking the grammar, arranging the words meaningfully, drawing the exact dictionary meaning of the words, relating this meaning of the sentence with the sentence just before it, and finally reinterpreting the actual meaning of the sentence. NLG is the process of generating meaningful phrases and sentences in the form of natural language from some

internal representation. It involves text planning, sentence planning, and text realization.

How Can this Methodology be Adopted in Medical Writing?

AI, when clubbed with NLP and NLG, automatically extracts information from a variety of data sets, whether they are organized or unstructured. It then analyses the extracted data to comprehend and categorize the content's substance and context, and stores the content and context data in a dynamic semantic model. Below is a representation of how NLP and NLG assist in the medical writing process, thus making it seamless.



NLP and NLG assisting the medical writing process

To meet the needs of various stakeholders in the Life Sciences ecosystem, MWA changes the information and context of the material when it needs to be reused or repurposed. The solution keeps a database of data that is conveniently searchable with natural language queries. Additionally, impact analysis is done to enhance change management anytime new content is made available or updated.

MWA is particularly helpful for repeated operations with a high degree of redundancy. Most of the time and labor that goes into creating these documents is spent gathering data from already-existing sources (such as study procedures, figures, tables, and statistical analyses) and organizing it under the appropriate section headings. The figure below explains how the AI/NLP solutions can reduce 50-80% time as compared to the traditional approach.

The traditional approach vs adopting AI/NLP solutions in Medical Writing

Although a medical writer's expertise is not necessarily required, their assistance would be valuable when it comes to refining the finished article and offering an expert scientific interpretation. It can also speed up the submissions and marketing authorizations by producing complex documents in a fraction of the time they typically take (days as opposed to weeks), which benefits the budget. Its capabilities are expanding, and it can be used to generate documents that need a higher degree of editorial expertise such as peer-reviewed articles, abstracts, or posters.

Adoption of Automation in Medical Writing

Several companies are now employing AI solutions like NLP to automate conventional writing processes that are time-consuming and tedious. As these companies have realized the importance of automation in the medical writing space, they have agreed to the fact that AI solutions can save up to 80% of the medical writer's time and can process and manipulate large amounts of data in a few minutes. Companies are adopting two (02) pronged approaches when it comes to automation. They are either developing internal automation capabilities for QC, data structuring, analysis, and generating documents, etc., or they are partnering with companies that have automation platforms.

As the industry is progressing in adopting automation in Medical Writing, we, at Freyr, are moving hand-in-hand with the industry and are adopting new technologies to ease your work and deliver quality deliverables in a shorter period. Partnering with Freyr will ensure you get quality documents and get them right the first time. Consult Freyr to know more about our medical writing capabilities.

AgileOne

Ranked Freyr #2

Freyr Ranked #2 in Regulatory and Scientific Staffing Solutions for One of the Top 5 Global Pharma Companies

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ICH Q12 TRANSFORMING GLOBAL REGULATORY POST-APPROVAL SUBMISSIONS

Country-specific requirements and maintaining documents containing different quality information for the same product have always been challenging. Excessive inventory segregation, the likelihood of manufacturing and Regulatory compliance errors, and varying submission, evaluation, and deployment deadlines all add to the complexity of product supply chain regulation worldwide. As a result, various legal frameworks around the globe are focusing on implementing innovative modifications or enhancements to increase process efficiency and robustness.

The ICH Q12 guideline: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management offers unique tools for streamlining and integrating post-approval Chemistry, Manufacturing, and Controls (CMC) changes. The tools, in collaboration with ICH guidelines Q8, Q9, Q10, and Q11, will assist in creating a more advanced Quality-by-Design (QbD) framework for post-approval submissions. As per the QbD concept, quality cannot be tested on the product, but it should be built into it, allowing continuous implementation of changes without delay.

Worldwide Implementation Scenario of ICH Q12

With the understanding to minimize the risk of drug inadequacy while ensuring high standards of quality, safety, and efficacy of the drugs, many markets have adopted the ICH Q12. Let's see the extent to which some of the largest markets in the world, like Europe, the US, Japan, and Canada, are managing the post-approval changes.

US FDA

The final ICH Q12 guideline and annexes published on the US FDA's website in May 2021 describe recommendations on identifying, submitting, and establishing the suggested Established Conditions (ECs). They also clarify the relationship between ICH Q12 Post-approval Change Management Protocols (PACMPs) and Food and Drug Administration (FDA) comparability protocols. It describes translating ICH Q12 post-approval change reporting aspects to the existing FDA supplement categories and offers specific examples of how to use a Product Life Cycle Management (PLCM) document.

EMA

The European Medicines Agency (EMA) was the first global Health Authority to employ ICH Q12 in January 2020, with implementation guidance authorized in March 2020. Following substantial discussions and negotiations during ICH Q12 drafting and approval, differences between certain concepts in ICH Q12 and the existing EU legislative system could not be completely resolved, restricting ICH Q12 from becoming fully integrated into the EU. The EMA's implementation guideline highlights that "the Regulatory framework invariably supersedes over scientific and technical regulations," which states that the requirements outlined in the current EU Variations Regulation and associated EU Variations Guidelines must always be followed. The European Commission recently announced that it has begun the process of revising the EU's pharmaceutical legislation, issuing a "combined evaluation roadmap/inception impact assessment."

PMDA

The Pharmaceutical and Medical Devices Agency (PMDA) in Japan has adopted an internal working group to facilitate the implementation of ICH Q12. One of the intriguing aspects that must be addressed is the relationship and potential for alignment between the Japanese Module 1 Application Form, which contains the "approved matters," and the ICH Q12 concepts of ECs with associated reporting categories and the PLCM document. In terms of PACMPs, there is currently no comparable concept in Japan, so a change in national regulations will be required to implement it.

Health Canada

Health Canada, in the second half of 2021, targeted implementing ICH Q12 to "allow sufficient time for regulators and stakeholders to prepare." To that end, Health Canada intended to launch stakeholder consultations in 2021 to gather feedback on the final elements of Q12 implementation in Canada. Similarly, there are some possibilities in Japan for alignment of the Canadian CPID with the ICH Q12 concepts of ECs and the PLCM document, as well as more widespread acceptance of PACMPs.

As individual companies started to adopt ECs and ICH Q12 concepts, it became clear that there was some disconnect in approaches and associated terminology addressed to Health Authorities. Recent engagements between industry leaders and Health Authorities have highlighted the key issues faced by regulators and sponsors in implementing ICH Q12, as well as a potential future path to a more harmonized approach for post-approval change management.

Country	Health Authority	Status	Considerations
The United States of America	USFDA	Implemented	Overall, the concept of EC is consistent with FDA regulations in 21 CFR 71 314.70(a)(1)(i), 314.97(a), and 601.12(a)(1).
Europe	EMA	In the process of implementation	Certain ICH Q12 elements such as ECs and PLCM documents are not compatible with the current legal framework. Recently announced EU legislation revision initiative may change this and enable the use of all ICH Q12 tools.
Japan	PMDA	Implemented	The EC and PLCM documents must be aligned with the Japanese Application Form. PACMP is a novel concept that requires the revision of the existing legal framework (ongoing).
Canada	Health Canada	In the process of Implementation	EC and PLCM will need to be aligned with the Canadian Certified Product Information Document (CPID). There has been limited experience with PACMPs so far.

ICH Official website: ICH

Worldwide adoption of ICH Q12 tools can provide a consistent approach to PLCM, with the potential for application in non-ICH countries as well. A Regulatory partner can assist in divulging the harmonized approach to post-approval change management described in ICH Q12. This will profit patients, manufacturers, and Regulatory authorities by promoting innovation and quality improvement in the pharmaceutical sector reinforcing quality checks, and increasing the availability of medicinal products.

HOW WILL WEB3 AND NFTs STOP COUNTERFEIT DRUGS AND ENHANCE TRACEABILITY?

As the world is moving towards digital transformation, the introduction of various tools is empowering many industries, including Pharmaceuticals and Life Sciences. In fact, the serialization and traceability of items can be improved even further as the world transitions to a digital economy. Currently, traditional approaches for achieving traceability in the Pharmaceutical supply chain are frequently centralized and sometimes lack transparency among supply chain participants. For this reason, Web3 tools, including Blockchain and Non-Fungible Tokens (NFTs), have several advantages including speed, security, traceability, transparency, and accessibility of data provenance that would allow manufacturers to fight against counterfeit drugs. Because of its distinctiveness and digital signature, NFT is difficult to trade with other systems. Therefore, the NFT can act as the ideal digital replica of any physical product disseminated throughout a supply chain. Such integration within the traceability process might offer an impenetrable solution against fake medicines. Although there is a process, pharmaceutical manufacturers must integrate to achieve this digital transformation.

In Europe, the 2011/62/EU Directive signifies that all prescription drugs must have a unique identifier and thus, have to be serialized to effectively fight against fake medicines. But what could be the actual steps to improve

traceability and reduce counterfeit drug circulation in the market using the Web3 applications is discussed below.

Firstly, the integration of Blockchain allows for making a decentralized system, which improves the traceability process and simplifies the integration among key players within the product distribution supply chain. With each step of the product distribution, users (such as manufacturers or hospitals) are issued private keys that allow them to perform fundamental functions of signing and retrieving data. Such keys can be variable in cryptography and used to encrypt or decrypt data, thus giving an extra layer of security and prevention of data breaches.

