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GLOBAL REGULATORY SOLUTIONS & SERVICES
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VOLUME 5 ISSUE 2

CONNECT

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LEAD STORY

DRUG MASTER FILE SUBMISSIONS

REGULATORY : CONSULTING | SUBMISSIONS | AFFAIRS | SUPPORT | INTELLIGENCE | LABELING | SOFTWARE

WHAT'S INSIDE ?

Regulatory Stories

Freyr 360°

CONTENT CONTRIBUTORS

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FOREWORD

Hello Everyone,

Welcome to another Issue of Freyr Connect!!!

JUST IN!!! We are pleased to announce that Freyr is growing by leaps and bounds; proven to be fast-growing, yet again by:

- accomplishing a milestone of 200+ clients
- being nominated for the Best Pharma Contract Services Company by the IAE Awards
- attaining a brand-new outlook for www.freyrsolutions.com

In addition, Freyr is now a 500+ team of global Regulatory experts with 700+ regional affiliates across 120+ countries. That's quite an achievement, we assert.

What's there inside Freyr CONNECT, this time? Here's a quick sneak peek. Emphasizing the need to be compliant with the United States Food and Drug Administration (USFDA's) upcoming mandate for Drug Master Files (DMFs), we start this edition with a comprehensive cover story on the DMF Submissions and the review process it entails. Following that, this edition reflects Freyr's thought leadership on various Regulatory aspects of the European Medical Device Regulations (EU MDR), Good Manufacturing Practices in Europe and the Brexit Effect, Global Cosmetics Regime and Region-specific Regulatory Pathways along with other stories.

This edition will also give you an opportunity to go through an exciting amalgamation of fun and business at Freyr. We bet you can't skip the fun elements and activities we have covered in the Festronix 2017, Freyr's Annual Day Event.

Thanking everybody who diligently contributed to this chapter of Freyr CONNECT, we hope this edition will enlighten your day.

Happy reading!

Rajiv Rangan
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Center of Excellence
Publishing & Submissions

THE DRUG MASTER FILE SUBMISSIONS

US FDA recognizes five different types of DMFs that are:

- Type I: Manufacturing Site, Facilities, Operating Procedures, and Personnel (no longer applicable)
- Type II: Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product
- Type III: Packaging Material
- Type IV: Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation
- Type V: FDA Accepted Reference Information

ADVANCEMENTS AT THE FDA

ALL the United States Food and Drug Administration (USFDA) Drug Master Files (DMFs) To Be Submitted in eCTD Format:

According to the legislation in the field, the FDA now requires all DMFs to be submitted in Electronic Common Technical Document (eCTD) format from May 5th, 2018 onwards, and all DMFs not submitted in this format after this date will be rejected.

If a DMF already exists in paper format with the FDA, it doesn't need to be resubmitted in the eCTD format. All new submissions post May 5th, 2018, however, will require to be submitted in the eCTD format. The DMF holder may continue to hold the same DMF number as before, with some minor changes. For instance, if the previous DMF number was 5678 , the DMF holder would now have to pad left with two zeros, to convert the number to a 6-digit format. Thus, 5678 would be converted into 005678 , when the DMF number is converted into eCTD format; but would essentially remain the same number.

Packaging Information not included in the DMF:

Packaging information, however, isn't required to be submitted to the FDA in the DMF. Applicants of an NDA, ANDA or BLA, or even the sponsors of an IND are responsible for providing information about packaging components. This information is generally mentioned in the application itself, and is provided to the applicant by the manufacturer of the mentioned packaging component or material

TYPE III DMF for Confidentiality:

In the case of confidentiality, or if the manufacturer wants to withhold certain proprietary information from the applicant or sponsor, all such information may then be placed in a Type III DMF and incorporated into the application, accompanied by an authorizing letter from the manufacturers which refers to the DMF. If a DMF already exists in paper format with the FDA, it doesn't need to be resubmitted in the eCTD format. However, after May 5th, 2018, all submissions will only be accepted in the eCTD format, thereby making the need for paper submissions redundant.

DMFs to be Updated Annually:

According to the DMF Guidance, DMF holders are recommended to update their DMFs annually. FDA also sends "Overdue Notification Letters" (ONLs) to DMF holders for DMFs that have not been regularly updated in the last three years. If a DMF holder fails to respond to an ONL, respective DMF may be closed by the FDA.

