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LEAD STORY

Pharma Sector in China - The Next Big Thing in Focus

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What's INSIDE?

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FOREWORD

Dear Patrons,

Greetings!

We hope you are all doing well and had a good first half of 2022. With great pleasure, we bring forth the latest Issue of Freyr CONNECT, Volume 10.

From acquiring 1000+ global Regulatory customers to Freyr SPAR being selected as the global RIMS solution by a Japanese pharma company, we have had several milestones in the past few months. Our aim is to offer disruptive Regulatory solutions to global pharma and life sciences companies, and thanks to our dedicated patrons, stakeholders, and employees, we are one of the leading providers of pioneering services worldwide.

In this ever-changing and technology-focused Regulatory environment, it is important to follow a streamlined and compliant process to minimize the cost and save time while following the revised mandates of the respective Health Authorities. Our latest Issue will act as a reference as it brings you the most recent updates for a compliant pathway.

So, here is a sneak peek of what's inside this Issue. We start off with a lead story on the current pharma sector in China and the market prospects therein. Subsequently, we have included Freyr's Thought Leadership on outsourcing medical writing and the process for an Rx to OTC switch in the USA. Moving on, we have described the FSSAI's recent mandate on the registration and inspection of foreign food facilities and a comparative analysis of TGA's 2018 and 2022 advertising codes. Finally, the Issue proves Freyr's mettle in Regulatory solutions through our case studies.

We hope that you will find this Issue meets your Regulatory needs and helps you with your overall business strategies.

Happy Reading!

Suren Dheenadayalan

CEO

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PHARMA SECTOR IN CHINA

THE NEXT BIG THING IN FOCUS

China is one of the fastest-growing pharmaceutical markets globally and is positioned second in medicinal product sales after the USA. With more than $150 billion worth, the Chinese pharmaceutical market has become a superpower for exports and imports of medicinal products. Additionally, China is the world's second-largest economy, which attracts reasonably high investments.

With the current scenario, market gurus opine that it is time for drug manufacturers or sponsors to enter the Chinese pharma market. China's pharmaceutical industry will be the world's largest in under ten (10) years. However, it requires clear-cut Regulatory strategies to comply with the National Medical Products Administration (NMPA) standards for streamlined market entry.

NMPA is the regulating body for food, drugs, and medical devices in China, and sponsors/manufacturers need to get the Agency's approval to market their products. Post-2015, the Chinese Government has made several radical changes to create an environment that is sustainable and focused on growth in the import and/or export of pharmaceutical goods. It is also important to consider that the NMPA is focused on providing safe medicinal products to the public.

The Chinese Government's ground-breaking initiatives stand true testimonies for releasing high-quality products. Let us look at some of the initiatives to get a better picture of the pharmaceutical market in China.

Healthcare System in China – An Overview

Being the most populous country in the world, China has not only been a lucrative market for pharma companies worldwide but also ensured that the quality of the drugs is not compromised.

Here is a comparative analysis of the market and the healthcare system pre-and post-2015.

Aspects	Pre 2015	Post 2015
Public Healthcare System	Non-structured with inadequate social health insurance plans and out-of-pocket payments for more than half of the health expenditure	Streamlined with the consolidation of public health insurance schemes under the National Healthcare Security Administration (NHSA)
Regulatory	Absence of defined Regulatory policies for the regulation of medicinal products	Evidence-based Regulatory decisions and policies
Quality	Lack of distinct Regulatory guidance to ensure the quality of medicinal products	Making evidence-based Regulatory decisions, thus addressing the quality of the products
Innovators	The disparity in health coverage led to benefits being polarized in the high-income areas	Development of effective pathways for national price negotiations to make the most of innovator medicinal products
Generics	Limited state investment and non-centralized policies	Creation of the Generic Quality Consistency Evaluation (GQCE) program to regulate generics and extensive state investment programs

Another notable national initiative for the long-term benefits of the public is the 'Healthy China 2030' program.

What is the 'Healthy China 2030' Plan?

The 'Healthy China 2030' plan was first announced in 2016 to centralize and streamline the public healthcare system. The whole plan is based on four (04) core principles – health priority, innovation, scientific development, and fairness & justice.

Here are the five (05) major aspects of the plan.

- Improvement in the level of health of the public in China
- Controlling major risk factors
- An increase in the health service capacity
- Scaling the health industry in terms of expansion
- An ideal healthcare system

Current Market Landscape

The Chinese State Food and Drug Administration (CFDA), which was replaced by the NMPA on September 01, 2018, joined hands with the International Council for Harmonization (ICH) in mid-2017 to transform its Regulatory landscape. The move to become an ICH member has opened the Chinese market to import and/or export drugs. Hence, the current pharmaceutical market in China seems promising and is expected to cross $160 billion by the end of the next year. It is estimated that the country will account for 30% of the global market share by 2023.

On the other hand, considering the huge population, the need for innovative and generic medicinal products is always high.

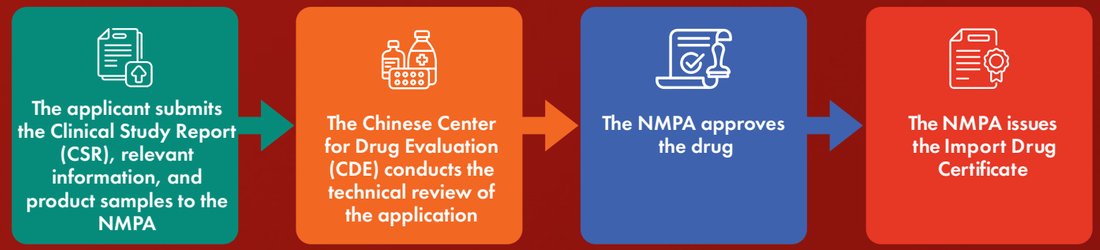
With the best drug R&D establishments, China is also considered one of the largest producers of safe, effective, and qualitative pharmaceutical products. It is the top manufacturer of Active Pharmaceutical Ingredients (APIs) globally, making it a hotspot for API exports.

Here is a brief account of China's current Regulatory landscape for distinct types of medicines and their respective registration processes.

Innovator Medicines & Registration Process in China

Innovator pharma companies that wish to enter China's market need to be listed for coverage under the National Reimbursement Drug List (NRDL). Since the prices of medicines are controlled to lower the burden on patients, listing in the NRDL is mandatory. The list is updated once every year.

The below figure depicts the registration process for Innovator Medicines:

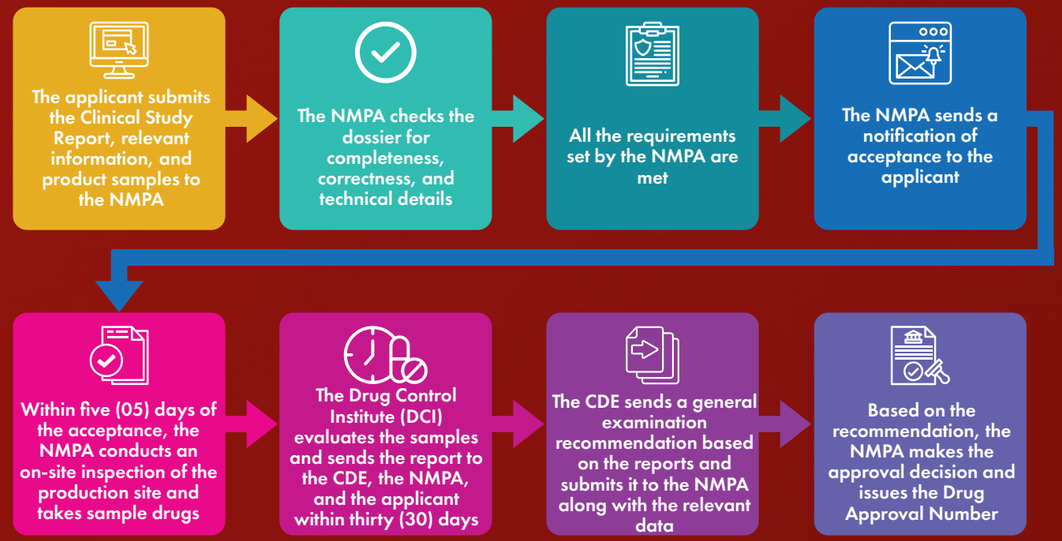


At the time of the technical review, the CDE may issue a single notification to the applicant for the submission of supplementary materials. The applicant has to submit all the necessary information/material in one (01) go to the CDE. Once the CDE reviews the supplementary data, it may or may not approve the drug. In the latter case, the application is returned to the applicant, citing the reason for the rejection.

Generic Drugs & Registration Process in China

90% of the drugs registered in China are Generic. The GQCE makes the bioequivalence test mandatory to maintain the quality of Generic drugs. Starting in 2018, the "4+7" pilot program of the GQCE procured thirty-one (31) Generic drugs across the country. It paved the way for a streamlined price-volume agreement and ensured that the pharmaceutical manufacturers met the quality and quantity requirements.

The following diagram shows the registration process for the Generic drugs in China:



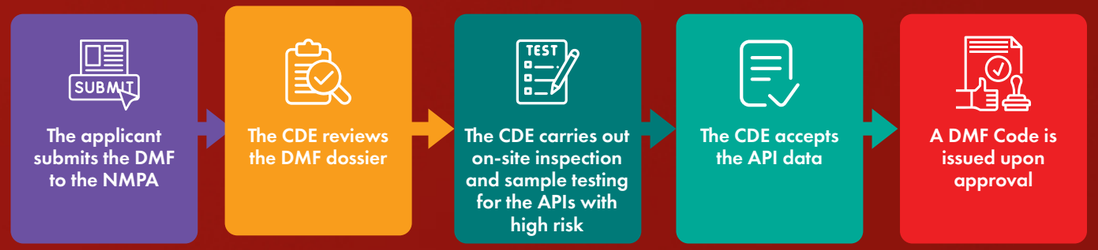
In case the requirements set by the NMPA are not met, the applicant is sent a list of reasons for the rejection, with an opportunity to reapply.

API's Market & Registration Process in China

The aging population, increased disposal incomes, and a need for novel medicinal products are the main reasons for the phenomenal growth of the API market in China. Several APIs are exported to the Northern American region, among other countries.

Strict regulations and a stringent Regulatory environment ensure that the quality of the APIs is maintained. Since January 01, 2018, APIs, pharmaceutical excipients, and pharmaceutical packaging materials have been approved for drug product application. Drug Master File (DMF) submissions have become mandatory for the approval of APIs.

Here is an overview of the registration process:

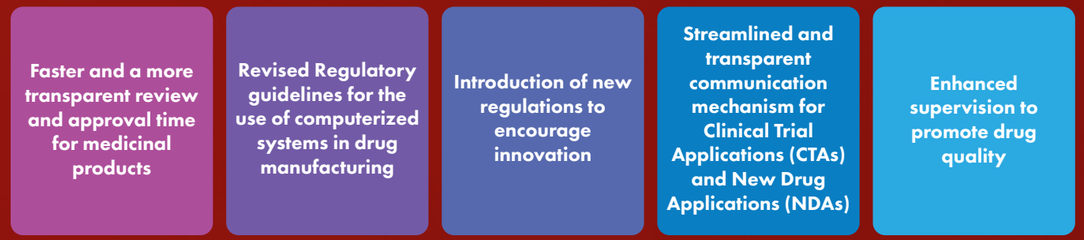


Traditional Chinese Medicine's (TCM) Market Landscape

TCMs make up more than 50% of the total pharmaceutical market in China. These are based on traditional concepts and include forms such as herbal medicine, acupuncture, massages, exercises, and dietary therapy. The medicinal products that fall under this category are inexpensive and promote the local drug manufacturing companies. Most of the geriatric population in China relies on TCM. In addition to China, other countries like Brazil and a few African countries use and support the TCMs owing to their effectiveness.

NMPA's Regulatory Best Practices

There are many reasons for China being one of the best import/export markets for pharmaceutical products. In the following figure, let us see a few of the NMPA's Regulatory best practices that help in creating a conducive market for the manufacture and sale of medicinal products:



Key Regulations Shaping Up the Chinese Pharmaceutical Industry

The Amended Drug Administration Law in China was passed on December 01, 2019, and it has brought about significant changes in the development of regulations by relevant Regulatory Agencies.

Following are the key pointers that pharmaceutical companies in China, and those willing to enter the Chinese market, should adhere to:

- Classification of reform actions and policies to provide a legal basis for Regulatory Agencies
- Sixty (60) working-days silent approval for clinical trials
- A nationalized Marketing Authorization Holder (MAH) system to differentiate between the manufacturers and product license holders
- Enablement of online sale of prescription drugs, making them more accessible to the public
- Abolishment of the certificate requirements of Good Clinical Practice (GCP), Good Supply Practice (GSP), and Good Manufacturing Practice (GMP). It saves time for manufacturers as they do not have to go through the mandatory certification process
- Revised definitions for counterfeit drugs and inferior drugs to reduce the risk of exposure
- Increased penalties for multiple violations such as manufacturing and selling counterfeit drugs, not adhering to the product-recall timelines, bribery, and violation of GCP, GSP, & GMP.

Recent NMPA Updates on Clinical Trials, Cosmetics, and Medical Devices

Following are a few of the recent updates from the NMPA pertaining to the Regulatory Affairs space in China:

- On April 29, 2022, the Center for Drug Evaluation under the NMPA issued **'the Guideline for Clinical Research and Development of New Drugs of Traditional Chinese Medicine Compound Preparations Based on Human Use Experiences (Trial) and the Guideline for Communication Under the Evidence System for Registration and Evaluation Based on "Combination of Traditional Chinese Medicine Theory, Human Use Experiences and Clinical Trials" (Trial) in order to promote the construction of an evidence system for the registration and evaluation of traditional Chinese medicine.'**
- From July 01, 2022, manufacturers, license holders, registrants, and other applicants of cosmetics must abide by the GMP requirements. Establishments that obtained the licenses before the aforementioned date need to upgrade their manufacturing sites accordingly.
- On March 09, 2022, NMPA released three (03) guidelines for regulating and supporting the quick development of digital health, which include:
  - Guideline for the implementation of Artificial Intelligence in medical devices registration
  - Guideline for registration of medical devices software
  - Guideline for medical device cybersecurity
- On January 11, 2022, the NMPA has set the technical evaluation of drug-device combination products as a research project in Regulatory science and has formulated two (02) guidelines, namely, the **'Guideline for Registration Review Drug-Device Combination Products with Device Taking Primary Mode of Action and the Guideline for Registration Review of Qualitative, and In Vitro Release Studies of Drugs in Drug-Device Combination Products with Device Taking Primary Mode of Action.'**

Conclusion

In the past seven (07) years, the Chinese pharmaceutical industry has witnessed numerous positive changes, making it one of the most dependable and growth-oriented markets. The market is open to global pharmaceutical manufacturers and sponsors. A growing population, the need for novel drugs, and the emergence of life-threatening diseases have made China the ideal market for potential market entrants. A strict yet transparent Regulatory space is another reason that attracts many countries to the Chinese pharma market.

To flourish in this rapidly growing environment, keeping up with the ever-changing Regulatory guidelines from the NMPA can be fruitful for pharma and life sciences companies. How can they do so? A proven and local Regulatory partner would always be the best option. Reach out to one to quickly enter the market and ensure compliance with the prevalent regulations.