However, a second item must be included in the equation to complete a successful Blockchain-based traceability solution. An NFT acts as a token that provides the confirmation of product identification and assigns ownership to the user. Once the medicinal product is manufactured and is ready to move from the manufacturing site to the pharmaceutical factory, an NFT event must update the owner with the rightful details to pass the ownership token to the wholesale distributor. This also indicates that the manufacturer must modify the new owner's public address of the NFT for the package. Once the wholesale distributor receives the package, a new event called 'delivered' is initiated within the Blockchain, along with additional details about the product's state. After the confirmation, the wholesaler initiates the token take over to the next user (the hospital or the pharmacy), which now acts as the last distributor and which must update the information about the received package in the system and guarantee that the product can be administered (or sold) to the patient. After the patient receives the product, the NFT is erased by transferring ownership to an unreachable address, preventing anybody else from ever changing the NFT data. A described supply chain can be seen in figure 1.

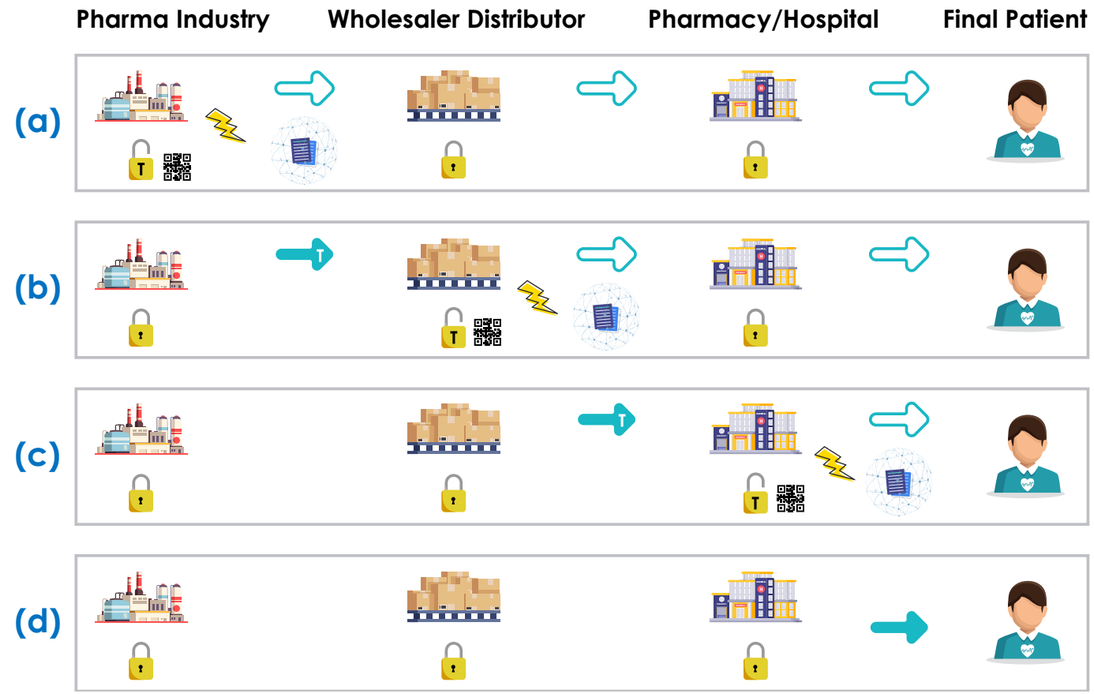

Figure 1 . A pipeline of track and trace processes using NFT serialization. (A) With the pipeline state of the product supply chain, the NFT is minted. (B) As the product moves to the distribution center, the ownership is passed to the warehouse. (C) Ownership is passed to the hospital retailer. (D) The NFT is burnt as soon as the product is administrated to the patient.

The traceability procedure that is discussed herein (Figure 1) gives the final customer an effective instrument for verifying the product's history and determining if it is in the right condition to be sold. The transparency of the blockchain throughout the entire production and distribution process enables all users to examine the status of each item by scanning the QR code with a Web3 application (Figure 2). This makes it possible to prevent and stop attempts at counterfeiting. Thus, the user who is receiving the package will be able to check the NFT's status and confirm the latest, even within the product distribution cycle, and whether the status of the movement was updated rightfully.

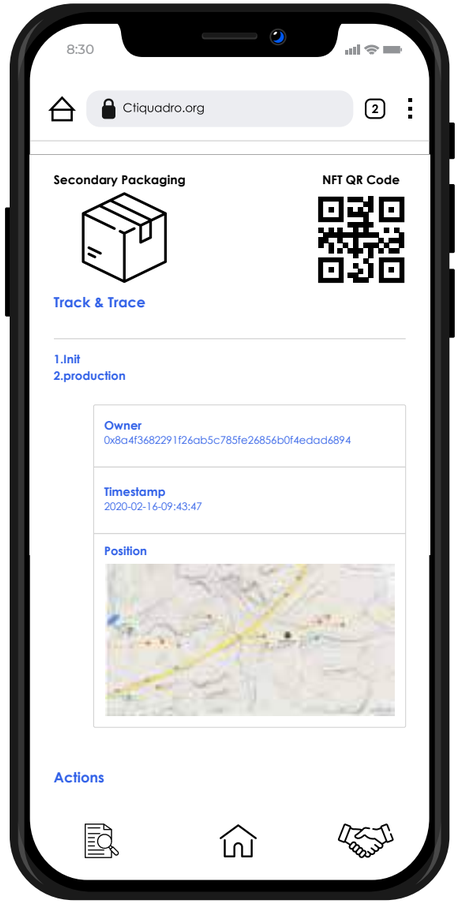

Figure 11. Prototype of the DAPP running within the VeChain Thor blockchain test network.

Figure 2. A developed progressive web decentralized application. This application displays information for each stage of a product's lifecycle, including the current status, the timestamp of the transaction, the public address of the owner who entered the data, and a link that opens a public blockchain explorer with the relevant transaction's full details.

Web3 and all the tools it has to offer, though, will be more integrated in the coming years. What current options for many manufacturers or the supporting operational bodies have is the efficient and compliant Artwork Management System, which ensures valid tracking of the manufactured product. Although establishing an effective Artwork and Labeling strategy may sound like an overwhelming task, Freyr provides expertise in the end-to-end Lifecycle Management of packaging Artwork services catering to a range of global Regulations. Our Regulatory experts guide pharmaceutical companies through every step of their product packaging journey.

To learn more about Freyr's Artwork lifecycle coordination services, we are more than happy to have a quick call to understand what you might be seeking.

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A PANORAMA OF QUALITY MANAGEMENT SYSTEM (QMS) IN PHARMACOVIGILANCE

The World Health Organization defines pharmacovigilance (PV) as the science and actions associated with identifying, evaluating, reporting, and preventing adverse effects or other drug-related issues. PV is a mandatory legal requirement for all Marketing Authorization Holders (MAHs). It is intended to improve patient care and patient safety concerning the use of pharmaceuticals and medical devices, as well as to support public health programmes by providing reliable, balanced information for the practical assessment of the risk-benefit profile. PV services offered by any MAH need a dedicated quality assurance division staffed by experts to ensure quality Regulatory submissions. Different types of organizations have different QMS goals. The QMS applicable to MAH and the service provider are different; the latter has many responsibilities besides providing the service.

Depending on the MAH's organizational structure, several names may be given to the same group whose job is to oversee the QMS goals outlined below:

Administrative Framework: This is the initial and foremost aspect of the QMS to define 'Who Does What.' This is accomplished by establishing departmental goals such as Individual Case Safety Report (ICSR) processing, aggregate reporting, and cross-functional liaison responsibilities. QMS could assist functional leads in establishing and allocating these positions based on an individual's profile.

Training:

Training is the most crucial purpose of a QMS as it can make or break the compliance of a whole system. QMS must first guarantee that all workers of the MAH, regardless of their functional departments, are trained on fundamental PV and understand their default role in PV. The second responsibility is to have precise processes, a training curriculum, a training plan, a training record, training conduct, attendance evidence for instructor-led training, and assessment findings for onboarding induction and on-the-job training.

Compliance: The criteria for reporting are incredibly severe and operate on calendar days. It is crucial to ensure that the processes and systems are in place to meet the timelines for various activities. The QMS should devise a specific turnaround time for every step and provide metrics for processing aspects to meet these overall timeline compliance requirements.

Documentation: Most Regulatory agencies require compliance with Good Documentation Practices (GDP) in PV. Also, as it is commonly stated in the pharmaceutical industry, "If it is not documented, it did not happen," it is crucial that the QMS has all the necessary documentation protocols in place and that all procedures are documented and appropriately referenced. Certain agencies require the maintenance of the pharmacovigilance system master file. These papers must be carefully categorized, periodically amended, officially authorized, properly stored, easily

accessible, and version controlled. Compliance with GDP is one side of the coin, with storage and retention being the other. Soft and hard copies play a crucial part in identifying the required procedures for document retention.

Safety Data Processing: Data processing for safety is fundamental to the PV system and is extremely extensive. Complete Regulatory requirements ensure the correct and timely reporting of safety information. Due to manual medical and non-medical judgment at different stages of data collection, databasing, and analysis of reported data at both the ICSR and aggregate reports levels, QMS must effectively monitor the processing processes. QMS is responsible for establishing measures to guarantee the truthfulness of the reported information. QMS is also responsible for assuring the risk minimization or mitigation activities.