To sum up, a run though of DMF developments:

- The last date for submissions of DMFs is May 5th, 2018
- All DMFs post May 5th, 2018 must henceforth be in eCTD format
- All DMFs post May 5th, 2018 not in eCTD format will be summarily rejected
- A DMF that already exists in paper with the FDA doesn't need to be resubmitted in eCTD format
- Post eCTD conversion, the DMF holder will continue to hold the same DMF number as before, with some minor changes
- Packaging information doesn't have to be submitted in the DMF
- Proprietary information which the manufacturer wants to withhold from the applicant can be incorporated in a Type III DMF
- DMF holders are required to update their DMFs annually
- The FDA sends Overdue Notification Letters (ONLs) to DMFs that haven't been regularly updated, and if the FDA receives no response to the ONL, the DMF will be closed

DMFs are not the same everywhere. While the US may encourage a certain submission process, health authorities elsewhere may find other methods more convenient. Thus, there exists a difference between regional DMFs - like the EDMF- prevalent across Europe, or the range of regional DMFs supported by various health authorities in their own countries.

THE EUROPEAN DRUG MASTER FILE (EDMF):

Active Substance Master File (ASMF) procedure, formerly known as the European Drug Master File (EDMF) procedure allows valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, simultaneously allowing the Applicant or Marketing Authorization (MA) holder to take full responsibility for the medicinal product and the quality and quality control of the active substance. National Competent Authorities/EMA thus have access to the complete information that is necessary for an evaluation of the suitability of the use of the active substance in the medicinal product.

Active Substance Master File (ASMF) commonly known as the European Drug Master File (EDMF) is a submission made to European Competent Authorities and / or EMEA in support of Marketing Authorization Application [MAA] or Marketing Authorization Variation [MAV] of a medicinal product. ASMF / EDMF shall be prepared in Common Technical Document (CTD) format.

The scientific information in the EDMF should be physically divided into:

- The Applicants Part (AP) - contains the information that the EDMF holder regards as non-confidential to the Applicant / MA holder
- The Restricted Part (RP) - contains the information that the EDMF holder regards as confidential

REGIONAL DMFS

The DMFs generated for regions (excluding USA and Europe) are covered under Regional DMFs for the following countries: Canada, Turkey, Brazil, Korea, South Africa, Australia, Syria, Saudi Arabia. Regional guidelines of the respective countries must be followed for generation and submission of the Regional Drug Master Files.

Freyr provides DMF holders with the necessary expertise when a DMF application needs to be made. Freyr is a leader in the regulatory industry and provides various benefits to DMF holders, including:

- Flexible eCTD publishing software, Freyr SUBMIT, for end-to-end Regulatory publishing and submission services
- Well-versed Regulatory team keeping track of ever-changing Regulatory guidelines
- Well defined processes for creating DMF/ASMF submissions - starting from articulating to publishing and dispatching DMFs
- Expert advice on region-specific DMF submission requirements and various other Regulatory submission formats
- Point of contact for each submission
- Submission dispatch availing Freyr gateway
- Effective dossier compilation and preparation within reduced timeframes
- Dedicated quality check teams
- Quick submission turnaround times

With the right expertise, filing DMF applications is a convenient and hassle-free experience. Freyr ensures that DMF holders face no obstacles in the process of filing DMF applications and that they are constantly up to date with the latest developments in the regulatory industry.

Reference Link:

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM511231.pdf

20+ CLIENTS...

Freyr has always placed a tremendous emphasis on delivering world-class Regulatory support and catering high-end technical excellence in terms of the custom-built Regulatory software.

WE THANK ALL OUR CUSTOMERS AND GLOBAL STAKEHOLDERS FOR BEING PART OF THIS INCREDIBLE JOURNEY.

500+
Global Regulatory Experts

700+
Regional Affiliates

120+
Countries

Center of Excellence
Artwork Pack Management

THE IMPACT OF IMPLEMENTING SAFETY FEATURES IN PHARMACEUTICAL PACKAGING & LABELLING

This article explains what labelling and packaging measures the manufacturers need to implement and how effectively they can do so with advanced packaging technologies to ensure the patients' safety. Besides, it explains how it is going to impact the outcomes of pharmaceutical companies and the need of an optimally designed labelling solution to meet the Regulatory needs without failure. Decode the end-to-end coverage of packaging and labelling safety features to be implemented.