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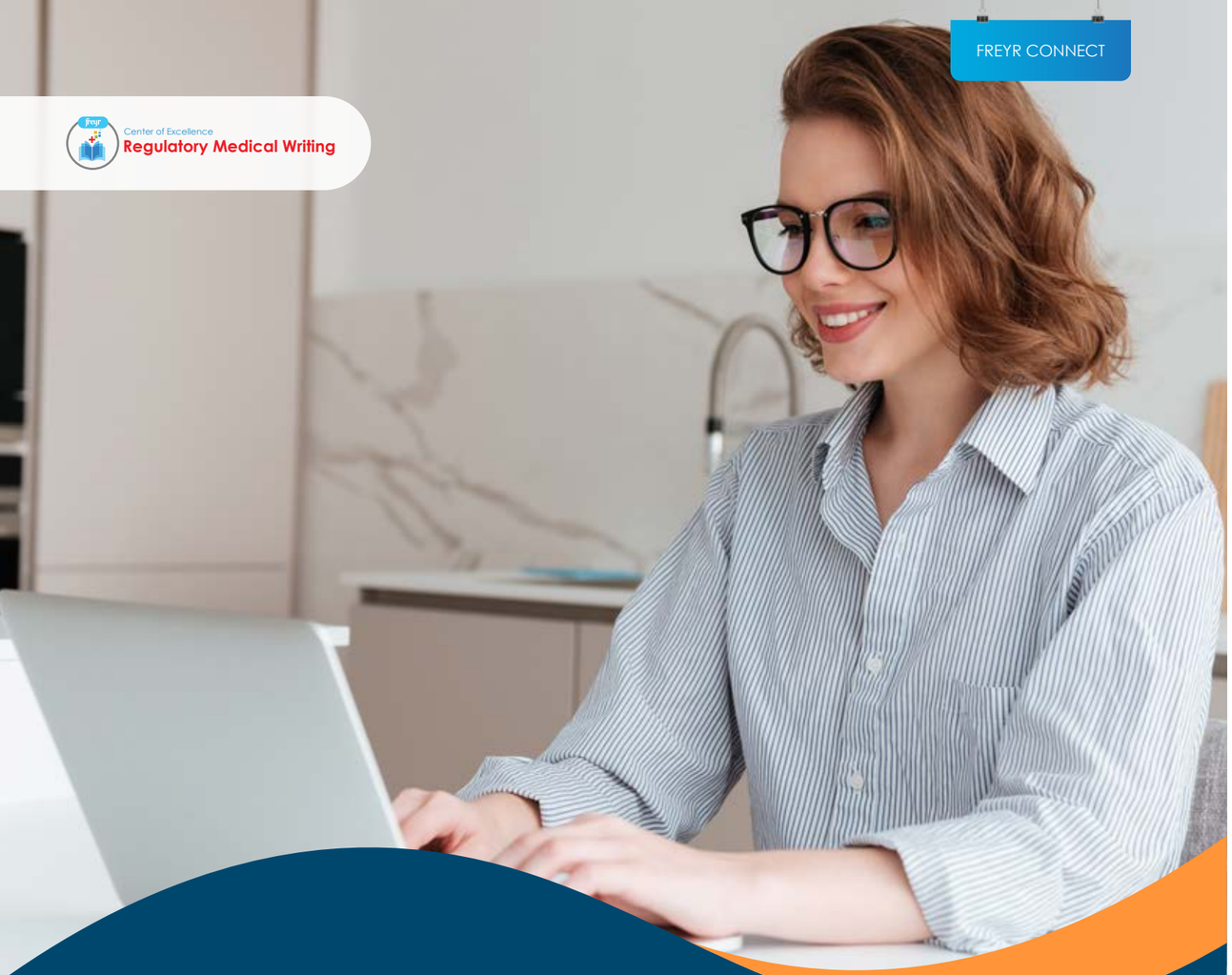

MEDICAL WRITING - AN OUTSOURCING COMPETENCY

Abstract

The history of medical writing began with the rise of the modern clinical trial. A medical writer can be your pivotal ally in a clinical trial. While clinic directors, data managers, and investigators in the pharmaceutical industry are required for clinical trials, medical writers are the glue that holds clinical trials together. The increase in the volume of clinical trials has already put a tremendous strain on journal editors and reviewers. A medical writer can play a key role in accelerating the publication of clinical trials, by preparing manuscripts and their current format in accordance with journals' requirements. As a result, well-designed manuscripts can be published faster, and results can reach the public faster and are more cost-effective

In 2009, 13% of all pharmaceutical expenditure worldwide was estimated to be spent on medical communication. Yet the role and the medical writer's impact on clinical trials is often misunderstood by sponsors, who don't realize how often they truly need medical writers. As pharmaceutical companies now look to outsourced medical writing service providers to augment their internal teams, the role and the agencies importance can no longer be underestimated.

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Medical writing involves developing clinical data into structured review documents such as protocols and reports that inform a drug's development, status tracking, and crisis management. Ideally, medical writing is carried out by skilled writers who can elicit crucial scientific information from expert scientists and condense and format the collected data into review documents for submission to Regulatory bodies.

Several challenges such as stringent timelines, need for accuracy, and cost requirements on medical writing, necessitate that the qualified writers are accompanied by an array of project managers and other resources. From a financial standpoint, medical writing differs from other activities in the pharmaceutical industry in many respects. It is labor-intensive, and so, the cost of high-caliber writers is more.

Additionally, increased product types and complexity in the Regulatory landscape means that medical writers have to be specialists in their content areas. As a result, companies are discovering that the supply of medical writers is lagging behind the demand.

There is also a supply and demand imbalance. Often, pharmaceutical companies hire a team of medical writers to handle a single project, resulting in writers on the "bench" post the completion of the said project.

On the other hand, medical writers are frequently required to live up to weekend working requirements, even though approval agencies and pharmaceutical companies are behind in setting their deadlines.

Agencies continue to mandate that medical writers be required to work long hours to meet submission deadlines. This results in experienced writers and other staff with professional and personal commitments to deter from pursuing careers in medical writing.

Due to the reasons mentioned above, pharmaceutical firms have begun to look at outsourcing as an alternative. This can alleviate the demand disparity and supply bottlenecks, lower risks associated with staff turnover, and reduce overall cost and cycle time for medical writing.

Among the dispute resolution mechanisms that encourage such outsourcing are modern and global interpretations of site selection criteria, provisions that allow the use of a custom site or subcontractor model, and approved dictators on a case-by-case basis.

One of the main reasons the pharmaceutical industry outsources medical writing is limited access to clinical trial sites. There is a well-documented global shortage of clinical trial centers and qualified investigators, which hinders the timely implementation of clinical trial protocols. Lack of real-life clinical settings and a low number of trained investigators in those centers create a bottleneck in drug development.

Drug companies usually outsource any subsequent trials once a drug gets through the Phase I clinical trials, and there is no perceptible benefit to being innovative for a higher end-patient population.

For example, a National Cancer Institute can provide investigator-initiated Phase I cancer trials for approximately 0.2% of the probable twenty-five hundred (2,500) researchers registered with the organization. This means that more than ninety-nine percent (99%) of the researchers registered with the NCI cannot receive funding for a Phase I trial.

In 2006, there was a similar situation at another Southern-American National Cancer Institute (INCA), with an estimated 50 investigators competing for a limited number of Phase I clinical trials. The slow rate of site acquisition is further compounded by the additional complications introduced by local culture - a counterpart to time and talent considerations. In several locations across Eastern Europe, some trials require multiple nurses, whereas, in other locations, it is acceptable to use graduate students instead.

For North American trials, there are often requirements so specific that they are written into the clinical protocols themselves. In Europe, the requirements lead to approval delays because of questions about feasibility. This is further complicated by a growing demand for international expansion, particularly into China and India. According to the publicly available data, nearly sixty percent (60%) of Phase II and III trials are now conducted in low or middle-income countries.

Nevertheless, cultural norms in countries like China, where the government is highly protective of intellectual property rights, may conflict with the Western rational trial designs. Specific centers like India only permit studies that treat pathological conditions present at a prevalence of thirteen percent (13%) or higher. These parameters present significant challenges from the point of view of writing tasks and timelines.

The authors of US drug development must submit their trial protocols and other reports to the Food and Drug

Administration's Center for Drug Evaluation and Research (CDER) and are often required by non-US Regulatory Authorities to submit to their specific offices as well.

These submission requirements are determined by strict formatting regulations and face a high risk of errors. The FDA guidance document on Study Reports, Investigational New Drugs (INDs), New Drug Applications (NDAs), and Regulatory Submissions indicate that one (01) reason for rejecting a report is if "insufficient time was spent on the protocol."

Report corrections often lead to approval delays, which in turn cause a setback to the drug approval and time-to-market. Moreover, according to the publicly available data, one (01) out of three (03) drug candidates on the final stages of the Regulatory process has more than one (01) "major milestone" and is delayed as a result. Such a lag happens once every three (03) months.

Based on this, if every project that receives approval is delayed by 2.4 months, six hundred and eighteen (618) potential medical breakthroughs would not be available. They would lose the jobs of fifty-one thousand seven hundred (51,700) Americans.

Due to a low number of medical writers, this year's survey on Regionalized Deficiencies & Site Adequacy for Phase I Trials in the Region indicates that approximately forty to fifty percent (40-50%) of all the US/European international trials for oncology and/or CNS related compounds are being outsourced on a vendor/custom site model.

Furthermore, two-thirds of trials are outsourced on a subcontracting model. However, the timing of authors' submission requirements must be taken into consideration when analyzing outsourcing data.

In the US, most trial conditions begin in the spring, peak in the summer, and abate in the fall. In Germany, on the other hand, investigators have more options in the early part of the year than later in the year.

The data sources bring forth challenges that prove that specific government policies impede clinical trials and hinder the commercial approval of new drugs. They are mentioned below.

Personnel – In addition to a host of site location, funding, and high prioritization issues, a significant challenge for timely approval of trials is the lack of appropriately trained personnel such as clinical research assistants and medical writers.

Regulatory Agencies – As the Regulatory framework is increasingly varied in different countries, it is difficult to obtain timely Regulatory approval. Examples include China challenging the United States Food and Drugs Administration (USFDA) and France challenging the European Medicines Agency (EMA).

Site Personnel – Capacity limitations, budget overruns, Service Level Agreements (SLAs), and local linguistic requirements are among the issues that affect site adherence.

Space – Outsourced trials have significant space requirements, including patient rooms for conducting trials and storage space for materials, drugs, and investigational products.

Global Subcontracting and Vendor Sites – In many cases, pharmaceutical companies do not have the resources to conduct trials at preferred sites or gain access to specialist medical writers. Because of this financially driven demand for specialized resources, some pharmaceutical companies have turned to third-party contractors to carry out higher-risk, non-core functions, including medical writing, primary research, and data-entry to meet financial and geographical requirements.

As pharmaceutical companies transition from in-house to vendor and subcontractor models, they continue to use some of the resources from their own companies, including empty sites, to lower costs.

Methods to Improve Access to Sites – Since medical writing is considered a high-risk function, the determination of what extent it should be outsourced is predicated by a site selection process that meets business, quality, technical, and legal criteria.

Several imperatives need to be in place for outsourcing medical writing. They are as follows.

Economic Calculations – Based on the current data, companies believe that using high-value enrolees in various settings would cost nearly five (05) times more than using a credentialed facility, as opposed to a hospital trial. However, product managers estimate that some of these costs can be saved by allowing medical meetings to be held virtually.

Quality and Safety – Effective communication between contracting companies and investigator sites and between

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research sites, Contract Research Organizations (CROs), sponsors and ethics committees are essential to ensure that all stakeholders are clear on what is required of them and their roles and responsibilities are well-defined.

Standard Processes and Contractual Limitations – In terms of core competencies, outsourcing functions to temporary service providers such as CROs and corporate departments require complex SLAs, precise language, clear site selection guidelines, and simple terms of appointment. If not established at the onset, this puts the entire project at risk.

Robust Data Management Systems – Typically, in handling clinical trial documentation, a meaningful site selection process and the subsequent output depend on the availability of high-quality clinical data capture and management systems. Offices utilizing such systems provide the means for real-time tracking of interactions and trials. As a result, site selection can often be fine-tuned as trials progress. Similarly, the rules for establishing a panel or a list of preferred investigational sites and/or subcontractors vary significantly by country and situation.

Legislative Hurdles – Laws and regulations on clinical trials such as the EU Clinical Trial Directive have similar mandates, including criteria related to patient safety, legitimate commercial aims, and scientific validity.

While these Regulations encourage the development of new drugs, they are not always flexible enough to accommodate real-world conditions, which has resulted in an ongoing debate.

Global Regulations – While the Regulatory criteria may differ across countries, a trend towards creating global and uniform systems has begun. Since these sites will likely be used for trials in many countries, adopting an international body of standards for investigative and medical writing site selection and evaluate and monitor trial sites. Such rules will likely require inputs from multiple industry stakeholders to standardize the practices globally and implement a global payment system for services uniformly.

Based on the sheer complexity of the sources above, outsourcing medical writing activities to a single-window competent agency proves to be the utilitarian and preferred alternative to ensure constant compliance.

This article was first published by

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BRIDGING THE GAP BETWEEN ERs AND GSPRs

The Medical Device Regulation (EU) 2017/745 came into effect on May 26, 2021, and now all the device manufacturers have to comply with these requirements to place and market their devices in the European Union. The Essential Requirements of the Medical Device Directives (93/42/EEC) have been repealed by the General Safety and Performance Requirements (GSPR). To establish compliance with the Medical Device Regulation (EU) 2017/745, manufacturers need to establish conformity to all relevant GSPRs, and herein lies the challenge. How does the manufacturer determine the relevant GSPRs? What data is required for demonstrating conformity with the different GSPRs? How different are the GSPRs from the ERs? What additional data is required when transitioning from the ERs to GSPRs? These are some of the questions that need to be considered when establishing MDR compliance for any medical device.

One of the main components of establishing compliance with the EU MDR lies in providing the appropriate evidence and data to prove conformity with the relevant GSPRs that are in line with the device's intended purpose. It is of utmost importance that all evidence, which includes data from non-clinical or clinical studies held by the manufacturer, data from published literature, data from PMS activities, is correctly identified and analyzed.

Article 61(1) of the MDR states – "Confirmation of conformity with relevant general safety and performance requirements set out in Annex I under the normal conditions of the intended use of the device, and the evaluation of the undesirable side-effects and of the acceptability of the benefit-risk ratio referred to in Sections 1 and 8 of Annex I, shall be based on clinical data providing sufficient clinical evidence, including where applicable relevant data as referred to in Annex III. The manufacturer shall specify and justify the level of clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements. That level of clinical evidence shall be appropriate in view of the characteristics of the device, clinical risks, and its intended purpose.

To that end, manufacturers shall plan, conduct, and document a clinical evaluation in accordance with this Article and Part A of Annex XIV".

As is apparent from the above clause, demonstrating conformity to the GSPRs is the cornerstone of establishing compliance with the EU MDR. There are no significant differences between the ERs of the MDD and the GSPRs of the MDR, but some of the requirements under the GSPRs are more stringent and require more clinical data to be presented and analyzed. There is a total of 23 GSPRs, while there were 13 ERs under the MDD and 16 ERs under the Active Implantable Medical Device Directives 90/385/EEC (AIMDD).

The requirements of GSPR are covered in Annex I of the MDR with three (03) chapters, such as:

- Chapter 1 – General requirements
- Chapter II – Requirements regarding design and manufacture
- Chapter III – Requirements regarding the information supplied with the device

The new GSPRs have expanded requirements under the labeling and risk sections. There is also an enhanced emphasis on cybersecurity for programmable electronic systems. Some of the new requirements relate to combination products, where there is a combination of a drug and device that contain substances of biological origin.