Transmission: Safety-related communications should only be transmitted promptly by authorized personnel to approved recipients on a need-to-know basis. These notifications include new/modified hazards, modifications to the Pharmacovigilance System Master File, Risk Management Plan, Corrective and Preventive Actions (CAPA), etc. QMS should be extremely careful to ensure that these needed contacts with internal and external stakeholders are made promptly.

Third-party Management: This involves contracts, Safety Data Exchange Agreements, and vendor administration. QMS should be aware that, according to contracts and agreements, only the obligations for MAH's responsibilities are passed to the service provider/vendor. At the same time, liability for those tasks remains with the MAH. In this regard, the QMS should design and ensure that the service provider carries out all the MAH's responsibilities based on the nature of the outsourced services employing Statement of Work (SOW), Service Level Agreement (SLA), metrics, Key Performance Indicators (KPI) monitoring, deviation/CAPA, audits, and training, among others.

Deviations and CAPA: "Human Error" is the root cause of issues and deviations. Therefore, regardless of the precautions planned or implemented, the presumption that our procedures are flawless is merely theoretical. As deviations from developed procedures for known, unknown, planned, and unexpected conditions are always possible, the QMS must constantly be prepared and equipped to handle such situations. This is accomplished through implementing continuous process improvement methodologies, which include documenting the deviation, analyzing its root cause, planning, implementing the symptomatic corrective actions, and planning and executing the preventive actions where necessary.

Information Technology: The majority are likely aware of the objective parts of IT and the IT-driven world of processes. It is correct to state that the QMS staff should possess IT fundamentals and PV domain expertise. Database support and maintenance, data transfers, encryption, security protocols, auto reporting rules, FTP server gateways, deployments, integration of multiple programs and dictionaries, validations, and so on, are all covered by IT Operations. Most of the time, due to a lack of fundamental functioning knowledge of IT, the QMS function faces numerous obstacles while communicating with this department. Knowledge of basic working styles such as agile, waterfall, prince2, PMBOK, etc., so that they may operate as a bridge between PV and IT and align themselves with PV governing regulations, is a straightforward solution. QMS must also ensure the recording and compliance of the Recovery Point Objective and Recovery Time Objective for servers under the IT Infrastructure.

Audits and Assessments: The immediate purpose addresses the system anomalies identified by the continuing development process. QMS should be aware that there is much room for deviations to go unreported in large, established procedures such as PV. Inspections and audits are designed to detect undetected anomalies in the PV system. These serve as quality checks for the QMS and sometimes necessitate fresh eyes.

Corporate Endurance: This is an intriguing and unique QMS aim related to the system's preparedness for unforeseen events. All other objectives would be applicable under normal working conditions; however, this target serves as a lifeline in the event of catastrophic setbacks. As there is always the possibility of a brief or extended period of noncooperation from nature and the environment, the QMS should identify all critical processes and resources, as well as their alternative approaches, to ensure that all essential dependent tasks of critical path steps are completed, regardless of external factors.
As the safety of the human population is involved with PV systems, quality is an essential need for all linked activities. A QMS should have a scientific approach to planning, plan adherence throughout implementation, assurance of implementation quality, and ongoing process improvement. Personnel of high quality are not perfect or always right, but rather those who accept responsibility for their actions, objectively evaluate them, and adjust, are better than before.

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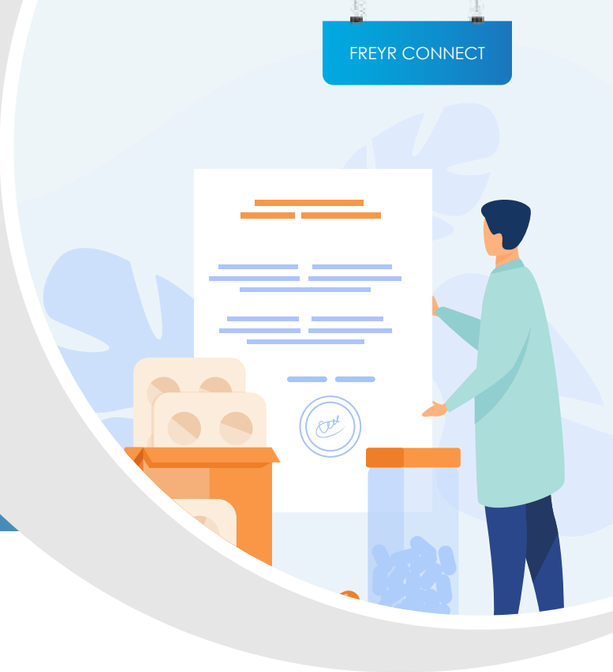
Regulatory Affairs

WHAT IS SUSMP?



SUSMP is an acronym for 'Standard for the Uniform Scheduling of Medicines and Poisons.' 'The Poison Standard' is the legal title of SUSMP. It was introduced under the Legislation Act 2003. The main objective of introducing SUSMP was to promote uniform labeling and packaging requirements throughout Australia.

The SUSMP is a legal document that consists of decisions regarding the classification of medicines and poisons into 'schedules' for inclusion in the relevant legislation of the states and territories. The classification considers a substance's toxicity profile, indications, dosage, pattern of use, product formulation, the potential for abuse, and the need for access. It contains model provisions regarding the containers and labels, along with a list of recommended products that need to be exempted from these provisions. It also includes directions on drug and poison control.

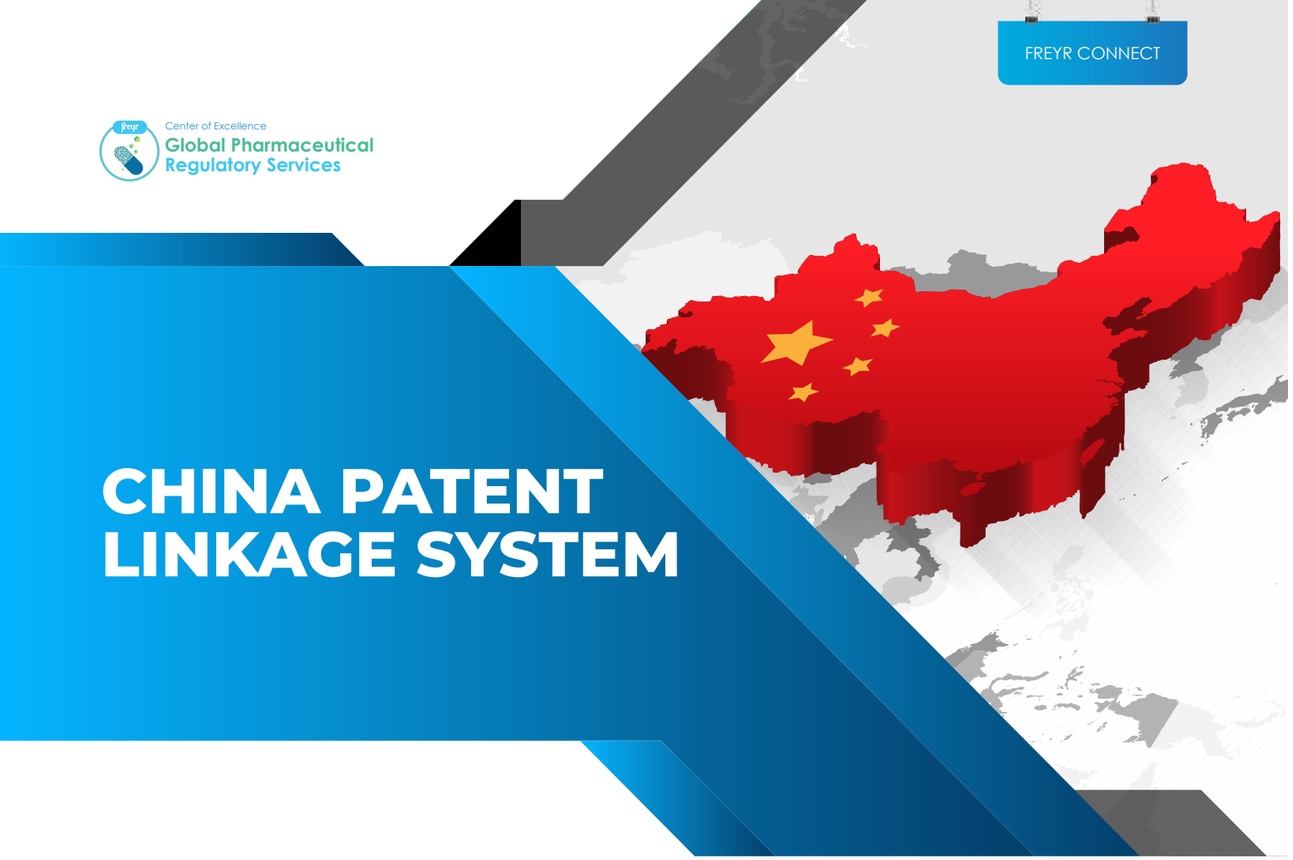
Prescription medicines are high-risk medicines that contain ingredients described in Schedule 4, Schedule 8, or Schedule 9 of the SUSMP and are available by prescription only. This group of medicines also includes some specified products such as sterile injectables.