Every year, over millions of dollars are being spent to develop drugs that not only provide the required patient treatment but are also safe for human consumption in a set of forms. With huge investments put-in, at the stage of manufacturing, are companies set to take up equivalent responsibility in following safety standards while marketing them? Several mislabelling and mispackaged instances suggest a big NO. There were instances that confirm poorly worded, unclear or ambiguously presented information of a drug has led to adverse reactions, and critically unfortunate incidents.

To cite a few cases: long ago, a soothing syrup meant for infants had been marketed without prominently labelling 'morphine,' led to numerous untoward incidents; the year 1982 saw another major series of incidents in Chicago due to drug tampering; similarly, in the year 2009, a renowned biopharmaceutical company had to recall a staggering number of its products in the US because it was not adhered to child-resistant packaging that met legal requirements. There have been several product recalls in the recent past due to labelling errors. One recall was initiated by a manufacturer of blood glucose test strips, wherein a labelling error omitted the strips' model number. The omission led to the use of these test strips in the wrong glucose meter which resulted to showcase incorrect results. Another renowned organization voluntarily recalled a mislabeled lot of its injectable anti-seizure medication following confirmed reports of particulate found in a single unit, that could severely harm patients.

Thus, even when the ever-increasing legislative demands for patient information on pharmaceutical labelling often poses a packaging challenge to both manufacturers and brand-owners, patient compliance is increasingly gaining enough importance beyond functional requirements and fulfilling legal obligations. The annual cost to non-adherence in the US healthcare system alone is close to a whopping US$100 billion, and there is an even greater responsibility on manufacturers to ensure that drug usage information is presented to the patient in a manner that is easy to understand and easy to refer to, not just when the drug is first used, but throughout the course of time. Fortunately, manufacturers and brand-owners are becoming increasingly aware of the importance of labelling on

healthcare products referring to the success rate of a drug.

Today, in most cases, the on-pack information seems to have a direct connection with the patient, helping improve user appeal, and most importantly impacting the direct effect on patient outcomes. Considering the enormous cost of developing, testing and launching an innovative drug in the market, using cheap and potentially less effective packaging that not only risks patient safety, but also questions the efficacy of the drug is not the right approach. With more scope for impactful labelling and packaging techniques than ever before, the growing realization is that a given drug is only as efficient as the usage information conveyed to the patient. This has resulted in a massive change in the mindsets of brand-owners and manufacturers who recognize the need for clearly-presented, easy-to-follow labelling and packaging measures that is conducive to positive patient outcomes. Some of them could be:

Types of safety measures for labelling

Even when strict guidelines are in place to ensure that the pharmacist provides the respective patient with accurate strength and quantity of a prescribed drug, under most circumstances it is extremely difficult to be absolutely sure that the patient would adhere to the prescribed course. For this reason alone, it is imperative that the guidelines within the labelling, provide the possible side effects due to incorrect dosage, among several other instructions. Cited below are some of the types of safety labelling measures undertaken by pharmaceutical companies to ensure maximum patient health safety.

- **Boxed Warnings:** A boxed warning consists of a summary of the information that is key for a prescriber to consider, including any restriction on distribution or use. Typically, there is a more detailed discussion of the risk elsewhere in the labelling that must be identified by a cross-reference.
- **Contraindications:** These refer to situations in which the medication should not be used. A drug should be contraindicated in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit. These are not based on theoretical possibilities but on known hazards.
- **Warnings & Precautions:** It is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are serious or are otherwise clinically significant because they have implications for prescribing decisions or for patient management.
- **Adverse Reactions:** This section lists all side effects observed in all studies of the drug and not just the dangerous side effects which are separately listed in 'Warnings' section. Separate lists are required for adverse reactions identified from clinical trials and those identified from spontaneous reports after a drug has been marketed.

Types of Packaging Safety Measures

Effective package management is an increasingly critical capability for pharmaceutical companies. Not only does optimal packaging bring benefits to the patient, but also to nurses, pharmacists, doctors and manufacturers alike. Proper packaging can reinforce brand preference, improve compliance, facilitate consumption, limit dosage errors and help prevent drug counterfeiting. Provided below are measures to ensure maximum patient safety:

Unique Identifier: A 2D data matrix code and human readable information are be placed on medical products that can be scanned at fixed points along the supply chain. It comprises of a product code which allows the identification of at least the name of the medicine, the common name, the pharmaceutical form, the strength, the pack size, and the pack type; a serial number which is a numeric or alphanumeric sequence of a maximum of 20 characters randomly generated; a batch number and an expiry date.