The new requirements are in line with the current industry standards or guidance and manufacturers may very well be compliant with these requirements but are now burdened with having to provide adequate data to support this. The state-of-the-art requirements mentioned in the harmonized standards are incorporated into the MDR's GSPRs. Under the MDR, the acceptability of the benefit-risk ratio banks on consideration of available alternate treatment options and the applicable and relevant data from post-market surveillance.

An essential part of the Clinical Evaluation Report (CER) is an objective analysis of data presented within the report to establish conformity with the GSPRs. A simple gap analysis between the ERs and GSPRs with confirmatory statements is not enough. A detailed analysis of the data citing what GSPRs are applicable and tracing the corresponding documents and/or data demonstrating compliance is required. It is also required to provide suitable justifications for GSPRs which are not applicable. The GSPRs 1, 3, 4, 6, and 8 are related to establishing the safety and performance of the device. It includes establishing the benefit-risk profile and the acceptability of the risk profile. Thus, the GSPRs are considered universally applicable to all medical devices.

Some of the significant updates in the GSPRs in comparison to the ERs are described below:

Devices Without a Medical Purpose

Devices without a medical purpose were out of the scope of MDD and AIMDD but are within the scope of MDR; hence understanding how to apply the GSPRs pertaining to safety and performance is challenging. The GSPR 9 covers the details of this requirement, which mentions that the device must not exceed the 'maximum acceptable risk' and must be consistent with a high-level of safety and protection of health. However, what would be considered as the maximum acceptable risk is not clearly defined in the MDR. It is expected that common specifications would be available that would provide clarity on this issue. Until these specifications become available, the manufacturer must justify the determined maximum acceptable risk and justify by referencing available industry standards pertaining to similar devices with a medical purpose.

Chemical, Physical, and Biological Properties

The GSPR 10, which is related to a medical device's chemical, physical, and biological properties, is an expansion of the ER 9 and requires additional evidence or data to establish conformity. Some of the other requirements under this GSPR include having to show

compatibility between different parts of an implantable device, establishing the validity of the intended purpose of the device followed by modeling or biophysical research, where applicable, mechanical properties of the materials used, surface properties, and confirmation that the device meets all the pre-defined chemical and physical specifications.

Having physical and chemical characterization of the device to establish safety is an important addition that needs to be considered when presenting data in the CER. There should be a robust justification if the characterization is unavailable or deemed not required.

The GSPR 10.4 on Hazardous Substances is especially important and is considerably different from the earlier requirements in the ER. This GSPR now mandates a detailed material characterization, leachable testing, and degradation analysis for devices that have the property of degradation or leaching. One must perform the extractable testing and make the related data available for analysis in the CER. If the material used for construction contains any toxic, Carcinogenic, Mutagenic, or toxic to Reproduction (CMR substances) or endocrine-disruptor substances, a robust justification must be provided for their presence. It must also be demonstrated that they do not lead to unacceptable effects when used under normal conditions.

Devices Incorporating Materials of Biological Origin

For devices that have derivatives of animal origin, there are additional requirements that are detailed under GSPR 13.1. A new requirement under the GSPR for devices in this category is that the manufacturers are expected to provide data to show that the processing, manufacturing, and design testing of the product has been carried out to ensure its safety to the user, the patient, or any other person involved in the handling of the product, including persons involved in the waste disposal.

Software as a Medical Device (SaMD)

The GSPRs also have much more detailed requirements for Software as a Medical Device (SaMD). There are specific requirements pertaining to the management of risk related to software as a system, including validation, cybersecurity, network potential risks, etc. When preparing a CER for software, the data to be included and analyzed must be in line with these requirements. Thus, it is necessary to provide the verification and validation reports in the CER to show the established conformity with the GSPRs.

Details regarding the quality management system must also be adequately highlighted in the CER to provide evidence to support the relevant GSPRs, which directly decide the conformity assessment route. For example, for Class I devices, it is not normally required to submit a clinical evaluation report to the Notified Body for assessment. However, they are still required to conform to the requirements of the MDR, demonstrate conformity to the GSPRs and suitability for the intended purpose and acceptability of benefit-risk profile that requires a clinical evaluation.

Thus, a clinical evaluation report must still be drafted for all Class I devices, and they must be written with the sufficient data to establish compliance with the MDR, especially for Class I devices that are supplied sterile and have a measurement function or are reusable surgical devices since they will be subject to audit by a Notified Body.

Conclusion

It is quite common for manufacturers to overlook some of the newer requirements under the GSPRs, some of which may warrant new clinical or non-clinical testing to be carried out by the manufacturer in order to be compliant. The manufacturers may also be required to update the risk management procedures and the related documents. The MDR must be carefully read and understood to ensure that the data is not inadvertently overlooked or misrepresented.

The best way to avoid non-conformity is to develop a detailed checklist that can help to track the documents/data. Also, the route that is being considered to establish conformity to the GSPRs i.e., the harmonized standard or the common specifications can help to avoid non-conformity.

This article was first published by

MPO MEDICAL PRODUCT OUTSOURCING

Infographic 1

Registration Process for Cosmetic Products in the UAE

DYK? Entering the cosmetic market of the UAE requires product registration with the Dubai Municipality (DM) and the Emirates Authority for Standardization and Metrology (ESMA).

For cosmetic product registration in the UAE, the company needs a local 'General trading' license. Hence, a local representative is required for registration.

Here is a quick outline of the cosmetic registration process in the UAE for both ESMA and DM.

Why Register with the ESMA?

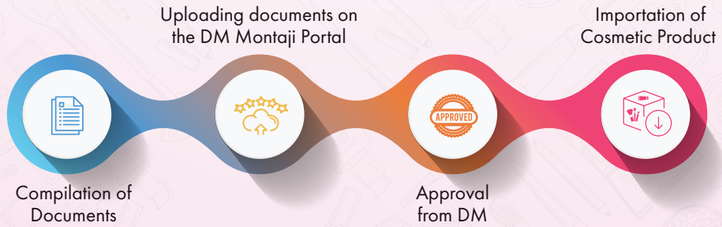
- ESMA controls products at customs
- Registration of 45 SKU's with the same intended use, same category, and same manufacturer is possible with one (01) application
- ESMA registration is valid for one (01) year

Why Register with the DM?

- DM registration is per SKU
- DM controls products that are sold in stores
- DM registration is valid for five (05) years

Cosmetic Product Registration with the ESMA

Cosmetic Product Registration with the DM



Click here to decode the process in detail

THE STEPS TO TAKE FOR A Rx-TO-OTC SWITCH IN THE UNITED STATES

Nearly 40% of all the over-the-counter medications in the U.S. were initially marketed as prescription drugs. For drugs to change from prescription to over-the-counter (Rx-to-OTC switch), they have to undergo scientifically robust evaluations by the Food and Drug Administration (FDA). The results are mostly data driven. The medicines that make this switch should demonstrate efficacy as well as a broad margin of safety.

When intended to be switched to an OTC category, a prescription drug should have the essential properties that can designate it to be self-medicated. The properties that a drug must possess to switch from prescription status to OTC include:

- A person should easily identify the intended symptom and condition with average intelligence
- The safety margin of the drug should be very high
- The dosage should not be complicated and must be easy to administer
- The drug must be non-addictive in nature
- It must not be a narcotic
- No underlying potentially dangerous condition was experienced by the drug
- The drug should not be for parenteral use

Purpose of the Rx-to-OTC Switch

Product lifecycle extension is one of the most significant reasons why a pharma company considers a Rx-to-OTC switch. When the branded product advances to its patent

expiration, competition from the generic manufacturers will increase. The scenario affects the profit unless the pharma company opts for other strategic measures to prolong a product's life span such as formulation changes, modifying the product drug delivery system, and new indications.

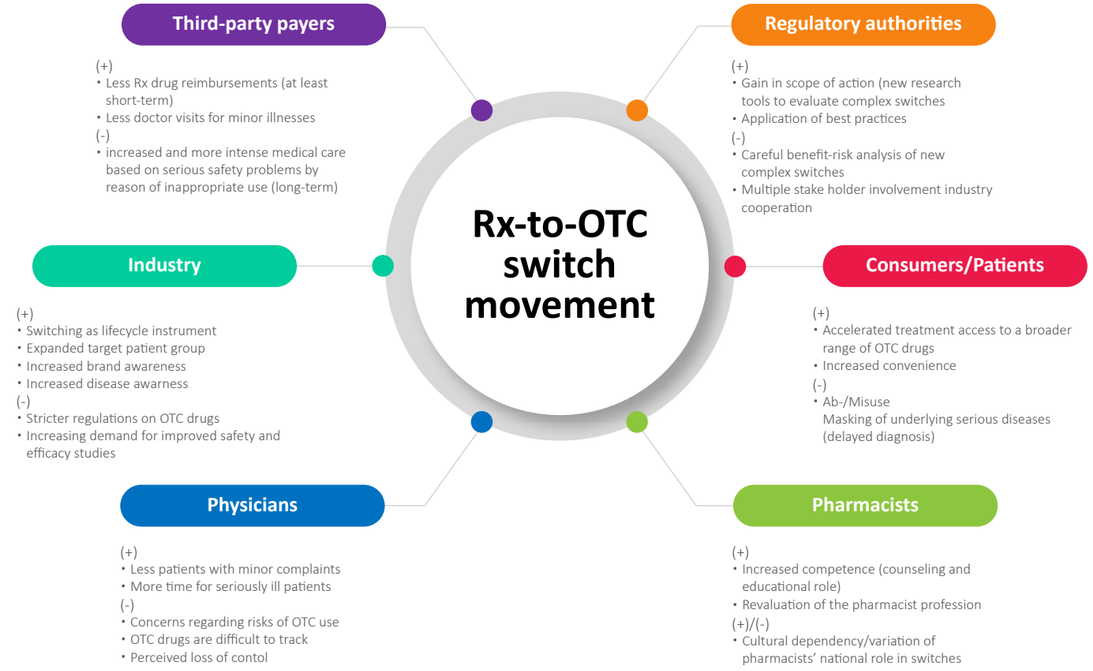
One can meet most of these options through the 505(b)(2) Regulatory pathway. This is preferred if the company wants to retain the prescription status of the product by extending its exclusivity period and lifecycle. The New Drug Application (NDA) applied through 505(b)(2) Regulatory strategy includes complete safety and efficacy data. This application can also be considered for switching the prescription products to OTC. In case the product does not meet the requirements as per the OTC monograph, the sponsor needs to submit an NDA to switch the product to OTC using 505(b)(1) or 505(b)(2) Regulatory pathway.

Pharma companies with both pharmaceutical and consumer health divisions can opt for Rx-to-OTC switch. Changing the product status to OTC helps in maintaining the revenue and growth of the product's lifetime. The duration of the exclusivity to products new to the OTC market granted by the FDA would typically be three (03) years.

Patients, vendors, manufacturers, and the health industry economy would also benefit from the Rx-to-OTC switch. Lower costs and self-administration of the medication without a physician's prescription is a significant advantage for patients. If the product had brand recognition earlier, this would benefit the vendors/dealers by having more sales options. It is estimated that billions of dollars are saved by the healthcare systems with the potential use of OTC drug products.

Apart from the lifecycle extension of the product, an increase in the demand for OTC medication encourages the pharma companies to opt for the Rx-to-OTC switch. The pharma industry would continue to grow as long as patients prefer OTC medications. There is a considerable demand from the end-users for approachable and varied treatment options that are consumer-friendly.

The figure below illustrates the implications of the Rx-to-OTC switch on various stakeholders such as Regulatory authorities, consumers/patients, third-party payers, the industry, physicians, and pharmacists.



Process/Mechanism Involved in the Rx-to-OTC Switch

Before applying for the switch, the sponsors should ensure that the intended product meets the OTC criteria by following the guidelines provided by the World Health Organization (WHO). A product should meet the following characteristics for OTC criteria:

- During the marketing period, the medicine intended for the OTC switch should have recorded high sales volume implying that consumers have used the product extensively.
- The prescription status of the product must have completed a sufficient period. However, the approved duration of this period varies from one country to another.
- The product's Post-Marketing Surveillance (PMS) data should not reveal any serious adverse events or safety concerns that increased in frequency during the marketing period.

Under normal circumstances, Regulatory authorities consider the safety and efficacy data submitted in the original NDA of the prescription version of the product along with the PMS data. However, the authorities also refer to additional information from the clinical trials conducted by sponsors to support the OTC class. When approving a Rx-to-OTC switch, they can recommend some changes to the prescription version of the product in terms of pack-size restrictions, OTC version approved indications, changes in the label inserts to comply with comprehensible language, etc.

The other factors that govern the Rx-to-OTC switch in any country are as follows:

- The literacy rate in the country
- Consumer awareness
- Socio-economic background
- General environment of the individual country

Brief Overview of the Process in the United States

There are two (02) distinctive methods that regulate the U.S.'s prescription and OTC statuses of products. OTC products can be introduced into the U.S. market without FDA pre-approval if the active ingredient, dose, formulation, and indication fall within pre-approved values as implemented in "OTC monograph." However, prescription products or new OTC products require an NDA.

The different ways companies can achieve the Rx-to-OTC switch are:

1. OTC Drug Review
2. Efficacy Supplement Submission to Existing NDA
3. New NDA

The Rx-to-OTC switch would be approved only when the FDA believes that the previous Rx designation is "not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and the drug is safe and effective for use in self-medication as directed in proposed labeling."

In addition to the data available for the original NDA, the safety and efficacy of an OTC product can be confirmed by conducting Consumer Behavior Studies, which evaluate the use of the intended drug in an OTC setting.

Consumer Behavior Studies comprise of the following:

1. Label Comprehension Studies (LC Studies)
2. Self-Selection Studies (SS Studies)
3. Actual Use Studies (AU Studies).

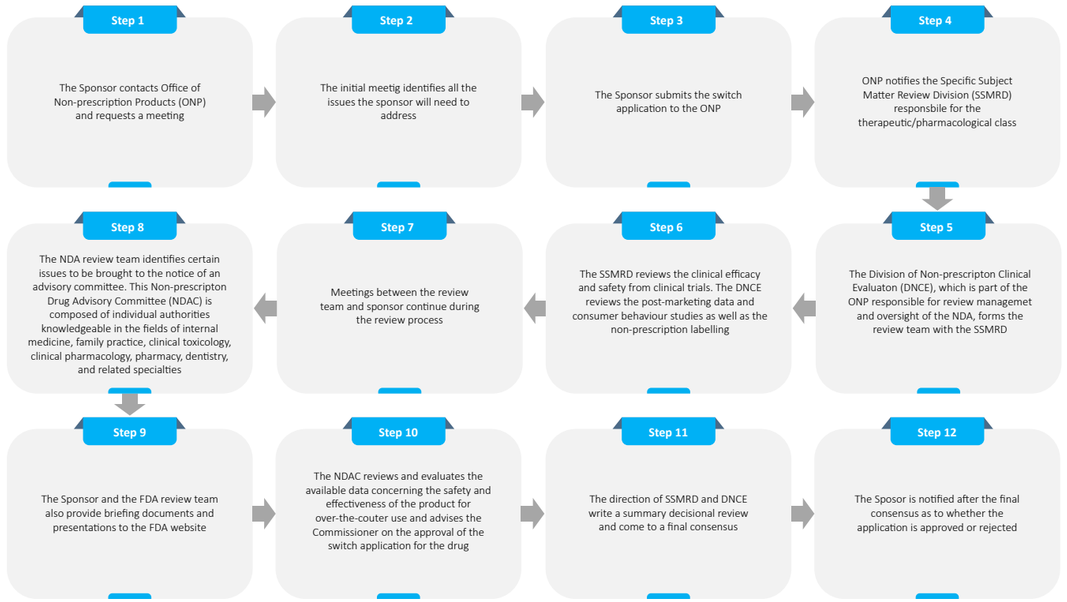
Details of each study process are summarized in the below table :

Consumer Behavior Studies

LC Studies	SS Studies	AU Studies
1. In these studies, subjects are asked to answer the questionnaire based on the OTC label provided. This label complies to a prerequisite format called, "Drug Facts Label."	1. SS studies are conducted after LC studies. With the help of LC studies, the most effective Drug Facts Label is developed.	1. AU studies are used to replicate the use of the OTC product. They help determine consumer behavior in relation to the safe and effective use of the product after self-selection.
2. The provided questionnaire evaluates the ease of the subject's understanding of the key facts on the OTC label.	2. The SS studies evaluate the level of consumer extrapolation of the information that is acquired from the OTC label in relation to the personal medical condition. They check if the consumer is able to make the correct self-treatment decision (i.e., to assess the safety of the OTC product for their use).	2. These studies determine that the intended product cannot be abused or misused by the consumer.
3. Based on the responses provided by the subjects, if it is noted that the subjects do not understand certain vital elements of the label, it is revised accordingly to emphasize the relevant section, and the LC study is repeated until it is proved that the subjects effectively understand the wordings in the label.		
4. LC studies are important for determining any potential new warnings generated from adverse events and PMS data, which are effectively communicated to the end-user.		