Schedule	Description	Use
S4: Prescription-only Medicine/ Prescription Animal Remedy	Prescription-only medicines for supply by a pharmacist only.	Therapeutic (drugs)
S8: Controlled Drug	Substances that require a restriction of manufacture, supply, distribution, possession, and use to reduce abuse, misuse, and physical or psychological dependence.	Therapeutic (drugs)
S9: Prohibited Substance	Substances that may be abused or misused; the manufacture, possession, sale, or use should be prohibited by law, except when required for medical or scientific research.	Medical or Scientific Research

The SUSMP is also available in an electronic form and can be accessed free of cost on the Federal Register of Legislation (FRL). The SUSMP is updated regularly. The latest edition is SUSMP No. 37, which was updated in October 2022. This includes numerous changes from the previous edition of June 2022 (SUSMP No. 36).

For more insights on the Therapeutic Goods Administration (TGA) updates, SUSMP, and TGA drug registration classification, contact Freyr.

CHINA PATENT LINKAGE SYSTEM



DYK? The National Medical Products Administration (NMPA), along with China National Intellectual Property Administration (CNIPA), has released "Measures for the Implementation **of Early Resolution Mechanisms for Drug Patent Disputes (Trial)**." It is a patent registration platform for chemical drugs, biological products, and traditional Chinese medicines. Along with this, the measures will also help by offering opportunities for market approval based on registered patents and judgment outcomes for chemical entities.

An exclusivity period is also awarded to the first generic applicant who succeeds in challenging registered patents. This is similar to the Hatch-Waxman Act under the US Generic Drug Framework. However, unlike US Food and Drug Administration's (US FDA's) Hatch-Waxman Act, the China Patent Linkage System is also applicable to biological products. In the US, the Regulatory framework for biosimilar products and publication of patent lists for reference biological products is given under the Biologics Price Competition and Innovation Act (BPCIA) and Biological Product Patent Transparency (BPPT), respectively.

What is the Patent Registration System? How is it Applicable to Chemical Drugs, Biologics, and Traditional Chinese Medicines?

In accordance with the measures, a patent registration system has been recognized for the Marketing Authorization Holder (MAH). The MAH can register applicable patents to the approved drug product and update the information in the Patent Registration System (information such as generic name, registration number, dosage form, and strength), patent information (patent number, patentee/licensee, title, issue date, expiration date, legal status, type of claims, and the relation of claims to the approved drug), and correspondence information (such as address and contact information of the contact person).

Registration for patents of chemical drugs, biologics, and traditional Chinese medicine can be done, but there are some limitations on the types of patents that can be registered. Patents that can be filed for a chemical drug are a patent covering the Active Pharmaceutical Ingredient (API), a patent covering the formulation comprising the API, and a patent directed to the medical use of the API. On the other hand, for biologics only patents cover the API in the form of structured information and the medical use associated with it.

The patent registration system in China serves the purpose of both Orange Book and Purple Book because it contains information on both chemical drugs as well as on biological products.

What is Patent Certification? How is it Applicable to Chemical Drugs?

To file a patent on an already patented innovator chemical drug, the generic product must file a patent covering any of the following types:

1. No relevant patents are registered
2. The patent for the innovator product has expired or been declared invalid or the generic applicant has a license
3. The registered patent in the name of the innovator exists, and generic products cannot be marketed until the expiry of the patent
4. A registered patent exists, but it must be invalid or does not include generic drugs

Generic drug companies need to provide patent certification along with supporting data to the innovator. This is done to provide the patent owner a full knowledge of the formulation so that the patent owner's patent is not infringed. The supporting data that is needed includes:

1. Technical description of the generic drug
2. Claim chart comprising the registered patents and the generic drug
3. Relevant technical materials

What are Patent Challenges and Bifurcated Judgement Systems? How are they Applicable to Chemical Drugs?

With an eye on the Type IV certificate, MAH or the owner of the patent has the alternative to either take the court's help or go with CNIPA's judgment as a means of reviewing the generic drug patent within forty-five (45) days. However, the court proceedings pre-empt a subsequent CNIPA proceeding for the same topic.

Upon the initiation of the court or CNIPA proceedings, NMPA holds off the approval of the focussed generic drug for nine (09) months. In these nine (09) months, the generic drug cannot get approval from NMPA unless it is proven to not infringe the existing patent or the patent is invalid, or MAH (or patent owner) withdraws the case. A lawsuit in a court or a proceeding in the CNPIA may initiate a period of nine (09) months' stay in China. However, in contrast to this, the hold-off period for ANDA approval by the FDA in the US is of thirty (30) months. In the US, the patent owner has to file a patent infringement suit in Federal Court against the generic drug applicant.

What is the Exclusivity Period?

An exclusivity period of up to twelve (12) months is awarded to the First to File (FTF) generic drug company that has challenged the already registered patent. However, the market exclusivity should not extend beyond the term of the patent.

On the contrary, an exclusivity period of one hundred and eighty (180) days is awarded to the FTF who has completed ANDA with para IV certification against a listed patent. These one hundred and eighty (180) days of exclusivity cannot exceed beyond the patent term specified in para IV certification because the generic manufacturer will not be eligible for exclusivity after the expiration of the patent, at which time the FDA may approve other eligible ANDAs.

By now you must have understood the need of in-depth knowledge of varied Regulatory subjects and of dynamic guidelines. Be it MAH support, timely submissions, a query from the Health Authority, or end-to-end Regulatory support across the globe, Freyr will be there! Contact us now!

Center of Excellence
Regulatory Labeling

CROSS LABELING: THE REIGN OF REGIMEN FOR COMBINATION THERAPY

A drug therapy regimen is diverse for drugs that can be approved to be used in combination with a previously approved drug or simultaneously developed two novel drugs, that synergistically enhance efficacy. Single-drug cancer therapies significantly showcased drug resistance as a major threat for patients undergoing treatments with anti-cancer drugs. Considering the diversity in combination therapy adopted for cancer treatments, two-drug regimens are gradually replacing monotherapy as a standard of care in patients. Over the decade, combination therapy has provided a better scope of treatment.

If you're an organization that's well aware of the paradigm shift in cancer drug development from single-drug development to novel-novel combinations, you must know that this advancement has led to increased requests to grant cross-labeling requests by the applicant. By recognizing conversations, the latest industry trends, and its current understanding of a sponsor's requirement, the US Food and Drug Administration (USFDA) has granted a set of guidelines to provide support with labeling changes for drug regimens with previously approved drug products.

Congratulations! Your request for cross-labeling guidance has been granted, if:

a. The indication for the requested combination regimen is approved under a similar **Drug Indication**
a. The **Dosage and Administration** section must highlight the recommended dosage for the sponsor's drug in a combination regimen
a. The **Clinical Study Data** must justify the combination benefits for all the drugs in the regimen
a. The **Warnings and Precautions** section must state the uniqueness of the combination regimen based on clinically significant data.
a. The **Adverse Reactions** must be highlighted as observed in the clinical trials
a. The **Patient Counselling Information Leaflet** must be limited to unique toxicities as per the formulation

Information related to the sponsor's drug alone must occupy the remaining sections of the label unless some

FREYR CONNECT

Critical Elements of your Cross Label

unique pharmacokinetic factors need to be mentioned. The approved guidance for cross-labeling specifically targets anti-cancer therapy products to state the foundational understanding of cross-labeling. To help sponsors with operational and Regulatory hindrances regarding label change, the guidance states:

1. Timelines

The applicants are expected to propose the draft content for cross-labeling with an evidence-based justification of the role of each product mentioned under the regimen, in their proposal for cross-labeling a new anti-cancer drug in a pre-NDA or BLA application.

Cross-labeling is expected to be identified for each drug under the regimen at the same time. However, the approval may be granted one after the other, in a sequence, due to the difference in the drug's timeline.

2. Regulatory Submission

Each applicant seeking a cross-label must apply through an original application or efficacy supplement for cross-labeling.

An applicant may choose to reference other applications' data to justify the synergistic benefits of the combination regimen.

While referencing data, the applicant:

- must ensure that the cross-referenced data has already been filed by the FDA
- must annotate each section of the applicant's data that is cross-referenced
- should include (below section) only information relevant to the applicant's drug:
  - BOXED WARNING (If Applicable)
  - DOSAGE FORMS AND STRENGTHS
  - CONTRAINDICATIONS
  - DRUG INTERACTIONS
  - USE IN SPECIFIC POPULATIONS
  - OVERDOSAGE
  - DESCRIPTION
  - CLINICAL PHARMACOLOGY
  - NONCLINICAL TOXICOLOGY
  - REFERENCES
  - HOW SUPPLIED/STORAGE AND HANDLING

Cross-labeling for anti-cancer drugs can help educate the patient population about dosage, efficacy, and merits of treatment outcomes. With an exponential rise of combination therapy as a standard method, cross-labels can prove beneficial in the enhancement or introduction of current therapeutic methods in place. Our seasoned experts at Freyr are well-versed in dynamic labeling challenges and can provide solutions to your labeling queries. Experience professional labeling support at its finest.

Center of Excellence
Global Medical Device
Regulatory Services

SYMBOLS AS A UNIVERSAL LANGUAGE FOR MEDICAL DEVICE LABELING

In a global marketplace with more than 7,100 spoken languages, manufacturers need to consider the local language and culture when developing medical device product labels. How does one make it possible to reach out to a diverse group of people?