- **Authenticity seals or tamper-evident labels:** Packaging having an indicator or barrier to entry which, if breached or missing, should provide visible or audible evidence to consumers that tampering has occurred. Film wrappers, shrinkable seals and bands, breakable caps, tape seals, blister packs, etc. are few examples of tamper-evident labels.

Product Authentication: Authentication features can be embedded either on the dose or on packaging of the medicines.

These may be overt, covert or forensic features.

Anti-counterfeit Measures: Another global challenge for this sector is the problem of product piracy. The worldwide trade in counterfeit medicines is a multi-million business that causes considerable loss for the pharmaceuticals industry and, more importantly, puts the health of numerous people at risk. The following are few measures undertaken jointly by the packaging and pharmaceuticals industry to prevent the distribution of counterfeit medicines:

- **Holograms:** Many major drug companies use holograms on at least some of their medicines in the form of labels, seals, hot-stamped patches, and blister-foils. The ability of the hologram to provide effective protection lies in the continuous innovation, invention, and evolution in holographic techniques that have succeeded in creating increasingly complex devices that are easily recognised yet difficult to copy accurately.
- **Track & trace system:** Another recent trend is the serialisation of holograms as part of systems that combine authentication with traceability. These systems link on-pack security devices with database management and field-tracking services. Manufacturers can tell where a pharmaceuticals consignment has been, where it is

located, and where it is headed. This is particularly important in identifying the source and provenance of products.

- Synthetic DNA and laser codes or special printing inks invisible to the naked eye. The impact of implementing

safety measures.

The impact of implementing safety measures

Having taken care of all the safety features to be incorporated with the packages and labels, there is going to be a huge impact on the outcomes for pharmaceutical companies. Right from streamlining procedural hiccups to reducing product recalls to saving costs to companies, safety best practices for packaging and labeling are set to be the driving factors for pharma industry.

No scope for product recalls: With the information provided in an accurate manner adhering to HA standards and with products packed with contaminant-free packages, companies can obtain approvals in minimal times making the drugs available in the market in quick TAT.

Ensuring the patient safety standards are met through with resistance towards external influences like moisture, oxygen, biological contamination, adulteration, and mechanical damage, the quality of the pharmaceutical products maintained as is as in production thus striking off any untoward events and product recalls.

Not only the patient safety, but also the brand identity will be safeguarded with advanced pharmaceutical packaging technology like tamper-evident features and integrated capsule sealing technology. There will be no counterfeits and brand value will be conserved.

Referring to the labelling information, organizations must take care of the medicinal information put out through labels. The information provided on labels should not only ensure the safety and efficacy but should also be clear and accurate.

Emphasising the same, health authorities worldwide released many safety measure guidelines for labelling and packaging best practices which the manufacturers could consider for integrated patient safety and for successful compliance. Concisely, here are few noteworthy guidelines:

- Health Canada has released a guidance document for Palin Language Labelling which came in effect from June 13th, 2015, for prescription drugs, and is expected to come in effect from June 13th, 2017, for non-prescription drugs.
- Australian Government Department of Health, the Therapeutic Goods Administration (TGA) followed suit and announced new labelling requirements which went effective from August 31, 2016. With new labelling requirements for Australian Medicines coming after so many years, a four-year transition time has been given to be compliant with the improved standards. That suggests the sponsors will have enough time for transition and from September 1, 2020, their new medicine labels will need to comply with the new improved regulations.
- The highly-debated FDA generic-drug labelling rule, which was due to be passed in mid-2016, has been further delayed and is now expected to be finalised in 2017. If the proposed rule is passed, generic-drug companies across the globe must strengthen their pharmacovigilance operations right from assessing safety signals to ensuring label compliance.
- To better protect children from serious risks, the FDA sought label changes for two types of opioid medications, codeine & tramadol with additional contraindications & warnings.
- The motto behind frequent labelling guidelines is to ensure labels should not only convey accurate drug information to the end user, but should also ensure drug safety by making the information easy to understand by the physician as well as patients.

The Challenges in Implementing Safety Features

The global nature of the pharmaceutical industry, with manufacturing sites and markets all around, results in a constantly evolving Regulatory landscape. New regulations emerging with increased pace call for frequent label and packaging changes. Moreover, entering new markets means accommodating new languages and country-specific rules.