Summary of the Rx to OTC Procedure

The complete process of switching a product from Rx to OTC in the U.S. is summarized below



The FDA's decision to switch a drug from prescription status to an OTC status is based on the benefit vs. risk analysis of the intended drug product. The contributing factor for benefit-risk analysis is the ability of the individual/ consumer to accurately identify and self-diagnose the symptoms of the condition. To summarize, the Rx-to-OTC switch should be based on a thorough and transparent scientific assessment of the relevant data. If successful, this switch will contribute to the enrichment of public health by raising disease awareness and encouraging individuals to take up the responsibility for their health and manage their own disease status rather than relying on the burdened healthcare system.

This article was first published by

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Global Cosmetics Regulatory Services

MICROPLASTIC RESTRICTION IN THE EU

Since microplastics are a major environmental problem, the EU is currently preparing to introduce legal restrictions. The cosmetics industry is affected to a considerable extent. Sonia Antkowiak knows the problems to be expected and the first reactions to them.

Microplastics are small pieces of plastic, typically smaller than 5mm, which are considered persistent and universal pollutants affecting oceans and seas. They are solid particles composed of mixtures of polymers and functional additives. Microplastics are associated with long-term permanence in the environment due to resistant and difficult (bio)degradation, which contributes to permanent and irreversible pollution of the marine environment. They can harm eco-systems and can be consumed by sea-life affecting the food chains.

Into the Environment

The two (02) main pathways have been established for microplastics getting released into the environment. They can be unintentionally formed when larger articles disintegrate, wear away, or break into fragments, like car tires, synthetic textiles, and plastic litter. These are called 'secondary' microplastics and their release is estimated to be around 176,000 tonnes a year to the European surface

waters. Additionally, microplastics are also deliberately manufactured and added to products like fertilizers, coated seeds, paints, cleaning, and laundry products as well as cosmetics. They are referred to as 'intentionally added' or 'primary' microplastics and it is estimated that each year around 42,000 tonnes of this type of microplastics ends up in the marine ecosystems. Irrespective of their source, their release to the environment should be reduced and controlled.

ECHA's Microplastics Restriction

In January 2019, the European Chemicals Agency (ECHA) decided to face the problem and restrict intentionally added microplastics. Even though the idea behind the restriction proposal is noble and necessary, from the cosmetic industry's perspective, the ECHAS's approach itself is surprising and disproportionate in its effects.

Based on the report prepared by the International Union for Conservation of Nature (IUCN), estimated microplastics releases are due to:

- firstly, the laundry of synthetic textiles (34.8%),
- secondly, the erosion of tires while driving (28.3%) and
- thirdly, the city dust (24.2%)

When combined, these sources contribute to over 85% of releases but they are not covered by the agency's restrictions. The reason is that the restriction proposal does not include microplastics formed in the environment (the 'secondary' microplastics) but focuses only on intentionally added microplastics. This approach narrows down the release sources so much that it does not fully address the problem, not to mention solving it.

Issues with the Definition

Surprisingly, the microplastic definition proposed by the ECHA does not refer to any plastic materials. Therefore, many polymers and non-plastic substances used in cosmetic products, which are not affecting the environment and are not part of the plastic pollution, might fall under the scope of any future restriction. In other words: the concept of polymers as used in the ECHA restriction proposal is wider than the concept of plastics as all plastics are polymers, but not all polymers are plastics.

What is more, the microplastic definition is so broad that it becomes hard to interpret. Many exemptions and conditions were indicated by the ECHA, which are not very straightforward and depend on specific conditions. A decision tree is necessary to understand if a specific ingredient could be considered a microplastic or not.

Additionally, the agency indicated a list of 520 polymers that may fall into the scope of the restriction. However, the list was created based on the ingredients' INCI name. Many raw materials can have the same INCI name but different properties, which are crucial to determine whether an ingredient can be considered a microplastic according to the specific properties and requirements from the proposed definition.

Due to that, it is challenging to evaluate which ingredients may or may not be restricted, having the same INCI name. Accordingly, a final list of ingredients that will be included in the restriction will never be created. The burden of correctly interpreting the definition and identifying microplastics in the raw materials will lie with the cosmetic companies.

Considering the restriction's scale and its impact on many industries, it is controversial to base any new legislation on such a broad and confusing definition.

Importance of these Ingredients

Many synthetic polymers have key functions in cosmetic products, without which the products cannot be manufactured, or which give the cosmetics some unique properties. They are used as film-forming ingredients, emulsifiers, thickeners, and opacifying agents. They stabilize UV filters and fragrances and allow the sorption of active ingredients like vitamins and oils, amongst others.

They can be found in all types of products, from toothpaste, shaving creams, make-up, and skincare products to hairstyling and shampoos. The proportion of polymers in a cosmetic formula can be as high as 90%, depending on the function it performs. Moreover, polymers are often mixtures of several substances and not individual components.

Therefore, there is no simple one-to-one substitution of such ingredients, and the entire base of the formulation will need to be reevaluated. The reformulation process would be long, complex, and expensive. What is more; contrary to the situations where innovation builds on an existing base with historical market experience, in the case of microplastics reformulations, there will be no historical experience to be reused in the assessment.

Red Flags

Several aspects of the restriction proposal itself were noted by the cosmetic industry as red flags. The main concern is the lack of proportionality in the ECHA's proposal with respect to individual industries. In its dossier, the ECHA has estimated the emissions of microplastics into the environment from specific industries and different types of products. Additionally, the agency has estimated the costs of reformulating the products to be borne by individual industries. The proposal states that 79.3% of the costs of the overall restriction (i.e., the costs of the restriction for all implicated sectors) will be borne by leave-on cosmetics products, yet, as the ECHA proposal states, leave-on cosmetics are estimated to be 2% of the overall emissions of intentionally added microplastics. It is completely disproportionate given their minor contribution to primary microplastics emissions.

Moreover, the dossier underestimates elements related to reformulation capacity by the cosmetic companies. The industry has repeatedly reported a lack of available alternatives for crucial polymers in leave-on products, which is a key factor as to whether a product can be reformulated or not. As mentioned before, a vast group of synthetic polymers in cosmetics are essential functional substances like emulsifiers, stabilizers, or thickeners, without which certain products could not be made. They ensure that personal care products are easy to apply and offer the desired quality, which is crucial for leave-on products. As Cosmetics Europe has consistently stated, there are no known alternatives for many critical functions.

The industry also does not agree with estimated timeframes to reformulate affected products assumed by the agency. Firstly, many alternatives will not be available immediately. Raw material suppliers need time to develop and produce new alternatives. Secondly, cosmetic manufacturers need time to work on how to formulate these new materials. A typical reformulation process lasts for 4.5 years on average, only if suitable alternatives are available. Finally, the proposed restriction forces companies to reformulate thousands of formulae at the same time. According to Cosmetics Europe, given the complexity of leave-on formulations, the lack of suitable alternatives and the complex, costly, and lengthy reformulation process, the transition periods proposed by the ECHA are unrealistic to meet by the industry.

ECHA's assumptions regarding Small and Medium-sized Enterprises (SMEs) should also be challenged. ECHA's dossier states that SMEs "tend to specialize in natural and organic cosmetics" which is not the case. Cosmetics Europe's current estimate is that only around 7% of SMEs in its membership focus only on niche organic and natural products. The restriction in its proposed format will result in a severe socio-economic burden on the personal care industry, resulting in an impact on competitiveness, jobs, and growth of the sector and on consumer choice, for a very limited benefit to the environment.

Cosmetics Industry Faught Back

Over the past two (02) years, the industry has been actively engaging in the legislation process and challenging ECHA's dossier by providing substantive evidence, scientific data as well as socio-economics analysis representative of the current status of the European cosmetic market. The industry asked for definition modification, derogation of different product types, the extension of the transitional periods for leave-on products, amongst others, but most importantly for a coherent approach across industry sectors when assessing their actual impact on the plastic pollution problem.

Early this year, the Committee for Risk Assessment (RAC) and the Committee for Socio-Economic Analysis (SEAC) has published a consolidated, joint opinion on microplastic restriction proposal, which will be considered by the European Commission and all the EU member states under the scrutiny of the Council and the European Parliament. This opens the last stage of the legislative work schedule, which may still change, provides for the publication of new regulations in 2022.

'Bad Guy' - Cosmetics Industry?

When we focus only on primary microplastics released to the ocean at on a global scale, leave-on cosmetics contribute for 2% and rinse-off products for 11.1% of the releases, according to the ECHA's dossier. However, it is known that the personal care industry in Europe places a major emphasis on proactive self-regulatory initiatives.

In October 2015, several years before the ECHA's initiative, Cosmetics Europe recommended to its members to discontinue, by 2020, the use of microbeads, a synthetic, solid, non-biodegradable, plastic particles used for

exfoliating and cleansing purposes in rinse-off products. As a result, an impressive decrease of 97.6% in the use of plastic microbeads was noted in wash-off cosmetics and personal care products, between 2012 and 2017.

Taking that into account, an obvious question arises: does it makes sense to restrict microplastics used as cosmetic ingredients? Self-regulation on rinse-off products works well, the environmental impact from leave-on cosmetics is low, the restriction itself will not solve the main problem, and the cosmetic industry will have to cover nearly 80% of the costs of the overall restriction from all implicated sectors. This ban will turn the whole industry upside down. Yet, the resulting beneficial impact on the environment will be minuscule. We are left with a disturbing thought - is the cosmetic industry really a 'bad guy' or rather a 'scapegoat'?

This article was first published by

COSSMA

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INNOVATOR DRUGS & AN IDEAL WAY TO AVOID NON-COMPLIANCE

The need for life-saving drugs is on a constant rise. Owing to novel diseases proving fatal, drug manufacturers are spending a lot of time and money on the research and development of chemical and biological drugs. As challenging as inventing innovator drugs is, it can be equally daunting for manufacturers to register them. From preparing and submitting the Investigational New Drug (IND) application to Clinical Trial Applications (CTAs) and Marketing Authorizations (MAs), there are a series of Regulatory procedures to be followed, as prescribed by the respective Health Authorities (HAs).

Manufacturers must get it right the first time so that the innovator drugs reach the market without delays. This will help meet the demand for life-saving drugs in specific markets and ensure Return on Investment (ROI) for the manufacturers.

The need for enhanced Regulatory solutions and compliant processes is, therefore, quite crucial. There are several reasons due to which manufacturers are unable to follow the appropriate pathway.

Regulatory Challenges Faced by the Innovator Drug Manufacturers

- Lack of understanding of the Regulatory complexities
- Limited knowledge of the various stages of submissions to be made to the HAs
- Timelines for submitting the medical dossiers, Common Technical Document (CTD), Clinical Study Reports (CSR), etc.
- Differences in regulations when the drugs are to be sold globally
- Lack of preparedness for dealing with any issues or difficulties arising in the manufacturing stage

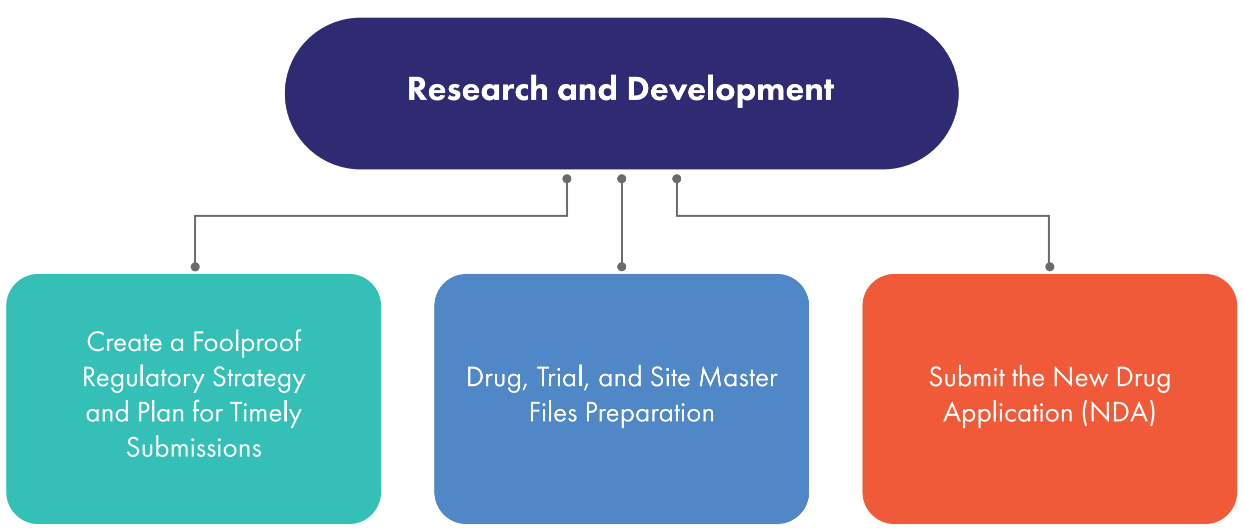
Advantages of Collaborating with the Right Regulatory Services/Solutions Provider