One of the time-tested ways is the use of medical device symbols. It can convey a significant amount of information in a small space. Although it is optional, using symbols on the labeling of medical devices is strongly advised. It offers benefits to both users and manufacturers, such as:

- Along with being easier to read and comprehend, symbols convey information with more clarity to the users, with fewer mistakes on the users' end
- Helps in the consistent portrayal of information even when consumers draw their supplies from several sources
- It helps save space on the labels. Translated texts take twice the space to convey the same information
- Symbols are universally recognized, so their use does not necessitate translation

Device manufacturers have three (03) options:

- They can choose not to use symbols
- They can use symbols with adjacent explanatory text (or)
- Stand-alone symbols are the standard symbols that are regulated by ISO 15223 and can be universally used

DYK? The International Organization for Standardization ISO 15223-1 version updated in 2016 is no longer valid. It is replaced by a new 2021 version, ISO 15223-1:2021. However, there is no set deadline for manufacturers to implement the update.

Commonly Used Symbols on Medical Devices

General Symbols: These symbols accompany the labels and provide the end user with general details about the device and provide its unique identification number.

MD	REF	UDI	A → 文
Identify the product as a medical device	The manufacturer's catalog number helps identify the device	Indicates a carrier that contains unique device-identified information	Translation symbol to be added when the manufacturers outsource the IFU translations

FREYR CONNECT

Economic Operators

The EU Medical Device Regulation (EU MDR) and In-Vitro Diagnostic is medical devices not exlcusive of EUIVDR? Regulation (EU IVDR) require the details of Economic Operators (EOs) to be included on the device label. The manufacturer, European Authorized Representative (EAR), importer, and distributor is considered Economic Operators (EOs), and the respective symbols can be used.

		EC REP
Manufacturer: The name and address of the manufacturer	Importer and distributor": Name and address of the importing or distributing entity	Local Representative in European Union": Name and address of the EAR*

**The immediate container does not need an EAR address unless it is the outer container.*

Manufacturing Symbols

These symbols provide the manufacturing details of a given device.

LOT	REF	SN	
Manufacturing batch code of the device	The catalog number traces the device to the manufacturer's catalog to identify the device	The manufacturer's serial number shall be included	Date of manufacture: Manufacturing date in YYYY-MM-DD or DD-MM-YYYY format

Storage Symbols

Storage instruction is very important for medical device users. The storage of the device determines its workability and longevity of the device. Factors like temperature, humidity, etc., can impact on the device.

The upper and lower limits of the temperature	Keep away from sunlight	Keep away from water	The device is "fragile" and to be handled with care	The packaging and device can be recycled

Safety for Use Symbols

Inappropriate use of some devices can pose a risk to the end user. These symbols are used to warn the users before use and reduce risk.

		LATEX		
Consult instruction for use: Advice the users to read through the IFU before use	"Do not reuse," "single-use," or "use only once" symbol	"Contains latex" warn the users that are allergic to latex to use it with caution	"Caution, consult accompanying documents" or "Attention, see instructions for use"	"Contains hazardous substance"

Sterility Symbols

These symbols communicate information about the sterility of the devices.

Non-sterile device and the procedure needs to be carried out before usee	"Do not resterilize": The device should not be resterilized	The device has been sterilized	"Double sterile barrier system" Minimizes the risk of asepsis. An additional dotted line is added when additional packaging is placed

Medical devices are sterilized in a variety of ways, including using moist heat (steam), dry heat, radiation, ethylene oxide gas, vaporized hydrogen peroxide, and other sterilization methods (for example, chlorine dioxide gas, vaporized peracetic acid, and nitrogen dioxide). To provide information to the consumers on the type of sterilization method used, symbols are placed next to the "sterile" symbol.

Sterile medical devices are processed using aseptic techniques	Sterilization using ethylene oxide	Sterilization using irradiation	Sterilization using vaporized hydrogen peroxide	Sterilization using steam or dry heat

In Vitro Diagnostic (IVD) Device Symbolss

IVDs are those reagents, instruments, and systems intended for use in diagnosing disease or other conditions, including determining the state of health to cure, mitigate, treat, or prevent disease or its sequelae.

In vitro diagnostic medical device: Identify IVD and not indicate that the device is for "In vitro use"	Control symbol: the presence of a control material that verifies the performance character of another medical device

Medical device labeling is a critical part of the production process for manufacturers. Devices cannot go to market without the required labels. Symbols form a universal language on the labels. ISO decides the requirement of these labels and the respective Regulatory authorities implements the same.

To know more about symbols used for and IVDs, contact Freyr today!

FREYR CONNECT

REGULATION OF COSMETIC PRESERVATIVES IN THE EU

Preservatives are used in cosmetic products to ensure their safety during their lifetime. As many cosmetics contain water, once exposed to the environment, they become prone to the growth of microorganisms. Furthermore, every time a consumer interacts with the product, it gets introduced to a new population of microorganisms directly from the air or skin.

Microbial contamination leads to product spoilage. It destroys the intrinsic properties of the product, thereby creating a health risk to the consumer. Hence, preservatives are extremely important in cosmetic products.

Preservatives used in a cosmetic product can be either natural or synthetic in nature. They are often used at low concentrations wherein the actual level is limited to the amount that is required to preserve the product during its lifetime.

In the European Union (EU), cosmetic preservatives must be safe for use and should be within the required concentration limits. Considering the same, preservatives used in cosmetics must comply with stringent evaluation to conform to the EU safety standards. Preservatives must undergo rigorous evaluation, including safety assessments and quality testing, before they are approved for use in the EU market.

The European Commission (EC) updates the list of scientifically evaluated safe preservatives for their use in cosmetic products and guides national authorities to monitor products in the EU market.

In the EU, cosmetic products are regulated by the EC under the Cosmetics Regulation EC No. 1223/2009, and preservatives used in cosmetics must also comply with the EU Regulatory guidelines. The list of substances that can be used as preservatives in cosmetics marketed in the EU is included in Annex V of the regulation. The list contains maximum concentration limits along with other restrictions for preservatives. It also contains specific warnings for product labeling and sixty (60) unique substances permissible for use in the EU as preservatives for cosmetics.

To ensure the proper usage of preservatives in your cosmetic products and for Regulatory assistance in the EU market, reach out to a Regulatory expert like Freyr.

WHAT ARE AUST R, AUST L(A), AND AUST L NUMBERS?

All the medicines enlisted in the Australian Register of Therapeutic Goods (ARTG) are allotted an AUST number. The AUST number identifies the product on the ARTG. This is also known as the ARTG ID or registration number, or list number. The AUST number can be either AUST R, AUST L, or AUST L (A).

Medicines with a relevant AUST number on their label ensure that the medicine has been approved (registered or listed) by the Therapeutic Goods Administration (TGA) for supply in Australia.

All registered medicines are always evaluated for efficacy as per their claims before they go for sale. However, not all listed medicines are evaluated for efficacy.

There are different types of AUST numbers, such as:

- AUST L: These are 'listed' medicines and have not been assessed for efficacy
- AUST L(A): These are 'assessed listed' medicines. These are the ones that have been assessed for efficacy
- AUST R: These are medicines that are assessed for efficacy and are also registered in the ARTG

FREYR CONNECT

Comparison Between Different Types of Medicines

Attribute	Listed	Assessed Listed	Registered
ARTG number	AUST L	AUST L(A)	AUST R
Pre-market efficacy assessment	No	Yes	Yes
Ingredients	From a list of pre-approved ingredients, only	From a list of pre-approved ingredients, only	Ingredients are assessed pre-market
Indications of the medicine	From a list of pre-approved conditions, only	From a list of pre-approved conditions, only	Conditions are assessed pre-market
Subject to post-market compliance reviews	Yes	Yes	No
Subject to post-market surveillance	Yes	Yes	Yes
Available off-the-shelf	Yes	Yes	Some
Need for a prescription from a health professional	No	No	Some
Able to use 'TGA assessed' claim	Yes	Yes	Yes, for registered complementary medicines

Any medicine, whether it is registered or listed in ARTG, must be manufactured in a licensed or approved facility in accordance with the principles of Good Manufacturing Practices (GMP).

To know more about drug registration in Australia and to avail end-to-end Regulatory support, contact Freyr.

Center of Excellence
Regulatory Labeling

MEDICAL DEVICE LABELING COMPLIANCE UNDER 21 CFR PART 801

Labeling is defined as the **"display of written, printed, or graphic matter upon the immediate container of any article**." Any medication that is intended to be distributed must be labeled as per the Parts of Title 21 of the Code of Federal Regulations (CFR).

General Labeling Provisions Under 21 CFR Part 801

The US Food and Drug Administration (FDA) medical device labeling requirements demand all risk classes to include mandatory information on the device labeling:

- Name of business of the manufacturer, packer, or distributor
- If the name of the person who did not manufacture the device is on the label - use abbreviations such as "Manufactured for___" or "Distributed by___"
- Abbreviations for "company "can be used
- Place of business - Business unit address, city, state, zip code
- Adequate directions for the use
- Frequency, duration, time, route of administration, and preparation for use
- Accepted format for date (YYYY-MM-DD) Eg; 2014-01-04 for January 04, 2014
- Every medical device label and package should bear FDA Unique Device Identifier (UDI) labeling requirements

Language Requirements Using Symbols

The required label statements must be in the English language. In territories where the predominant language is not English, the language may be substituted, such as Spanish in Puerto Rico.