To consistently meet Regulatory compliance standards in terms of both labeling and packaging, an optimally designed labeling solution is the right resort. Pharmaceutical companies also require a solution that is standardised and centralised, to be more operationally efficient and saving on organisational costs, avoiding expensive mistakes, and ensuring that even the most remote facility follows governmental and industry, and health agency regulations, while also meeting overall internal branding standards.

Labeling and artwork pack management is perhaps one of the most challenging functions to be effectively handled, managed and run by most life sciences and Pharma companies. With touch points across most of the major divisions, the function requires implementing a robust Artwork Management System (AMS) that can scale and evolve at the same time to be effective with the growing needs of the pharma companies.

Center of Excellence
Compliance & Validation

GOOD MANUFACTURING PRACTICE (GMP)

THE NEED AND WAYS TO PRACTICE

Between 10/1/2015 and 9/30/2016, the United States Food and Drug Administration (USFDA) through its system has issued almost three thousand nine hundred and five 483s to Biologics (84), Medical Devices (934), Drugs (691), and Food (2196) manufacturers. The number shows that there has been a significant rise in manufacturing violations during health inspections of these manufacturer's facilities by the USFDA. Instances of companies failing to adhere to cGMP (current Good Manufacturing Practice) were observed and eventually they were issued warning letters followed by closure of their facilities, thus causing severe cost burdens to manufacturers.

To give you a handful of examples,

- In a recent incident, a reputed East Asian Pharmaceutical Company was issued a 483 with a warning letter, following which the company was also subjected to keen scrutiny in all future cases even if it clears the inspection with a 'no observation.'
- Another major Indian pharmaceutical firm, because of the 483s it received from the US health authority had to encounter an overnight downfall in the share market. However, after improving their facilities and activities and ensuring their standards were GMP compliant, they regained the reputation soon after and received a 'no observation' from the agency, which boosted their market price overnight

Similar results have been taken into consideration in multiple cases, thus reiterating the importance of adhering to GMP standards and emphasising its benefits for organisations. In this scenario, it is of utmost importance for manufacturers to be aware of how they come off such observations and what's the role of GMP standards in doing so.

Why should you adhere to the GMP standards?

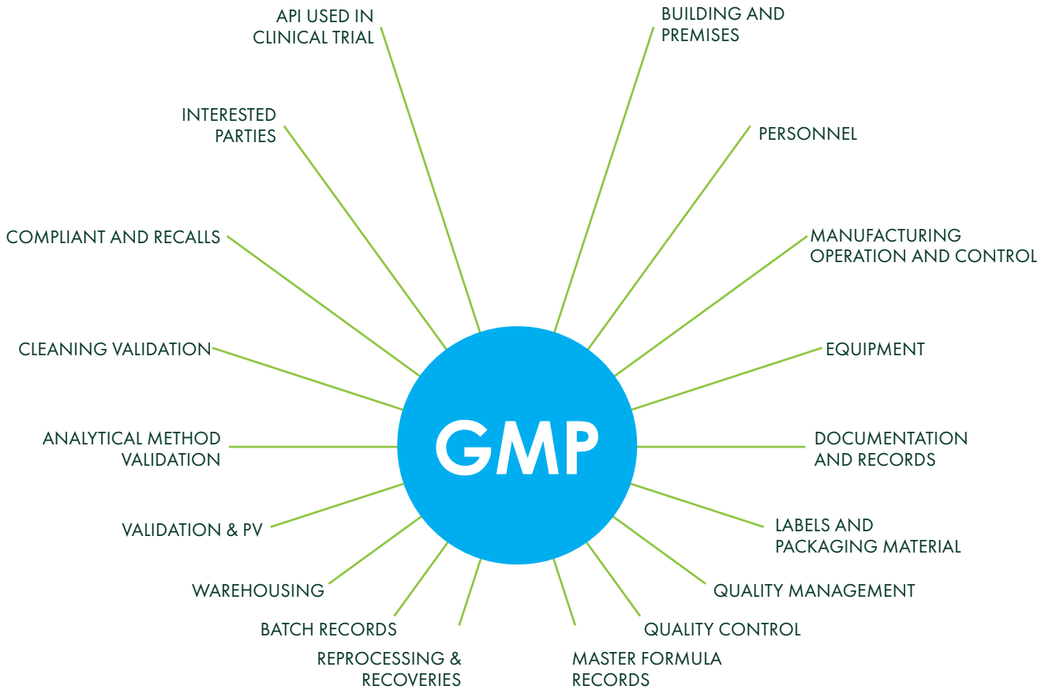
As is widely known, implementing GMP not only serves to safeguard the safety, quality and efficacy of the products being manufactured, but it also serves to secure a company's brand image in the eyes of Regulatory bodies across the world. In addition, it reduces the number

of batch recalls, and keeps the ratio of adverse reactions reported across the globe in control. It should be performed

- to enable consistent market growth through the ease of business transition it offers
- to reduce the organization's operating costs with no need to rework/realign and zero penalties to address
- to help all stakeholders develop a positive perception towards the organization's manufacturing procedures

What needs to be done?