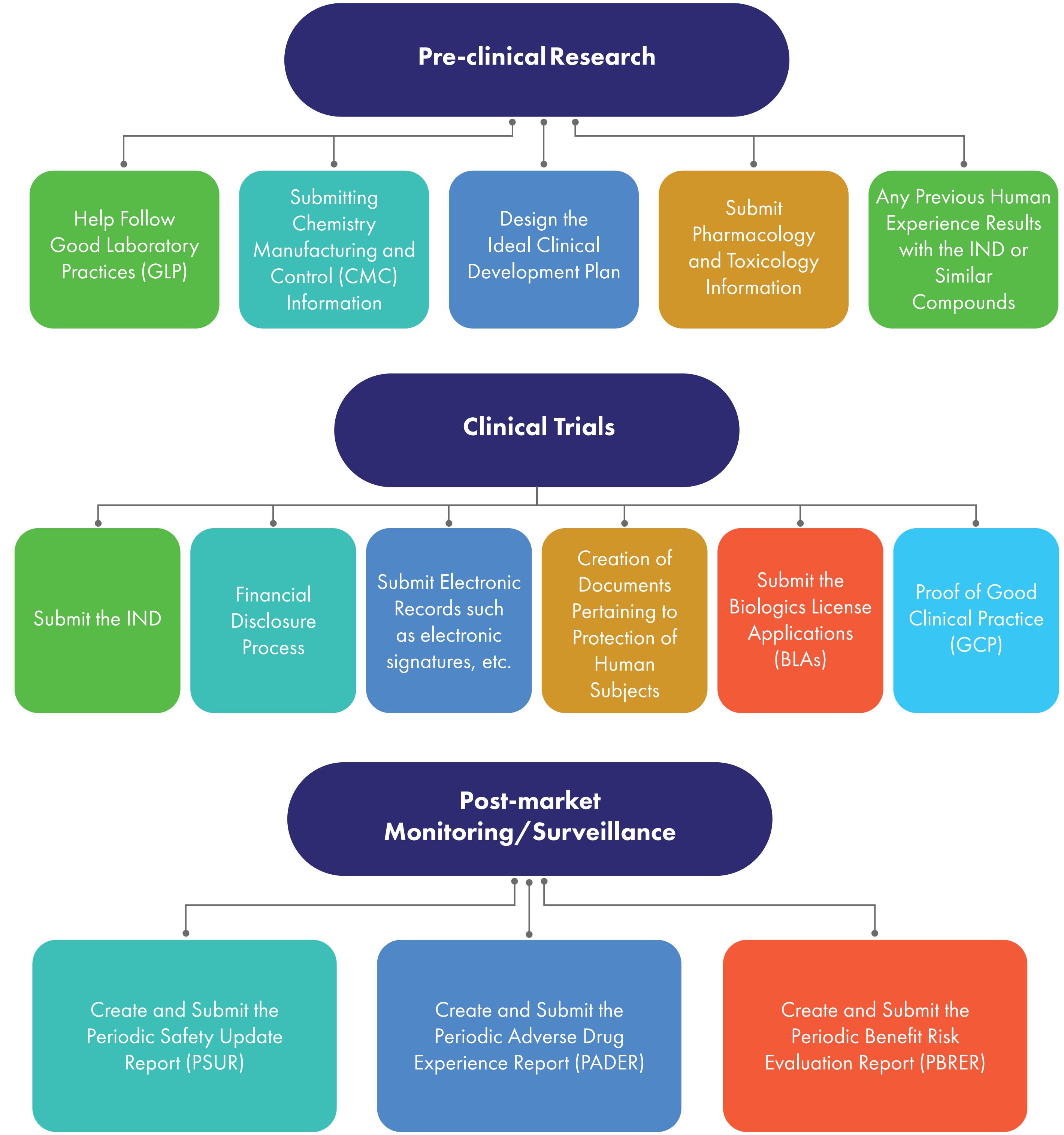
The right partner will ensure that all the drug-manufacturing steps are compliant with the relevant Regulatory bodies and lead to timely submissions.

There are four (04) stages of Innovator Drug manufacture. They are as follows:

- Research and Development
- Pre-clinical Research/Trials
- Clinical Trials
- Post-market Monitoring/Surveillance

Every stage of drug development requires a series of documents that need to be submitted to the HAs. Here is a depiction of how an established Regulatory services provider will help in all the phases.





Final Word

With the increasing life expectancy among the global population, there is a need to discover new drugs. Innovation in the life sciences field has led to several inventions in life-saving drugs. Many of them are at various stages of manufacturing. Whatever the stage your product is in, collaborating with a global Regulatory service provider like Freyr, who has expertise in registering Innovator drugs, can help you avoid non-compliance and ensure that the new drugs reach the market on time. Stay informed. Stay compliant.

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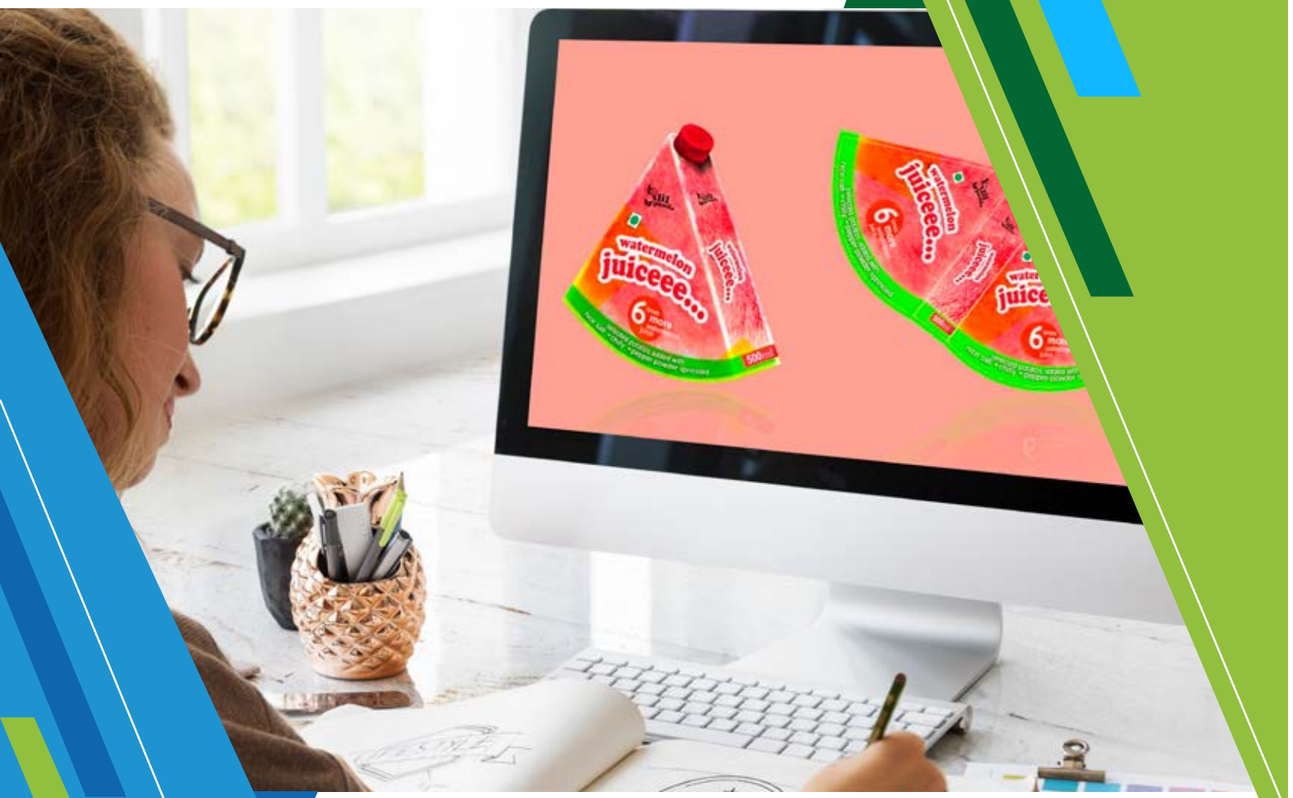

UK IMPLEMENTS NATASHA'S LAW FOR PREPACKED FOOD LABELS

Any food product or ingredient, such as nuts, seafood, peanuts, gluten-containing cereal, latex, penicillin, etc., can pose allergies when ingested into a human body. According to research, generally, food allergies affect 2.5% of the general population.

On October 1, 2021, the UK passed a new labeling law, 'Natasha's Law,' requiring all food retailers to display an entire list of ingredients and allergen labeling on each food item made on the premises and prepacked for direct sale. This law is named after Natasha Ednan-Laperouse, a teenager who died after eating a prepacked baguette containing sesame, which did not require allergen labeling at the time. After this event, the Government decided to implement severe laws that would protect the consumer from ingesting food with allergic ingredients.

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According to the law, a prepacked food label must include 14 major allergens. They are listed below:

- Celery
- Cereals containing gluten – including wheat (such as spelt and Khorasan), rye, barley, and oats
- Crustaceans – such as prawns, crabs, and lobsters
- Eggs
- Fish
- Lupin
- Milk
- Molluscs – such as mussels and oysters
- Mustard
- Tree nuts – including almonds, hazelnuts, walnuts, Brazil nuts, cashews, pecans, pistachios, and macadamia nuts
- Peanuts
- Sesame seeds
- Soybeans
- Sulphur dioxide and sulfites (if they are at a concentration of more than ten parts per million)

What is Prepacked Food?

Prepacked food is any food that is placed into packaging before it is ready for sale. According to the new rules, Prepacked for Direct Sales (PPDS) food must display the below information on the packaging:

- Name of the food
- Full ingredient list, especially emphasizing on allergenic ingredients by making it bold, or adding contrasting color or by underlining such ingredients

Labeling for such prepacked foods must align with the legal requirements that apply to naming the food and listing ingredients.

'Natasha's Law' came into force in October 2021, giving businesses a transition period to prepare for the new rules. This law, eventually, is expected to bring more consistency in the labeling regulations of prepacked food products besides preventing end consumers from consuming food that has allergic ingredients.

To be compliant, it is crucial to evaluate the preparedness of the prepacked food manufacturers for the new rule. Reach out to the Food Regulatory experts at Freyr to stay compliant with the latest regulations.

Stay informed. Stay updated.

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Regulatory Affairs

DECODING COMMON MISCONCEPTIONS ABOUT MEETINGS WITH THE MHRA

Applicants often misunderstand the scope of the meetings with the Medicines and Healthcare products Regulatory Agency (MHRA) and fail to comply with the legislative requirements of such meetings. These misunderstandings create prejudice against the procedure and affect the success rate of the meetings.

Scientific advice meetings with the MHRA can be held in the following phases.

- At any stage of the initial product development
- Before submission of the application for Marketing Authorization (MA)
- During the pre-submission period for a variation to the existing MA

Meetings with the MHRA can also be arranged to discuss:

- Pharmacovigilance
- Promotional material

- Recommendation on labeling or package leaflet changes
- Post-authorization measures

Pre-meeting submissions help to fasten the procedure by avoiding unnecessary 'Request for Further Information' documents. Before the meeting, applicants must provide the MHRA with a brief about their intentions to avoid unnecessary discussions (which is anticipated for ten (10) to fifteen (15) minutes). The timeline for the MHRA meetings is not more than ninety (90) minutes. The submission of all the supporting documents is mandatory for review.

On such interactions with the MHRA, there are a few misconceptions. Here we list the most common ones.

Misconception 1
Meetings with the MHRA are not conclusive

Setting up and attending a meeting with the MHRA can be tedious. Nevertheless, the MHRA and its staff ensure that a proper advice letter is sent to the applicant within fifteen (15) days, right after the applicant submits the meeting notes. In case of any confusion related to the advice stated in the letter, the applicant can ask for clarification. The MHRA takes care that the issues of the applicants are addressed responsibly in a written form. An applicant can request a joint scientific advice meeting with the MHRA and the National Institute for Healthcare and Excellence (NICE) to discuss an in-depth evaluation of Regulatory issues and health technology assessment. This meeting also offers an opportunity to discuss the evaluation of clinical study design, pharmacovigilance, advertising, labeling/PIL changes, and post-authorization measures that satisfy Regulatory and NICE requirements. A separate document addressing the issues raised is maintained.

Misconception 2
Meetings with the MHRA are product-specific

MHRA offers relevant advice to the applicant depending on the need for the meeting/stage of development/nature of questions, where there would be two (02) options for conducting a meeting - a specific scientific objective related to a product or a broader extensive objective not associated with one (01) product. In broader scope meetings, general issues related to product development, choice of study endpoints in a specific indication, the study design, its management, and analysis, as well as the Reference Medicinal Product (RMP) and permissible reclassification of the products, are discussed. The Regulatory questions of the medicinal product should also include concerns related to future development.

Misconception 3
Small and medium-sized enterprises are not eligible for meetings with the MHRA

Small or medium-sized enterprises can also request to schedule a meeting with the MHRA. However, to obtain the status of Small and Mid-sized Enterprise (SME), the company audit details needs to be attached along with the SME status application and submitted on the sales.invoices@mhra.gov.uk mail ID. If the requirements of the MHRA are met, the company must submit the scientific advice application. The SMEs are eligible for a certain easement concerning the payment of the meeting. For instance, for a new active substance, the applicant can pay twenty-five (25) % of the application fee at the time of application, and the remaining seventy-five (75) % can be paid once the MA is determined.

Misconception 4
The MHRA conducts only one development meeting/product/year

Applicants can have multiple meetings with the MHRA, unlike the FDA (which recommends only one development meeting/product/year), provided that further advice will be considered as a new request. Also, the scientific advice meeting decision provided in the MHRA letter is not final. Applicants still have the leverage to ask for clarification on scientific advice, provided which is carried out through email communication/teleconference.

Amid all these misconceptions, how are you planning to go ahead with the Health Authority interactions? A planned and structured approach to HA communication saves time, effort, and cost and helps fast-track applications and query resolution. For the best Regulatory support, contact Freyr now.

DIGITAL AUTOMATION - THE POLE STAR IN YOUR REGULATORY JOURNEY

The post-pandemic world is realizing that the intersection of technology and a traditional way of doing business already exists with us. The highly competitive nature of our business only exemplifies the need of incorporating innovative technologies to augment and support customers in the ever-evolving Regulatory landscape. Trends show that the global automation market, especially in the life sciences industry, is poised to grow close to $2.5 bn by 2025 with a CAGR of approximately 7.5%. Many companies are already moving in this direction and gaining focus by incorporating investments to strengthen and protect their strategic assets like Regulatory information.

Regulatory affairs divisions at life sciences companies must deal with a lot of manual processes. Monitoring dossiers for drugs and/or devices across different Health Authorities in various stages of their "Lifecycle," updating files for manufacturing or labeling, etc., are arduous tasks with little or no scope of oversight or misses. Non-compliance and sub-optimized performance are simply unacceptable since they have an adverse implication on not just the financial aspect, but also the brand reputation. Employees should be able to easily access documents and information while compiling reports for Regulatory purposes. Automation tools, driven by Artificial Intelligence (AI)/Machine Learning (ML)/Robotic Process Automation (RPA), do not just provide quick and reliable data collection, but also faster access and better compilation of data when it is most needed. Digital transformation and implementation of new technologies to counter the existing and the upcoming challenges is the only way forward.

Digital transformation trends in the biotech and pharma Regulatory market point towards an infusion of innovation and automation tools available, thereby transforming traditional service delivery leading to exponential and immediate value-addition to the customers. They consist of simple, creative, and quickly deployable innovative toolsets that lead towards a transformational process or task improvement with significant benefits and outcomes that can be realized immediately.

With AI, ML, NLP, and other automation tools, companies can improve efficiency, enhance productivity, ensure safe drugs and devices, hasten market entry, and remain in those markets, ultimately driving better business outcomes.