An FDA-recognised or standards development organization (SDO) established symbol can be used without an explanatory text. Otherwise, the symbols must be accompanied by English explanatory text. For regions where English is not predominant, the respective regional language can be used.

Labeling Requirements for Over-the-Counter (OTC) Devices

The principal display panel must include all the mandatory label information without causing any crowding, conspicuousness, and obscuring design. The labeling must include the following:

- Statement of identity, including the common name of the device and accurate principal intended action(s) of the device
- The declaration of accurate net quantity of contents
- Reasonable variations caused by loss or gain of moisture during distribution should not be large and should be stated
- The declaration is in letters and numerals such that it fits well in the display panel. It should be uniform for all packages

The OTC devices containing or manufactured with Chlorofluorocarbons (CFC), halons, carbon, ozone tetrachloride, methyl chloride, or any other Environmental Protection Agency (EPA) Class I substances shall carry one of the warnings either on the immediate container, outer packaging, or labeling component. The use of CFCs in devices as propellants in self-pressurized containers is generally prohibited. The below warning statement is a must.

EPA warning statement- "Contains [or Manufactured with, if applicable] [insert name of substance], a substance which harms public health and environment by destroying ozone in the upper atmosphere."

In addition to the EPA warning statement, the Federal government's Clean Air Act for all products requires the underneath statement for devices containing or manufactured with CFCs.

"Consult with your physician, health professional, or supplier if you have any questions about the use of this product."

Device-specific Labeling Requirements

Repairing or Refitting Dentures

Wearing improperly repaired or refitted dentures continuously causes increased bone resorption and other irreparable damage to the oral cavity. **The FDA medical device labeling guidelines** regard labeling claims exaggerating the usefulness or the safety or failing to disclose all facts of the material as false and misleading. Such products are considered unsafe and misbranded unless the labeling:

- Limits directions for the use of denture repair kits for emergency repairing, denture recliners, pads, and cushions to temporary refitting
- Contains the word that precedes "emergency" for denture repair kits and the word "temporary" preceding recliners, pads, and cushions in the IFU
- Includes a conspicuous warning statement to the effect:

1. For denture repair kits: "Warning - For emergency repairs only. Long-term use of home-repaired dentures may cause faster bone loss, continuing irritation, sores, and tumors. This kit is for emergency uses only. See Dentist without delay."
2. For denture recliners, pads, and cushions: "Warning - For temporary use only. Long-term use of this product may lead to faster bone loss, continuing irritation, sores, and tumors. For use only until a Dentist can be seen."

- Adequate directions for use must have full information for the layman to understand the limitations of usefulness
- A warning statement should be included if the denture relining or repairing material forms a permanent bond with the denture

"This recliner becomes fixed to the denture, and a completely new denture may be required because of its use."

Labeling for Prescription Hearing Aid

The outer and inner packaging labels should include a warning for prior medical evaluation from a doctor, preferably an Ear, Nose, and Throat (ENT) in cases of users younger than 18 years, and the conditions when to consult a doctor. The labeling must communicate to the user what to expect from the use of a hearing aid, information on the function of all controls intended for user adjustment, description of any accessory that accompanies the prescription hearing aid, maintenance, and care, expected battery life, whether it is rechargeable or single-use, type of battery needed and method of changing it, any side effects and when the patient should meet the ENT. The labeling must include information on:

- Serial number of the device
- Statement of build condition on the outer package whether the hearing aid is used or rebuilt
- If the prescription hearing aid is used or rebuilt, the manufacturer shall physically attach a removable tag to the hearing aid declaring that fact

- Battery information on the outer package –type and number of batteries (if included in pack)
- Indication of control platform – indicate if the mobile device or other non-included control platform is required, the type of platform, and how the platform connects to the device
- If the battery is removable, a "+" symbol indicates a positive terminal for battery insertion unless physical design prevents inserting the battery in the reversed position
- Pre-requisites for dispensing hearing aid and determining the right prospect
- List of possible adverse events, device reporting manufacturer, and the market complaint process

Warnings

- Special warning for dispensing hearing aids with an output of over 132 dB SPL
- Not using the device for hearing protection
- To reduce the volume/remove the piece if the sound output is painful or uncomfortable
- To seek medical help in case the device is stuck in the ear
- Information on ear wax build-up drops, immersion in water, or exposure to heat
- Information on how and where to obtain repair service or replacements, including at least one specific address where the user can go or send the prescription hearing aid
- Technical specifications must be included in the user instructional brochure. Software labeling about compatibility, minimum operating requirements, any fees, or payments

Labeling for Menstrual Tampon

Toxic Shock Syndrome (TSS), a rare but sometimes fatal, is associated with the use of menstrual tampons. The label must bear below information on warning signs of TSS, e.g., sudden fever (usually 102° or more) and vomiting, diarrhea, fainting or near fainting when standing up, dizziness, or a rash that looks like a sunburn, what to do if these or other signs of TSS appear, including the need to remove the tampon at once and seek medical attention immediately. The label must include the following:

- Absorbency terms
- A description of how consumers can use the range of absorbency, and its absorbency term, to make comparisons

This helps in tampon selection with the minimum absorbency needed to control menstrual flow, reducing the risk of contracting TSS.

Labeling Requirements for Condoms Containing LATEX

The condoms are made with spermicidal lubricant formed from latex films. The material integrity of latex condoms degrades over time and hence must bear an expiration date that is supported by testing, displayed prominently and legibly on primary packaging. The condoms qualifying the physical and mechanical integrity tests can bear an expiration date of up to five (05) years from the date of product packaging. In the case of a spermicide-containing latex condom, if the expiration date based on spermicidal stability testing and latex integrity testing are different, the product shall bear only the earlier expiration date.

Labeling Requirements for Condoms Containing Natural Rubber

Applicable to products containing natural rubber latex, dry natural rubber, and synthetic latex or synthetic rubber that contains natural rubber in its formulation. Natural rubber may cause severe anaphylactic reactions, and the labeling is intended to minimize the risk to individuals sensitive to natural latex proteins. The inclusion of the term "hypoallergenic" is prohibited as it can be misleading. The labeling statement must be in bold print, prominently, and legibly displayed.

"This Product Contains Dry Natural Rubber"

Labeling isn't just about a sticker or engraving on a device. It covers important details associated with the medical device. **FDA medical device labeling guidelines** consider the label misbranded when any of these above instructions are not followed accurately. Incorrect labeling is one of the top five (05) reasons globally for device recalls. While designing a medical device label, it is important to consider the Regulatory pathway we chose to pursue along with the exemptions that apply. It is imperative to address the labeling requirements early on in planning so one can be prepared when it is needed.

Complying with **21 CFR part 801 labeling** guidelines is critical for organizations. How aligned are you? To know more about **21 CFR part 801**, contact our Regulatory experts at Freyr.

IMPORTANCE OF QUALIFIED PERSON FOR PHARMACOVIGILANCE (QPPV) AND LOCAL RESPONSIBLE PERSON (LRP)

Marketing Authorization Holders (MAHs) with medicinal products authorized for marketing in the European Economic Area (EEA) have a legal responsibility of establishing a PV system for accomplishing PV obligations for their products. To this end, the MAHs in the European Union (EU) must appoint an appropriately qualified person for PV (QPPV). The role and responsibilities of the QPPV include, but are not limited to:

- Establishment and maintenance of the MAH's PV system
- Round-the-clock (24/7) availability as the single PV point of contact for the European Medicines Agency (EMA) and other National Competent Authorities (NCA)
- Monitoring product safety, emerging safety concerns, and risk-benefit balance of the MAH products

- Oversight over the functioning of the PV system in all aspects, including the quality system
- Access to the PV System Master File (PSMF) and ensuring that the information contained therein is an accurate description of the PV system under the QPPV

The QPPV must be available to the MAH permanently and continuously and reside and operate in a member state of the EEA (which includes Norway, Iceland, and Liechtenstein). Back-up procedures must be in place in case of the absence of the QPPV. For the United Kingdom (UK), where a QPPV does not reside in the UK, a local responsible person for PV (LRP-PV) residing in the UK must be appointed.

The MAH must ensure that the QPPV has adequate skills for the management of PV systems, in addition to key areas such as medicine, pharmaceutical sciences, epidemiology, and biostatistics. If the QPPV has not completed his/her basic medical training, the MAH must ensure that the QPPV is assisted by a medically trained person. The role of the QPPV and the medically trained person support can be outsourced on a need basis.

Many European (and non-European) countries may legally require an LRP-PV (also called local QPPV, or National Person Responsible for PV (NPRP)) at the country level, who may report to the EU QPPV (for example, an LRP-PV for Germany is called Stufenplanbeauftragter). Despite the use of different titles used to describe the person performing this role, they all represent the same role of representing an MAH at the country level, and the efficient functioning of PV systems and processes are also regarded as the same.

The LRP-PV must be an experienced person, a resident of the country where the LRP-PV services are required and should be fluent in the national/local language.