Some of the processes in Regulatory functions where incremental and disruptive innovation are proving to be increasingly helpful are:

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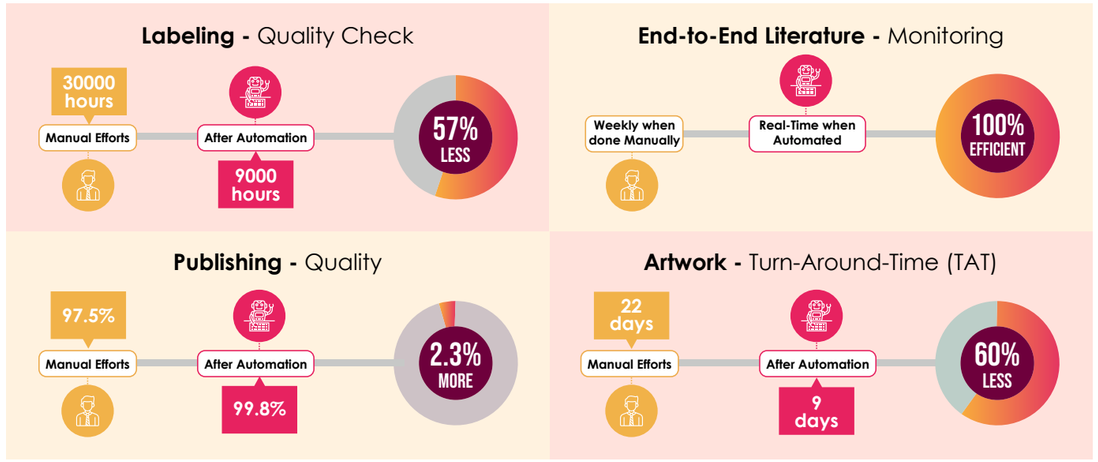
- CTD Auto File Mapping
- Global Classification and Registration Widget for Medical Devices
- Publishing Automation
- Smart Translation of Scientific Documents
- Content to Carton Platform with Automated Label/ Artwork Content Generation
- Individual Case Study Report (ICSR) Automation
- Clinical Performance Report (CPR) Automation for Medical Devices
- NLP-based Quality Control of Medical Writing Function
- Automated Translation Bots for Pre-defined Clinical Documents

In addition to these intelligent product suites that the strategic partners offer customers; they also assist clients in moving the automation scale forward. Consulting services for the evaluation of processes and automating routine operational activities and scientific activities from traditional processes across safety, medical writing, labeling, clinical & Regulatory streams are the top trends that will transform the biotech and pharma Regulatory market.

Incremental Innovation Category	Cross Functions	Automation Tool Description
Smart Content and Document Processing	Artwork	Auto annotations of Artwork PDFs from given inputs
	Clinical Safety, Regulatory Quality, and Compliance, MA	QC/formatting standards for any word documents and NLP-based QC using Amazon Comprehend
	Regulatory Operations	Automated document-level publishing and submission-level eCTD publishing of dossiers
Smart Search and Translation Automation	Safety, Medical Writing, Labeling, Clinical, and Regulatory	Amazon web-services-based translation/ transcoding of scientific documents
		Bulk multilingual keyword and contextual search
Robotic Process Automation	Medical Device Regulatory Affairs	Global Medical Device classification tracker
	Safety, Medical Writing, Labeling, Clinical, and Regulatory	Smart web crawlers for real-time screening for new journals and articles
	Global Regulatory Intelligence	RPA/NLP based internal and external decision support systems

The applicability of automation in some other functional areas can be best described as below:

Some of the realized real-world benefits are

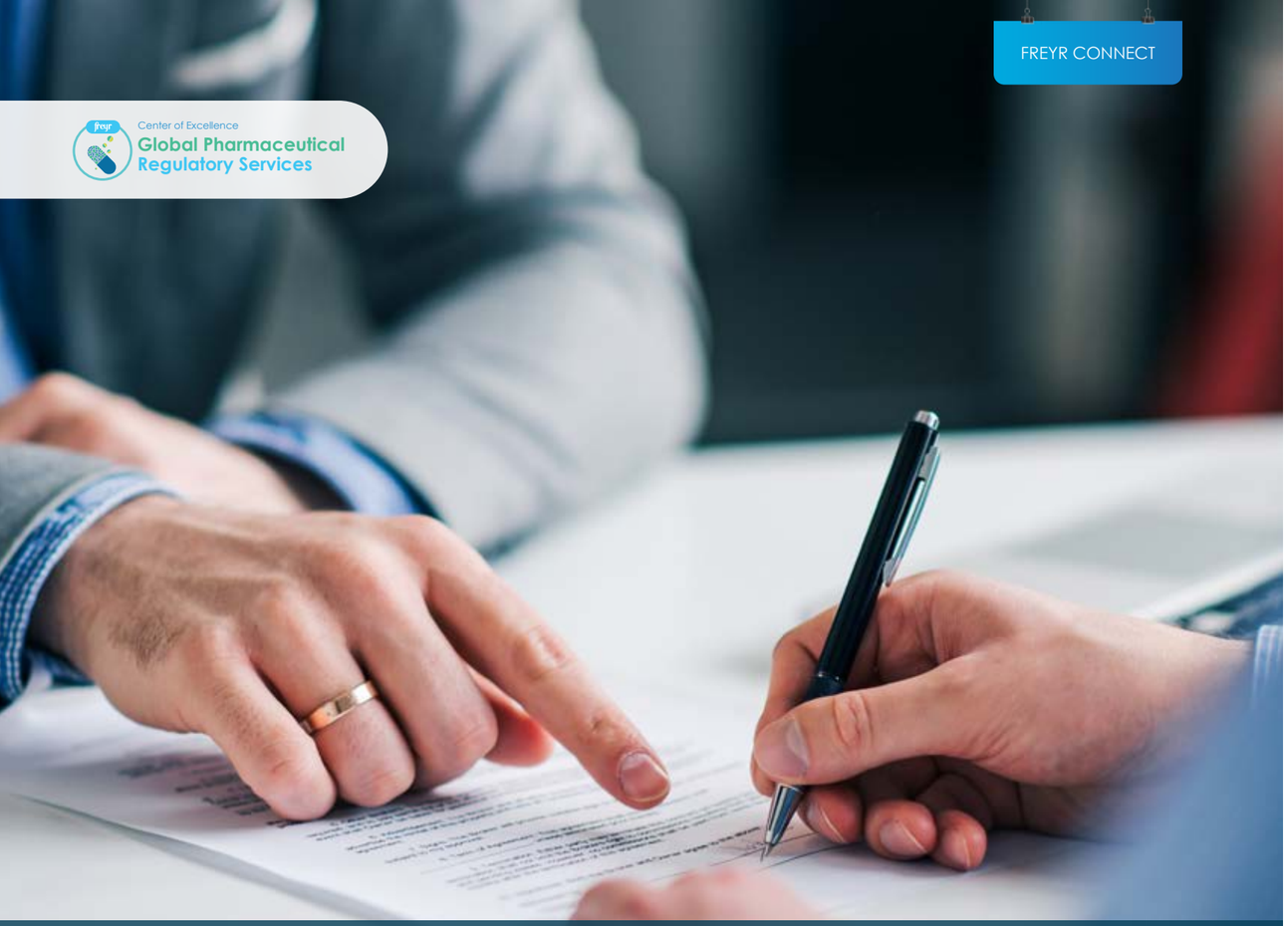


To guide companies through the entire process of digital transformation from creating a strategy, to discovering redundant processes, designing optimal automation, testing, and full-scale use as well as effectiveness monitoring, it is best to partner with a proven Regulatory consulting partner.

Experts in Regulatory automation can assist pharmaceutical, life sciences, consumer products, and medical device companies with their digital transformation efforts by:

- Establishing and developing an automation strategy
- Evaluating, comprehending, and documenting redundant business processes
- Establishing operational models breaking the silos
- Determining technical infrastructure needs for deploying state-of-the-art automation solutions
- Training employees and assisting in the creation of an "automation-friendly" environment, in which each team member seeks out additional automation opportunities to aid in the company's digital transition. By educating team members (train-the-trainer) on how to create, operate, and manage automation solutions, the companies become self-sufficient in a short time
- Using digital software, attain quick resolution to challenges that arise in day-to-day Regulatory compliance activities
- Round the clock support for the company's adoption of automation technology
- Assisting in the planning and establishment of Regulatory Automation Center of Excellence or Digital Transformation Centers to facilitate organization-wide automation processes

If you are not sure where to begin or how to improve your company's process automation and digitization with cutting-edge technological solutions, consult a strategic Regulatory partner like Freyr on how to approach your company's AI/ML/RPA automation effort.



EXTREME COST-CONTAINMENT POLICIES AFFECT GENERIC DRUG PRICING AND INNOVATION IN THE EU

A new report from a European generics trade association says that extreme cost-containment policies can adversely affect the generics supply chain vide consolidation of generics drug production and withdrawal of such products from the market. A recent press release by the Medicines for Europe further states that there is evidence that extreme cost-containment policies are producing counterproductive effects on generic medicines. The European Union (EU) market is also facing a withdrawal risk for important and less expensive medicines owing to the same. Dated November 23, 2021, the report draws references from the European Commission report from 2018, which offers patent protection for up to thirteen (13) years for innovator drugs. Supplementary protection certificates for Active Pharmaceutical Ingredient (API) for five (05) more years make an extended total of up to twenty-five (25) years of API protection in the EU market. During this period, the price of the product remains the same, and it is saved from competitor products.

Manufacturers who prefer off-patent innovation find it to be a cost-effective alternative. Though the total cost of off-patent products is about/more than half of that

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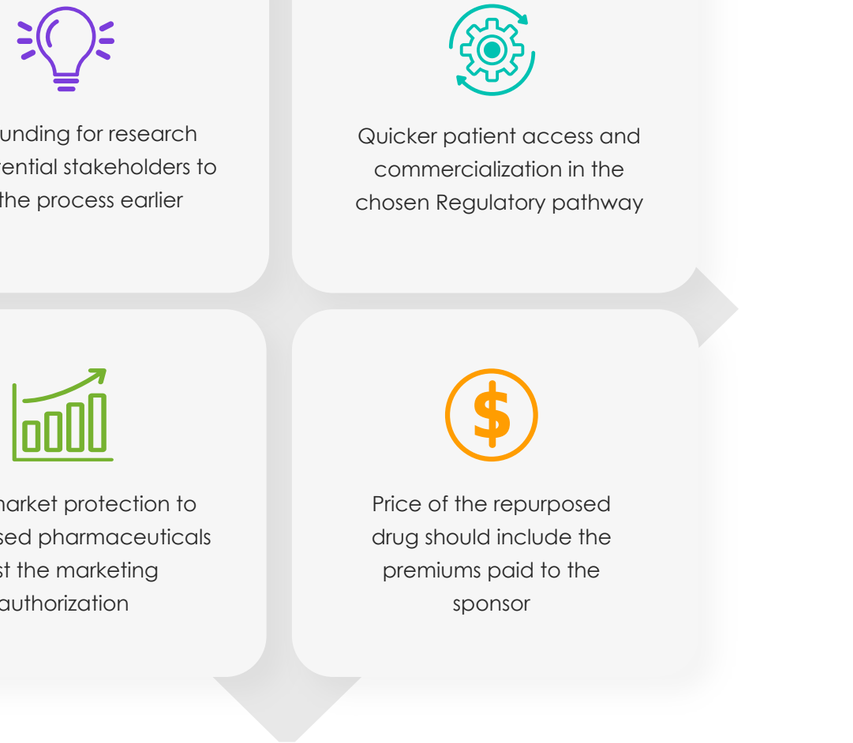
when developing a de novo pharmaceutical (a drug design involving an iterative process in which the three-dimensional structure of the receptor is used to design novel molecules), it is coming off as a better option.

Most drug manufacturers are finding drug repurposing to be the ideal option in off-patent innovation. This is a process in which existing drugs are investigated for identifying new therapeutic uses. Also known as drug repositioning, several pharmaceutical companies are developing new drugs using this efficient, time-saving, and cost-effective strategy.

The Commission report of 2018 contains the protocol to be followed for drug repositioning. It also includes the Regulatory incentives that are available to Marketing Authorization Holders (MAHs) of certain pharmaceuticals. According to the latest report from the aforementioned trade association, the following four (04) benefits should be offered at different stages of the repurposing/repositioning process.



To encourage off-patent innovation in the EU market, much work has been carried out in the recent past. This includes building a public-private framework for drug repurposing by a team of experts. The current report bases its findings on this framework that was launched in October 2021. It aims to make the most of the untapped source of innovation in the pharmaceutical space to match the unmet demand for life-saving drugs.

If you are a generics manufacturer looking for EU market entry, timely information on the latest Regulatory updates and consultation with a partner like Freyr can make you practice the best compliance procedures and save you a lot of costs. Stay informed. Stay compliant.

FSSAI MANDATES REGISTRATION AND INSPECTION OF FOREIGN FOOD FACILITIES

Food Safety and Standards Association of India (FSSAI) has recently 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) must comply with all the Regulations from June 01, 2022.

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

Registration of Foreign Food Manufacturing Facilities

Based on the risk, the FSSAI specifies the categories of food products intended for export to India. All foreign food manufacturing facilities that fall under the specified categories must register their food products with the FSSAI before exporting to India. The manufacturing facility can apply for registration directly or via an authorized representative through "Form 16," along with the documents specified in Annexure-1.

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Application Processing for Registration of Foreign Food Manufacturing Facilities

Upon scrutiny of the application, the FSSAI may request any additional information providing thirty days (30) of notice. If the applicant submits the additional information, the Authority may process the application for inspection or reject the application. If the applicant fails to submit the required information within the stipulated time, the application shall stand rejected.

Inspection of Foreign Food Manufacturing Facilities

When deemed necessary, the Foreign Food Manufacturing Facility/Facilities may be inspected as per the FSSAI standards. The officials from FSSAI and relevant ministry/department/organization/recognized auditing agency shall be nominated by the Food Authority to inspect the Foreign Food Manufacturing Facilities. The FSSAI may prescribe the cost of inspection, which shall be borne by the Foreign Food Manufacturing Facility/Facilities.