In contrast to the EU QPPV, whose role and responsibilities are specified in the EU legislation, LRP-PV is subjected to relevant national legislation. The role and responsibilities of the LRP-PV/NPRP include, but are not limited to:

- Intake and local-level processing of Individual Case Safety Reports (ICSR)
- Local submissions of Regulatory documents
- Local literature monitoring (non-indexed)
- Implementation of additional risk minimization measures (ARMM), locally
- Providing PV or product-specific training
- Compliance monitoring
- Fulfilling all local PV requirements as laid down by the NCA/local Regulatory authority
- Acting as the liaison for the MAH and NCA, facilitating communication at a local level

The following is the current EU member state requirement regarding the nomination of an LRP-PV at the national level:

Required	Not Required
Belgium	Austria
Bulgaria	Estonia
Croatia	Finland
Cyprus	Iceland
Czech Republic	Ireland
Denmark	Italy
France	Malta
Germany	Norway
Greece	Slovenia
Hungary	Sweden
Latvia	
Lithuania	
Luxembourg	
Netherlands	

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Required	Not Required
Poland	
Romania	
Slovakia	
Spain	

Freyr currently has its QPPV based out of Germany and Poland and can cater to the QP needs of the EU region. Freyr also has a Deputy QPPV in Romania. Freyr's extensive affiliate network across the globe also allows us to cater to LRP-PV support for the majority of the EU countries. With an increasing demand for QPPV-like requirements outside of the EU, Freyr can cater to such needs with its vast and growing global network. Consult Freyr!

Press Release

Freyr Records

450

HBEL Report Submissions in 2022

Freyr Records 450 HBEL (PDE/ADE & OEL) Report Submissions in 2022

Know more

Center of Excellence
Chemicals Safety and Regulatory Affairs

Infographic 1

PET FOODS REGULATORY SNAPSHOT

(US, EU, CANADA & JAPAN)

In the major global markets, pet foods are regulated at every stage; from the raw materials used, through the production process to marketing, sales, imports, and exports. While some of the markets implement a pre-market approval process like registration or notification for all pet food, animal feed, and feed additives, others do not have a pre-market approval process but regulate the ingredients and additives used in pet foods.

A REGULATORY SNAPSHOT OF PET FOODS IN THE US, EU, CANADA, AND JAPAN

Country	US	EU	Canada	Japan
Regulated By	FDA, CVM	EC, EFSA	CFIA	MoE, MAFF, MIC
Positive List Present	Yes	Yes	Yes	Yes
Product Registration	Federal: Not Required; State: Required	Required	Not Required	Not Required
Site Registration	Required	Required	Not Required	Not Required
Importer Registration	Required	Required	Required	Not Required
GMP	Required	Required	Not Required	Required
Timeline	State-wise Variation	6-24 months	NA	NA
Cost	State-wise Variation	>Euro 6000	Max. $1,324	211,900 Yen
Length of Authorization	Unlimited	10 Years	Unlimited	Unlimited
Major Regulations	**21 CFR:** • Part 507 • Part 509 • Part 573 • Part 582 • Part 584 • Part 589	**Regulation (EC):** • No.178/2002 • No.183/2005 • No.68/2013 • No.1831/2003 • No.2020/354 • No.152/2009 • No.1069/2009 **Council Directive:** • 2002/32/EC	• Packaging and Labeling Act • Competition Act • **Schedules IV and V:** Approved Feed Ingredients	• Safety of Pet Food • Specifications and Standards of Pet Foods

Explore the best practices for Regulatory compliance in the US, EU, Canada, and Japan markets

Consult More

Center of Excellence
Global Medical Device Regulatory Services

FREYR CONNECT

Infographic 2

Foreign Manufacturer Registration (FMR) in Japan

DYK? Japan's Pharmaceuticals and Medical Devices Act (PMD Act) mandates all foreign manufacturers to register their relevant manufacturing facilities through the Foreign Manufacturer Registration process (TOUROKU).

Pre-requisites for Foreign Manufacturer Registration (FMR)

Manufacturers must ensure that certain prerequisites are fulfilled before submitting the FMR application. All the documents must be in Japanese language only.

Appointing MAH/DMAH
All foreign manufacturers must appoint a MAH/DMAH

Business Number Registration
Obtain a Business Number for each manufacturing facility

Facility Map
Drawings, floor plans, pictures, etc. of the building(s) in scope

"Shomeisho"
Self-Declaration of Medical Condition (Shomeisho) of the Senior Manager representing the manufacturer

Types of Manufacturing Facilities that Require FMR

Manufacturing facilities are evaluated to ensure that the foreign manufacturer is qualified to participate in the product registration procedure. The following sites need to be registered for each medical device product:

TYPE 01 — Design Facility
The location where the product is developed, and development records are kept

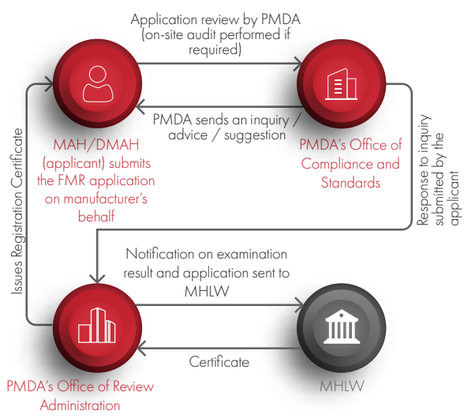
TYPE 02 — Main Assembling Plant
The facility executes assembly processes and is largely accountable for ensuring that the QMS requirements are followed or for the manufacturing of products

TYPE 03 — Sterilizer
The location where the sterilising process is carried out (for sterile medical device products)

TYPE 04 — Domestic Distribution Center in Japan
The location that stores and handles the product's final distribution to the Japanese market.

FMR Review Process

The FMR certificate is valid for five (05) years. The Ministry of Health, Labour and Welfare (MHLW) advises starting the renewal procedure at least five (05) months before the certificate is due to expire.



Decode more about Foreign Manufacturer Registration (FMR) in detail

Consult More

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Success Story

Freyr PRO SUBMIT

EAEU COMPLIANT eCTD SUBMISSIONS USING FREYR SUBMIT PRO

About Customer

US-based, global biopharmaceutical company with major focus on Hematology, Cardiovascular, Immunology, Fibrotic Diseases, and Neuroscience-based products.

Business Needs

The goal was to implement a system that can create EAEU eCTD compliant submissions.

- An electronic system to compile, validate, publish, track and manage the dossiers in eCTD format for the EAEU region
- Tracking lifecycle management and submissions variations
- Support in understanding the developing changing regulations and altering Regulatory standards

Key Objectives

To compile, validate, and publish EAEU Regulatory submissions efficiently based on decisions and rules set by different Health Agencies

- Supports current eCTD folder structure and XML format
- Allows validation for an expanded variety of application types like Original, Generic, Hybrid, Biosimilar, Vaccines, etc.
- Provides intuitive dashboard and reporting capabilities
- Integrates with Electronic Document Management

System (eDMS)
- User-friendly life cycle management with powerful audit trails

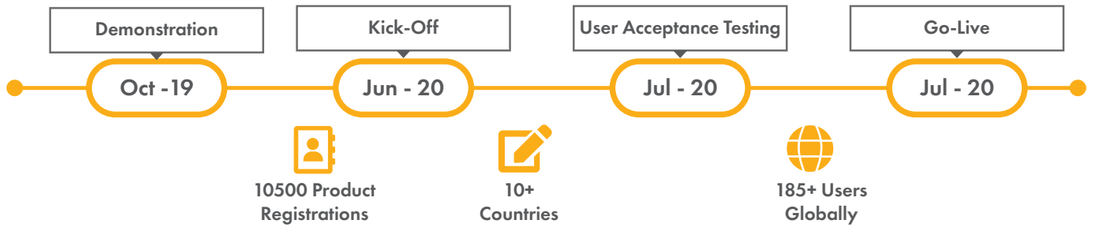
Scope

- A robust and an user-friendly eCTD submission platform with EAEU Regulatory compliant folder structure and XML backbone
- Compile, validate, publish, track, and manage dossiers for all the existing submissions

Freyr Solution Offered

- User-friendly eCTD Regulatory publishing and submission software for lifecycle management, powerful search, notifications, tracking, and reporting for EAEU
- Powerful audit trails and dashboards for submission metrics
- Available eCTD templates/folder structures for EAEU as per the regulations
- Integration with DMS

Implementation Timeline

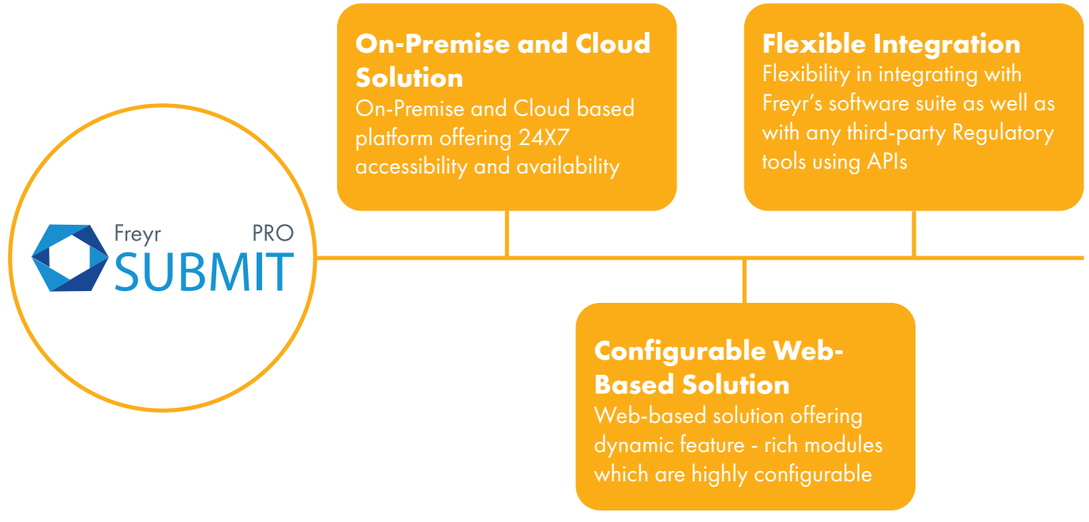


Key Benefits Delivered

Solution Advantage

- Hassle free data entry and management with existing Freyr centralized data entry team
- Regulatory compliance eCTD submissions
- Supports all type of response submissions
- Validated eCTD submissions
- Role based users for better control over submissions
- Significant cost savings and leveraging existing investments
- One stop eCTD submission management platform
- Annex 11 compliant and validated system

Platform Advantage



Case Study 3

Center of Excellence
Global Pharmaceutical Regulatory Services

REGULATORY SUPPORT IN LCM SUBMISSIONS FOR IND APPLICATIONS WITH ZERO ERRORS

Client
China-based Biotechnology Company for Oncology Products

Freyr CoE/Products
Publishing & Submissions

Industry
Pharmaceuticals

Service Region
USA

Client Location
USA

Therapeutic Area/Indication
Immunology

Health Authority
USFDA

Service Offering
LCM Submissions for IND Applications

BENEFIT HIGHLIGHTS
- Ensuring **100%** Accuracy
- **Zero Defects** and High-quality Delivery
- Quick Turnaround Time

Business Imperatives

- Filing of LCM submissions for IND applications to the USFDA
- Client was looking for quality submissions to be delivered in swift timelines

Challenges

- Tracking versions of frequently changed documents and replacing the same in eCTD
- Freyr team was challenged to work on large volumes of documents in a defined period
- Freyr delivered the submissions in very stringent timelines

Freyr Solutions & Services

Freyr also provided a diverse set of services that included:

- Granular Document Level Publishing (DLP)
- Quick review of all the source documents for additional questions
- Detailed tracker creation to track all the version changes made throughout the publishing cycle
- Validation using appropriate industry-accepted/Agency-recommended tools

Client Benefits

- Provided valid submissions with zero errors and warnings
- Maintained transparency through the process
- Played an important role in accelerating ahead of the competition with swift approvals of submissions
- Dedicated full-time resources with continuous support

FREYR CONNECT

Freyr
Regulatory Radio

Freyr Podcast
Season 2
Pharma Advertising and Promotions

Episode 1: Zimbabwe
Episode 2: Australia
Episode 3: Lithuania
Episode 4: The United Kingdom
Episode 5: Mexico
Episode 6: Canada

Scan QR code

To Listen now all these

Scan QR code

To Listen now all these

Stay tuned for Freyr Regulatory Radio,
Season 3
The US Market Entry

Freyr Webinar Series

In a view to making 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 the following topics:

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

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

Know More

“Client Testimonials”

Kyowa Kirin – Publishing and Submissions

I am impressed by the team Freyr. I have worked with other vendors that provided publishing support, but what sets Freyr apart is that they act more like team members, adding expertise to changes in guidance and advice on navigating rather than just taking a publishing task and providing an output. In my experience, other vendors needed detailed instructions. But Freyr better understands what is needed by partnering with RA and fostering open lines of communication.

Associate Director, Regulatory Operations
Japan-based, innovative Pharmaceutical Company

Microlabs – Staffing Services

Thank you, Freyr. Our team had a good experience with your team, both in the past and now. We will require your services again in the near future.

Sr. Vice President - Regulatory Affairs
India-based, Leading, Multi-faceted Pharmaceutical Company

Mallinckrodt Pharmaceuticals – Publishing and Submissions

Dear Freyr team, I wanted to tell you how lucky/grateful/appreciative/thankful we are to have a support team like you to support our last-minute submissions for our new drug approval. This is a continuum of support from the team, but the recent one was another demonstration of excellence. Thank you!

Executive Director, Regulatory Affairs
Ireland-based, Global Specialty Pharmaceutical Company

Brij Strategic Consultations (FDAMAP.com) – SPL

Thanks for the final file. I really appreciate all the hard work put into this by Freyr. Looking forward to working with you again, soon.

Regulatory Affairs Consultant
US -based Leading Lifesciences Consulting Firm

ECSTATIC ENERGETIC ENTHUSIASTIC

GANESH GOPAL PARKAR
FOR EMPOWERING PERSPECTIVES

Hi Ganesh. We are grateful to have you strategizing our future at Freyr. Wishing you an inspiring journey ahead.

Thank you!

As you may know, Freyr has completed a decade in the industry and is leaping toward celebrating the next big milestone. As a chief strategist spearheading the overall organizational transformation, where do you see Freyr heading towards, and what should we Freyrians commit to in the process?

At Freyr, we are in a unique position. There is tremendous market momentum for our vision, and to capitalize on this, we have set ourselves a very audacious goal - to be a billion-dollar organization by 2030. To achieve this goal, I would request our Freyrians to first have a strong belief that the goal can be achieved and, secondly, work as one team towards the same. Being "one" as a team is very important because of the speed and agility required as the organization goes through growth spurts. The one thing that we, as leaders, can commit back to you is that by being part of the journey, each one of you will have accelerated growth in your expertise and work areas.

In any such phase of organizational transformation, to maintain or regain control over a process/es, there will always be a situation that threatens to become chaotic. We wish that you never had to come across such scenarios at Freyr. In general, how do you see these situations, and what best can one do to overcome/address/streamline/resolve them?

We, as Freyr, are changing the wheels on a moving train. It will be utopian to say that all of this will happen with zero disruption. However, the chaos that emerges can be managed by transparency and overcommunication.

We have renewed our focus on revisiting and restructuring our SOPs to synergize with our new working methods. We, as leaders, are trying to get better at talking about the "WHYs" - the reasons for the changes being made. I would encourage the team to voice their questions and their concerns. It may bring to our notice certain scenarios that we may not have thought through and allow us the opportunity to resolve them.

From the little we know, we see Ganesh's philosophical side in the conversations. Referring to the same, what can you suggest about life to the many younger lot flocking Freyr?

I would suggest one thing to the much younger folk flocking to Freyr. The habits that you form in the early part of your career define your career trajectory for life. These habits could be around how you absorb knowledge, how you work with your teams, how you communicate, and how you share and receive feedback. Please give yourself a little time to think about the actions that you do every day and see if they are helping you form the right habits. One example of forming a habit is always being on time for a meeting. Another habit could be reading a topic every week about the work that you do. There is a book that articulates what I just described – Atomic Habits. In my opinion, it's a must-read during the early part of your career.

Calculated strategy targeted for the benefit of the organization vs. long-carried emotion and loyalty for a trustworthy future; which one would you vote for, and why?

These two terms are not mutually exclusive. Any "explosive" strategy has objective goals and measures, but the same can only happen if passion and emotion exist. A strategy without an enabling culture that has belief in the goal will not lead to spectacular results. Belief comes with first acknowledging that the goal an organization has embarked upon is beneficial to the organization and self. Once the belief sets in, all the emotion and passion can be directed towards making the same happen.

Among the 3000 books that you have read, which one is your favorite, and which one would you suggest everyone at Freyr must, at least, try reading the preface?

I have many, and I could fill this page talking about the same. However, to be brief, "Catch-22" by Joseph Heller is my all-time favorite book. There is a lot of humor and a lot of underlying pathos. However, it may not be everyone's cup of tea. Therefore, the book that I would recommend is one of my recent favorites, "The Book Thief," by Markus Zusak, a beautiful homage to the goodness of human beings.

What is your best mantra for work-life balance in the era of false flexibility?

The era of always-on connectivity has also translated to always "On Availability." As leaders, we are trying to be respectful of the working hours and defined limits. We are also mentoring our teams across the organization on the same.

My mantra is that work-life balance is my responsibility and is not defined by external factors. If I plan my day well, for the most part, I can take care of my family and personal obligations.

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Complying with the General Data Protection Regulations (GDPR), we have changed how we collect, store, process, and transfer data. We hope you understand Freyr's efforts in complying with mandatory GDPR requirements. Let us be compliant together.

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.

Globally, Freyr is a Strategic **Regulatory Solutions** and **Services** Partner to

8 Product labeling and Artwork management

4 Forbes Global Top 10 Health Care Equipment & Services

3 Forbes Global Top 10 Household & Personal Product Companie

2 Forbes Global Top 10 Chemicals Companies

2 Forbes Global Top 10 Food & Drink Companies

1100+ Customers

135+ Innovator Pharma Companies

50+ Bio-Tech/Bio-Similar Companies

135+ CROs/Consulting Companies

280+ Medical Device Companies

370+ Consumer Companies (Cosmetics/Food and Food Supplements)

180+ Generic Companies/API Manufacturers

USA | UK | Germany | UAE | India | Canada | Mexico | Malaysia | South Africa | Singapore
Slovenia | Sri Lanka | Australia | Poland | France | Switzerland | China | Japan | Brazil

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