Issuance of Registration

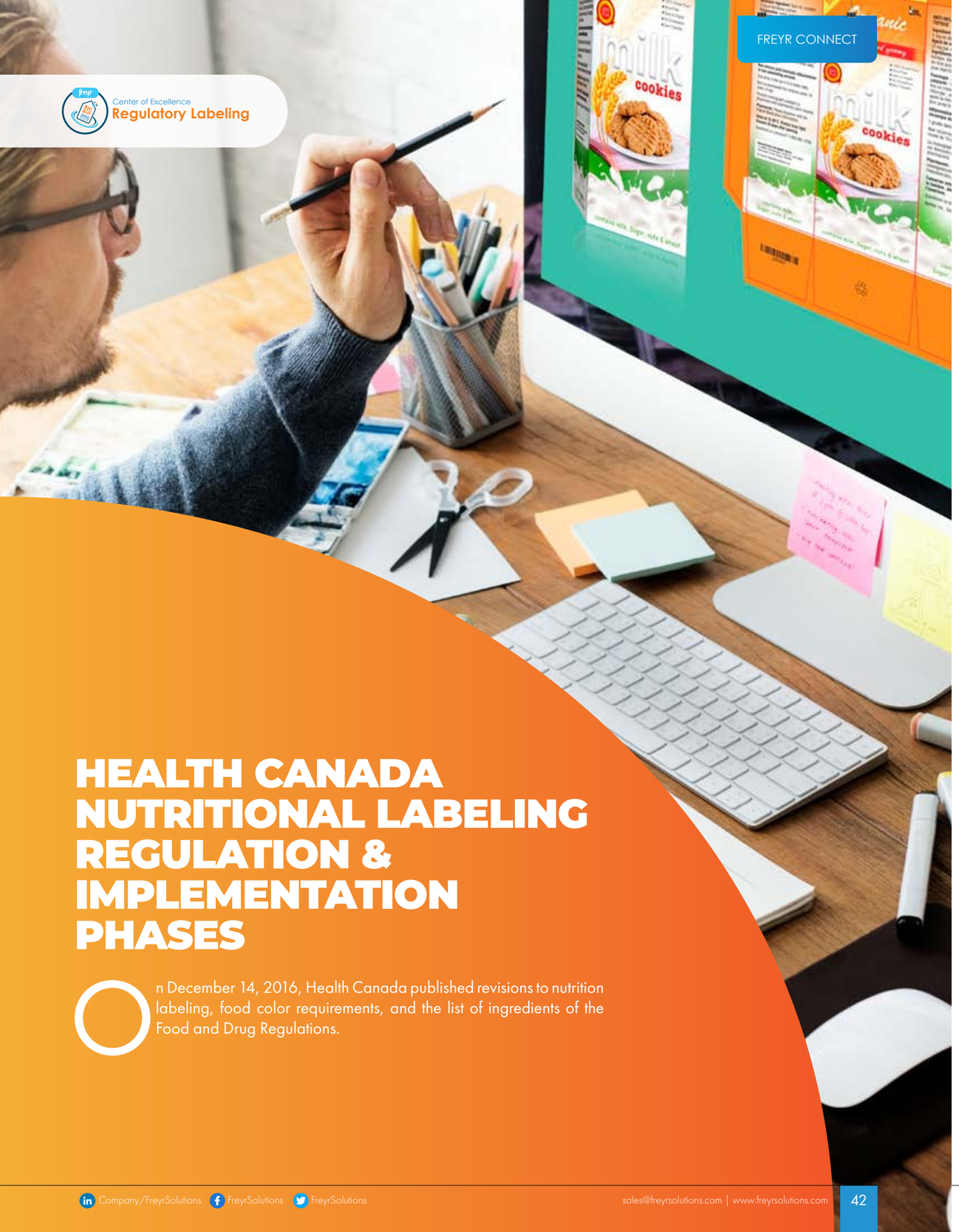
If the facility is compliant with the regulations of the FSSAI, it shall be registered as a Foreign Food Manufacturing Facility for two (02) years. The registration number shall be communicated in 'Form 17.' And, if the facility is not compliant with the standards of the FSSAI, the application shall be rejected. The applicant can take the necessary remedial action and apply for recognition again. Renewal of registration of Foreign Food Manufacturing Facility must be made through Form 16, at least thirty (30) days before the expiry date.

Suspension or Cancellation of Registration

If the Foreign Food Manufacturing Facility or their food products intended for export to India are found not compliant with the FSSAI regulations, their registration shall be suspended or cancelled.

In a nutshell, all the Foreign Food Manufacturing Facilities must be compliant with the FSSAI regulations and register with the authority to market their food products in India.

With the right strategy, FBOs can avoid the hassles in the registration process. Reach out to our experts at Freyr for the right-first-time registration of your food facilities.



Center of Excellence
Regulatory Labeling

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.

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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

DYK? The transition period to meet the labeling requirements ended on December 14, 2021. Until December 14, 2022, the Canadian Food Inspection Agency (CFIA) will be focusing on compliance promotion. Later, the CFIA will apply enforcement discretion in cases of non-compliance. Therefore, organizations must either comply or provide a detailed plan on how to comply with the regulations at the earliest possible date, which must be on or before December 14, 2023. Also, the CFIA has the authority to act if there is inaccurate, false, or misleading labeling information.

Dec 14, 2016, to Dec 14, 2021	Dec 15, 2021, to Dec 14, 2022	Dec 15, 2022, to Dec 14, 2023	After Dec 14, 2023
• Transition Period • New or old labels valid • CFIA focus on education and compliance promotion	• End of transition • New labeling requirements apply • CFIA will continue to focus on education and compliance promotion	• Organizations must comply with the new labeling provisions or have a detailed plan to achieve compliance	• Organizations must comply with the new labeling provisions

In a nutshell, organizations must comply 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. Would you like to explore the compliance strategies for nutritional labeling? Get in touch with our experts at Freyr to avoid Regulatory roadblocks.

THE OBLIGATIONS FOR ECONOMIC OPERATORS (EOs) - UNDER SWISSMEDIC'S MEDICAL DEVICE ORDINANCE (MedDO)

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There are various Economic Operators (EOs) who play a vital role in a device supply chain while delivering them to the point of use. Given the importance of each role, the Swiss Medical Device Ordinance (MedDO; SR 812.213) has set out the roles and responsibilities for each of these EOs. The three (03) major Economic Operators (EOs) in the supply chain are the Swiss Authorized Representative (Swiss AR/CH-Rep), importers, and distributors.

The Swiss AR plays a critical role in ensuring only safe devices are placed in Switzerland. The importers and distributors are mainly involved in the storage and transportation, and the Swiss ARs play no role in the storage or transportation of the devices. The Swiss AR and importers must register with Swissmedic and obtain a CHRN number, whereas the Swiss distributors need not register with the Health Agency.

On a mandatory note, the Swiss AR must have a written mandate with the manufacturer, whereas such mandate is not a Regulatory requirement for the importers and distributors. The importers and distributors may agree to have such mandate with their manufacturer as per mutual understanding. The Swiss AR must appoint a Person Responsible for Regulatory Compliance (PRRC), and the importers and distributors do not require such a role.

The distributor is not obliged to archive or have any device documents. On the other hand, the importers must have access to declarations of conformity and certificates. The Swiss ARs must retain the device technical documents along with the declarations of conformity and certificates. Such documents shall be available for ten (10) years after the last device is placed on the market. In the case of implantable devices, they should be archived and made available for fifteen (15 years).

Post-market Obligations

All the EOs, i.e., Importers, Distributors, and the Swiss ARs are responsible for tracing the devices placed in the Swiss market. The devices shall be traceable for at least ten (10) years from the date of placing the last device in the market. In the case of implants, the traceability information shall be available for fifteen (15) years.

The Swiss AR ensures that all the reports on serious incidents, safety corrective actions, and related trend reports are submitted to Swissmedic. All economic operators must, without fail, forward any complaints or reports of suspected incidents to the manufacturer. The importers and distributors must maintain an updated complaints list, and the Swiss AR must have access to technical documentation, including the Post Market Surveillance (PMS) data.

The Swiss AR is not obliged to take part in the complaint investigation. Though not a Regulatory obligation for the Swiss AR, the manufacturers and the Swiss AR may discuss, mutually agree, and include the obligations in the written mandate. However, the Swiss AR must co-operate with the Swissmedic on Corrective And Preventive Actions (CAPA). Being part of the supply chain, the importers and distributors are obliged to obtain and share the required information with the manufacturer or the Swiss AR to carry out the complaint investigation. The importers and distributors must also support executing corrective and preventive actions such as product recalls.

The manufacturers should make a point to identify the stakeholders involved in the supply chain and identify each stakeholder's role. They should ensure that the roles and responsibilities of each of the stakeholders are agreed upon during the business discussion, and a written agreement for the same is in place. The manufacturer can also ask the Economic Operators (EOs) for a quarterly or half-yearly summary report to keep track of all the activities that they carry out. The manufacturer should periodically monitor if the EOs are fulfilling their roles and are always compliant.

Are you looking for a trusted and compliant Swiss AR to market your devices in the Swiss market? Contact Freyr - a trusted Swiss AR for medical device and IVD manufacturers.

COMPARATIVE ANALYSIS OF TGA'S 2018 AND 2021 ADVERTISING CODES

To educate patients and Health Care Professionals (HCPs) and promote treatment options, the pharmaceutical industry like many other industries dedicates billions of dollars to advertise and promote prescription drugs. The legislative framework of advertising in Australia comes under Section 42BAA of the Therapeutic Good Act 1989. The Therapeutic Goods Advertising Code outlines the minimum requirements to be followed by the drug manufacturers while advertising therapeutic goods to Australian consumers.

The Therapeutic Goods Advertising Code 2021 came into effect after eighteen (18) months of consultation with the stakeholders, on January 01, 2022. The amended Code provides clarity on therapeutic goods advertised to consumers and protects them from advertisements that lead to 'fear and distress'.

The newly published Advertising Code 2021 permits a transition period of six (06) months to all the applicants allowing them to comply with the 2018 Code until June 30, 2022. The Code is divided into different parts to enhance readability. For instance, Part 4 is for mandatory statements, while Part 3 is for claims made in advertisements.

Commonalities between the 2018 and 2021 Codes

The overall structure of the advertising Codes remains the same. For example, advertising certain therapeutic goods are prohibited, and these include Schedule 3 (pharmacist only), Schedule 4 (prescription only), and Schedule 8 (controlled substances). Therapeutic goods for serious conditions still cannot be advertised without prior approval from the TGA.

The 2018 and 2021 Codes have been implemented to ensure ethical standards are followed by the drug manufacturers in a manner that they:

- Promote therapeutic goods which are safe and effective
- Do not mislead or project any misinformation related to the drug
- Do not influence the HCPs to favor a preferred drug product
- Are consistent with the current public health campaigns

Comparative Analysis: Major Changes Between the Codes

Requirements	2021 Code	2018 Code
Mandatory Statements	• The mandatory statements have been revised and are limited to Direct-To-Consumer (DTC) advertising, where consumers cannot inspect the goods voluntarily before purchase. • Additional mandatory statements have been included. For example: 1. Advertisement of pharmacist-only products, 'ask your pharmacist about this product' statement is mandatory. 2. Advertisement of therapeutic goods specific to HCP must include the statement, 'this product is not available for purchase by the general public.' 3. Short form advertisements must include the 'Always follow the directions for use' statement.	1. Medicines claiming to relate to a specific symptom of disease should include the mandatory statement, "If symptoms persist, worsen or change unexpectedly, talk to your healthcare professional." 2. Advertisement of pharmacist-only medicine, "Ask your pharmacist – they must decide if this product is right for you." 3. Direct/Indirect advertising of medicine must include,' Always read the Label.'
The List of Product Samples	Under Section 25 (Part 7), the 2021 Code expanded the list of samples that can be advertised. This list includes face masks and gloves, certain sanitary products, hand sanitizers, specific nicotine replacement therapies, and COVID-19 rapid antigen tests.	Included under Section 20 of the Code. Advertisers cannot advertise their products with a sample except for products listed in Schedule 3.

Requirements	2021 Code	2018 Code
The Rules for 'Safe and Proper Use' of Therapeutic Goods	Advertisement must ensure that the therapeutic good represented: • Is consistent with the directions or Instructions For Use (IFU) for the product • Does not overstate efficacy or performance of the good • Does not lead consumers to use the goods inappropriately or excessively • Eliminates the advertising, which causes alarms of fear and distress	Advertisement must ensure: 1. Proper use of medicine 2. Medicine doesn't show delayed effect 3. Medicine doesn't claim 'cannot harm' 4. Medicine doesn't mislead the consumers by stating it to be a miraculous, assured cure
Health Warnings	Relevant warnings apply only on the direct purchase of drugs advertised, facilitating any purchase. These are applicable for physical and online purchases of therapeutic goods.	Health warnings prescribed for medicines in Schedule 1 of the Code has been removed.
The Testimonial and Endorsement Advertising Rules	Section 24 (Part 6) • Consolidated testimonial requirements under section 24. • The 2021 Code clarifies the prohibition of paid or incentivized endorsement and testimonials.	**Sections 16 - Endorsement** • Section 16(1)(b) is not applicable for non-prescription medicines. • Section 16(1)(a) is not applicable for Testimonial under s(17). **Section 17 - Testimonial** • Testimonial section is divided into three (03) sub-sections • s17(1) - Therapeutic good claim made by a person using the medicine • s17(2)(a) - Characteristics of a person • s17(2)(b)(c) - Obligation of the testimonial before being advertised • s17(3) - Information disclosed in the ad about the testimonial
The Definition	Includes modified information for the active ingredient, use, health warning, and price	Includes health warnings, prominently displayed, or communicated statements

Applicants must carefully assess the changes put forward by the TGA and comply with Code 2021 from July 01, 2022. The transitional period also allows the advertiser to check and evaluate if their current advertising is accurate and balanced. A seasoned Regulatory partner can assist in reviewing the promotional material as per the updated norms to comply with the Local Authority guidance and avoid any discrepancies with the new regulations and Codes alongside the transitional period. Explore Freyr's expertise across ad promo services today.

Center of Excellence
Global Cosmetics
Regulatory Services

REGULATION FOR HAIR COLORANTS IN THE EU

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Hair colorants are classified as cosmetic products by the European Commission (EC) and are regulated under the regulation (EC) No: 1223/2009. Hair colorants contain a mixture of substances called hair dyes that are used to change the color of hair or to restore the original hair color. They are classified into the following three (03) categories based on their color fastness:

- Temporary hair dyes
- Semi-permanent hair dyes
- Permanent hair dyes

Temporary hair dyes and semi-permanent hair dyes are non-oxidative (non-permanent) in nature and are used for temporary color changes. In contrast, permanent hair dyes are oxidative and use hydrogen peroxide as an oxidizing agent to impart color to the hair for a prolonged time. Permanent hair dyes are also resistant to shampooing. They constitute 70–80% of the EU coloring products market.

Safety of Hair Colorants in the EU

A significant amount of scientific research supports the safety of hair dyes marketed and sold in the EU. The EU cosmetic regulation requires hair colorants to be safe for use, and all products need to undergo rigorous safety assessments before being placed in the market. The assessment of hair dye products is conducted by a professionally qualified safety assessor based on the following factors:

- Finished product
- All the ingredients used to manufacture the product (irrespective of their source)
- Instructions on using the product
- Frequency of use
- Warnings and indications
- Target consumer group

Not adhering to the safety norms laid down by the EU Commission may lead to legal consequences. To successfully sell and market hair dye products in the EU, manufacturers and brand owners need to achieve compliance with the European Regulatory requirements. Consult a Regulatory expert like Freyr to decode the cosmetic Regulatory requirements of the hair coloring products in the EU market. Stay informed. Stay compliant.

Center of Excellence
Global Food and Food Supplements
Regulatory Services

WHAT IS THE TOLERABLE UPPER INTAKE LEVEL (UL)?

The Tolerable Upper Intake Level (UL) is the maximum level of nutrient intake that possesses no adverse health risk if consumed by the general population.

UL is considered the Dietary Reference Value (DRV), and is not a recommended level of Intake; rather, it is a scientifically-derived 'threshold' below which the potential risk is minimized, and if the intake is above the considered value, then the health risk is more pertinent.

Some European countries have recently asked the European Food Safety Authority (EFSA) to set a science-based Tolerable Upper Intake Level (UL) for dietary sugars from all sources. The scientific experts of the EFSA conducted reviews of 25,000 scientific papers in 2018 and 7,500 in 2020. One of the study bases was the linkage between the intake of sugar and different health problems such as the effects of pregnancy, dental caries, and chronic metabolic diseases.

However, the Upper Level of intake was not established since the health risk was increasing across all the doses, and due to this, no threshold value was identified. Therefore, the EFSA concluded that the consumption level of added or free sugars should be as minimum as possible. Public consultation with the EFSA on the draft opinion is still open for any scientific insights until the end of 2021.

For comprehensive insights on compliance best practices, reach out to Freyr – a proven Regulatory expert.

Center of Excellence
Chemicals Safety and
Regulatory Affairs

WHAT IS A UNIQUE FORMULA IDENTIFIER (UFI)?

Any hazardous mixture or product would be labeled with a unique code, called a Unique Formula Identifier (UFI). It is a requirement to Annex VIII to CLP (harmonizing the information related to emergency health response) and is a unique sixteen (16) digit alpha-numeric code separated by hyphens in four (04) blocks (Ex: UFI: E600-30P1-S00Y-5079). The code links the submitted information on the mixture placed in the market and the medical emergency needed (information needed to treat patients).

The UFI is a mandatory requirement in the EU for hazardous mixtures, and the code needs to be presented on the product label. Manufacturers should include this information while performing Poison Centre Notification (PCN) and further print the same on the product label. The transition period for PCN will end in Jan 2025. An entity has to submit the VAT number and the formulation number of the product mixture to generate a UFI.

Importance of the UFI

- Forty percent (40%) of calls to Poison Centers have problems with the identification of products.
- UFI provides more accurate advice on precautions and treatment.
- It is helpful to distinguish two (02) mixtures with the same trade name.
- Poison Centers will be able to decode the information on mixture composition from the UFI.

Would you like to learn more about UFI? Or would you like to understand best compliance practices to align with the Poison Centers? Reach out to a regional Regulatory expert.

Center of Excellence
Chemicals Safety and Regulatory Affairs

Application Process for EU Eco Label

What is an Eco Label?

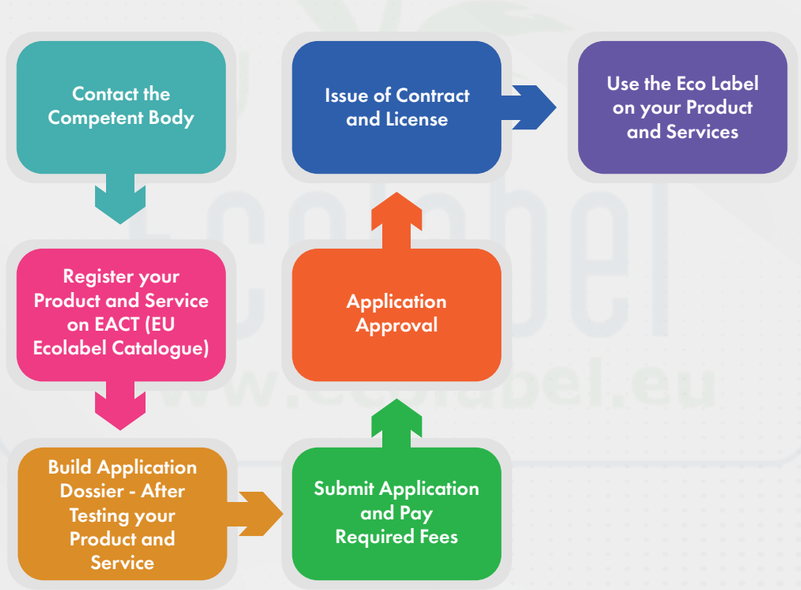
An Ecolabel is a voluntary certificate awarded to Products and Services which have a minimal negative impact on the environment

Why is an Eco Label important?

An Eco Label indicates that the Product or Service is environmentally sustainable.

It differentiates the product from similar products in its category by endorsing its eco-friendly nature and plays a key role during purchasing behaviour

Application Process



Do you have any query on the approval process? Decode it thoroughly with the help of a local Regulatory expert. Consult. https://csra.freyrsolutions.com

BE TECHNOLOGY-DRIVEN WITH PRAVEEN BEZAWADA

Innovative and technology-driven solutions have been two crucial aspects in the Regulatory space of the Life Sciences industry. Understanding and balancing both will truly lead to digital transformation and the success of any organization. Let us proudly introduce a Visionary who perfectly does such kind of balancing act at Freyr for streamlining the Regulatory processes of our customers for end-to-end compliance. Here is a candid conversation with **Praveen Bezawada, Chief Technology Officer (CTO),** whose resilience and commitment have made him a leader by example.

1. **Hello Praveen, A warm welcome and best wishes to you.**

   Thank you.

2. **Ten (10) years of successful business completion, the launch of Freyr Digital, and Praveen taking over as a CTO; almost all of them happened in quick succession. Does it in any way mean the evolution of disrupting/ hard-hitting service line from Freyr?**

   Freyr has had a very successful ten (10) years, building a gold mine of knowledge of Regulatory affairs and Regulatory processes and highly experienced experts. We have a strong knowledge foundation ripe for exploitation to build products and services that can help our customers automate and bring efficiencies using our knowledge base.

   Yes, we have laid the foundations by streamlining our development processes with Agile for agility; by introducing DevOps for making incremental and continuous delivery of our products with high quality; by fully embracing automation with AI/ML and RPA to introduce innovative solutions and services; and by working towards reorganizing product engineering to put more focus on people development. All these changes will allow us to bring disruptive solutions and services to the market to help solve our customer problems.

3. **We are witnessing that technology-driven solutions are the new normal in most industries. Do you think the Regulatory space of Life Sciences game for this?**

   We are amid the 4th Industrial Revolution, which is generating massive productivity gain across all industries. While the 3rd Industrial Revolution was driven by Electronics, Computers, the Internet, and Telecommunication have now been seamlessly integrated into Human societies. Cloud and AI are driving the 4th Industrial Revolution and IoT, bringing technologies closer to people and making the integration easier and more seamless.

   In a way, the 4th Industrial Revolution is building on the previous one and making it more accessible to people and societies in general. In this, Life Science and specifically Regulatory space are no exception. Technology has already laid the foundation in the Regulatory space, where vast amounts of data has been digitized. Building on this data and human expertise will drive innovation in Life Sciences.

4. **What does digital transformation mean to you? Given the data safety and security in the Life Sciences industry and the conservative nature of the Pharma industry, would it be possible to ensure the end-to-end digital transformation of an organization?**

   I view digital transformation as a massive change in the way people seamlessly use and think about digital tools and solutions. The transformation will include both incremental innovation with small and continuous improvements in existing workflows and disruptive innovation, which builds on the incremental to deliver end-to-end workflows and bring in Cloud and AI/ML for solutions that transform the industry.

5. **Data science is one of the powerful technologies that drive business transformation. Do you think customers in the Regulatory field are inclined to integrate the raw data into in-depth insights with dashboards and cloud-based logs?**

   Yes. Data is the new oil – here, I refer to Data as digitized knowledge, be it documents stored in digital formats, processes recorded with RPA, insights created by subject matter experts, actions performed recorded as output log, and metadata associated with the data.

6. **Combining human expertise with AI and ML boosts business efficiency. What is your take on it? And is it measurable in the practical sense?**

   That is definitely true. AI/ML aid in creating automation for tasks and processes which can be programmed easily, especially those where human expertise is needed. Human expertise is expensive in terms of costs and time but crucial. Solutions that allow us to combine human expertise with AI/ML can bring speed while utilizing human expertise. For example, in Pharmacovigilance where AI/ML solution developed by Freyr can identify adverse events with high recall, which is the fraction of adverse events correctly identified that are then reviewed by a human expert to validate. As the number of adverse events in a given dataset tends to be small compared to the size of the datasets - AI/ML helps significantly reduce the efforts of human expertise without impacting the overall accuracy of adverse event detection.

FREYR CONNECT

   Another great example is the ML-assisted translation solution which is the core functionality of the Impact-L product. Here we have integrated ML translation workflows which have significantly reduced the efforts needed by human experts.

   An important measure of the benefit is the reduction in the time taken to perform the tasks- AI/ML allows human experts to offload many time-consuming aspects of a task and focus on a few critical steps where their expertise is most beneficial.

7. **Could you introduce us to the Praveen off the work and technology?**

   I think my main personality trait is curiosity. Curiosity to know, understand and experience. My two main passions outside of work are fitness and reading. I spent a significant portion of my free time in the gym or on a bicycle. Rest is spent reading.

8. **Customized and function-specific tools and AI/ML-oriented methodologies. Freyr has come a long way as a proven technology solutions provider simplifying and streamlining the Regulatory processes. What more is cooking at Freyr for the Regulatory space, and how the Regulatory provider is being prepared?**

   There is so much happening in Freyr in this space that it is hard to decide where to begin. We have made so much progress recently in our product development process with the introduction of Agile SOP. We have streamlined our infrastructure by fully focussing on Cloud. We have adopted continuous integration and deployment by adopting DevOps principles; we have invested heavily in automation and AI/ML by hiring experts and building competencies in our existing staff in the areas of Agile, CI/CD, Cloud, and Automation.

9. **If you were not techy?**

   My childhood dream was to be an Astronaut.

10. **One more license/ certification or a vacation?**

    It will definitely be a vacation where I can read and prepare for a certification.

The Customer: US based, Leading Skincare Products Company

Project Details: Regulatory Support for Cosmetics and OTC Products

The Customer: Romania based, Leading Food Products Manufacturing Company

Project Details: Product Compliance Service in India

The Customer: Singapore based, Leading Global Online Retailer Products Company

Project Details: Product Registration and LR Support for Mexico Market

The Customer: US based, Leading Healthcare and Beauty Products Company

Project Details: Freyr iReady

The Customer: Indonesia based, Leading Household and Personal Care Products Company

Project Details: Product Registration and LR Support for South Africa Market

The Customer: Spain-based, Global Pharmaceuticals Company

Project Details: RA Support in Bolivia & Peru and Regulatory Submissions for the EMA/the FDA

The Customer: India based, Leading Wellness and Personal Care Products Company

Project Details: End-to-End Regulatory Support for the EU and the UK

The Customer: Singapore Based, Leading Biopharmaceutical Company

Project Details: End-to-End Regulatory Support in Mexico

The Customer: Poland based, Skincare Products Company

Project Details: Product Compliance Check for the USA

The Customer: China based, Global Consulting Firm

Project Details: Product Compliance Check Service for Cosmetics Products in Mexico

The Customer: Australia-based, Leading Wellness Devices Company

Project Details: Regulatory Services for Device Registration in Australia

The Customer: South Korea based, Leading Food Manufacturing Company

Project Details: Regulatory Consulting Suport for FSSAI Regulations in India

Case Study 1

Center of Excellence
Compliance, Audit and Validation

Compliance Check for Hair Care Products in Malaysia

Client
India-based Leading Consumer Goods Company

Health Authority
National Pharmaceutical Regulatory Agency (NPRA)

Solution/CoE
General Cosmetics

Service Offering
Product Compliance Check

Industry
Cosmetics

BENEFIT HIGHLIGHTS

- Market-specific process adherence
- Efficient reports
- Easy market entry

Service Region
Malaysia

Client Location
India

Therapeutic Area/Indication
Hair Care Products

FREYR CONNECT

Business Imperatives

- The client is one of the India's leading consumer goods companies operating in health, beauty and wellness space.
- The client approached Freyr for support in the product compliance check involving a thorough review of formulation, label and claims for their products.

Challenges

- The product in scope was a herbal product, the regulations for which are not clearly defined.
- The client was insistent to retain some of the claims, which were of therapeutic origin, and hence, it was a challenge to remove those claims while maintaining the USP of the product.
- Due to presence of such claims, the labels were non-compliant with the Health Authority regulations.
- Stringent timelines for project delivery.

Freyr Solutions and Services

- Freyr performed a thorough review of ingredients/formula, label and claims for acceptability against the Malaysian cosmetic regulations.
- Freyr suggested the client about the required changes in label according to the Malaysian cosmetic labeling guidelines.
- Claims were accordingly modified to retain the cosmetic category of the product.

Client Benefits

- Freyr ensured products to be fully compliant and aligned with the current Malaysian cosmetics regulations.
- Extensive report on the product compliance check in terms of formula, label and claims was provided.

Case Study 2

Freyr iREADY

Effective Compliance of Cosmetics Formulae with Freyr iREADY

Client
US-based Leading Healthcare Company

Health Authority
Multiple HAs

Freyr CoE/Products
Formulation Assessment

Service Offering
Formulation Assessment, Ingredient Data, Regulatory and Safety Data

Industry
Cosmetics

Service Region
Australia, Singapore, Japan, Africa, South America, EU

Client Location
USA

Therapeutic Area/Indication
Cosmetics

BENEFIT HIGHLIGHTS

- Quick Turn-Around-Time
- Finalized formula in R&D stage
- Limits were recommended to the client for each formula
- Successful Product Launch

FREYR CONNECT

Business Imperatives

- The client is a US-based corporation that is solely focused on developing innovative supplements to help in naturally maximizing the human body's efficiency.
- The client approached Freyr to evaluate compliance of 15 product formulae for 10 major markets during the R&D stage of the product development.
- The client needed assistance for quality assurance of Regulatory services, ensuring data security and compliance check as per the business scenario.

Challenges

- Major challenge faced by the client was access to a single, reliable and centralized data repository of Global Ingredient Regulations & Restrictions and other intelligence.
- Another roadblock was the inadequacy of data to gain a better perspective while deciding on the Target Markets/Countries where the client wanted to release their formulae.
- Lack of domain expertise and technology access were other factors restraining them from quicker decision-making.
- No medium to assess compliance of the user-created product formulae for a new product against the Regulatory and safety information in various Target Markets/Countries.

Freyr Solutions & Services

- Freyr offered the client with the perfect solution to the requirements by providing them with access to a centralized and secure database (Freyr iREADY) and by ensuring current and accurate information about Ingredient Regulations globally.
- Freyr iREADY allows users to create any number of formulae in their secure user space and assess their compliance in various Target Markets/Countries.
- Freyr iREADY provides flexible textual and graphical views of Global Ingredient Regulations.
- Freyr iREADY also maintains the latest Regulatory Intelligence from the industry globally.

Client Benefits

- The challenges faced by the client were overcome with the help of Freyr iREADY and our in-house experts by suggesting limits to help them devise the right product formulae.
- Improved decision-making while targeting various Markets/Countries for a new product's release.
- Compliance needs were met with the help of a single, centralized, secure cloud-based solution.
- The client also achieved significant cost-savings in their formulae compliance activities with Freyr iREADY subscription and consulting services.

Glimpses from

F10

YEARS ANNIVERSARY

FESTRONIX 2022

SPORTS - SHOWS - SAGAS


MDV-Practice,

FREYR CONNECT

Client **Testimonials**

We would like to thank Freyr and the team for the accurate advice and performance, the great commitment, and timely support in successfully completing the MHRA registration process during Y2021 for more than 700 devices. We also appreciate the way Freyr accommodates all our requests in a relationship of mutual trust and respect.

We are very satisfied with collaborating with Freyr and looking forward to working with you in Y2022.

Director, Regulatory Affairs
An American Medical Device Manufacturer

FREYR CONNECT

Thank you, Freyr team, for all your hard work and excellent support for this IND. I especially want to highlight your work over this past weekend and address the comments by Monday morning.

Overall, module 3 looked really, really amazing, with all the links and bookmarks in place, which I know took a great deal of work, and it was done in a very short period of time. Bravo!

Manager, Global Regulatory Affairs, CMC
A Speciality Pharmaceutical Company

Freyr's services are very good. We will move with other projects too.

Pharmaceutics Lead – R&D
A Singapore-based Wellness & Fitness Company

The report is very clear and detailed with many valuable insights, which are of high quality. Very friendly and fast communication and support. Clear roles and responsibilities in the project, presented in a good way.

Regulatory Affairs Specialist
A Denmark-based Food Ingredient Manufacturing Company

Brilliant, as always. I appreciate the work you have done.

Global Director of Regulatory Affairs
A South Korean Pharmaceutical Company

Documentation was very satisfactory. I thank Freyr for the participation throughout the NDIN process.

Global RA Deputy Manager
A South Korean Pharmaceutical Company

We would like to thank Freyr for their work on label suitability in the US market. Freyr's expertise, punctuality, flexibility, enthusiasm, and prompt responses were all appreciated during the project. We are very satisfied with our collaboration, and we hope we can work together in the future again!"

Business Development & Alliance Lead
A Switzerland-based Nutritional Products Manufacturing Company

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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.

About Freyr

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

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