To export manufactured drugs and devices to other regions, it is essential to comply with the regional requirements of the concerned importer. Despite continuous efforts at international harmonization, there may be hidden procedural gaps which demand one's attention. Each functional aspect of the GMP should be decoded in a comprehensive manner. Freyr performs around 700 checks at a preliminary level spread across 18-19 GMP functional areas such as:



In conclusion, to ensure the manufacturing processes are compliant and aligned with global GMP guidelines, manufacturers must practice some of the basic key notes such as:

- Manufacturing facility should be clean and hygienic
- Standard Operating Procedures (SOPs) should be clearly defined and controlled
- Good documentation practices should be followed
- Facilities should be able to prevent cross-contamination
- Qualified and trained staff should be deployed

Reference Link:

This article was published in European Pharmaceutical Review

https://www.freyrsolutions.com/freyr-in-media/european-pharmaceutical-review-publishes-freyrs-standpoint-on-good-manufacturing-practice-in-europe-and-brexit-effect

Center of Excellence
Global Cosmetics
Regulatory Services

GLOBAL COSMETICS REGIME & REGION-SPECIFIC REGULATORY PATHWAYS

Cosmetics have now become daily use products and are expected to reach a CAGR US $428 billion business value by 2022. The last few decades have seen a major rise in the use of cosmetics with due credit to lifestyle changes and increased capabilities for personal care expenditure. Adding to general cosmetics, the industry can be classified into Functional Cosmetics, Grade -I and Grade-II Cosmetics, Controlled cosmetics (CC), Specially controlled cosmetics (SCC) etc.

The industry is widely spread and with so many regulations across the world, often strategizing the market expansion might be challenging for manufacturers. Across the globe, there exist different filing procedures and requirements for Cosmetics compliance and certain markets put forward very specific requirements that constantly evolve. Tracking down each geography's requirements is time-consuming and tedious for companies and failing to do so might, sometimes, deter their business expansion plans. To safeguard a cosmetic product launch or registration across the globe or in specific markets, companies should be well versed with various Regulatory forms, complex registration procedures and filing requirements in respective regions.

Giving you the best of Regulatory information, here we provide comprehensive data required for Cosmetics regulations in selected markets.

Country	Regulatory Authority	Regulatory Status	Submission Format	Delivery mode for Submission
Argentina	National Administration of Medicines, Food and Medical Technology (ANMAT)	Grade I cosmetics: Electronic filing or listing; Grade II cosmetics: Registration	Grade I cosmetics: Applicant needs only to mark the product details on the electronic application. Additional documents need not be attached; Grade II cosmetics: National Format	Grade I cosmetics: Electronic filing system; Grade II cosmetics: Not Found
Australia	Department of Health- National Industrial Chemicals Notification and Assessment Scheme (NICNAS)	Cosmetics in Australia do not need registration or notification before they are marketed; however, 'New Industrial Chemical' should be notified to NICNAS	National Format	By Post or Courier
Brazil	National Health Surveillance Agency (ANVISA)	Grade I Products require Notification; Grade II Products require Registration		Grade I Products: Online through Customer Service System; Grade II Products: Online through Petitioning System
Canada	Health Canada	Notification	National Format	Online
China	China Food and Drug Administration	Registration	National Format	Paper or Online
Egypt	Egyptian Ministry of Health (MOH)	Registration Required		Hard copy
EU and Non-EU	European Union (EU); The Cosmetics Regulation (1223/2009)	Cosmetic Registration	Online Notification Portal CPNP	Online
Hong Kong	Consumers Good Safety Ordinance	Not Required	NA	NA
India	Central Drugs Standard Control Organization (CDSCO)	Registration	National Format	Hard copy
Indonesia	The National Agency of Drug and Food Control (NA-DFC or BPOM)	Notification	National Format	Electronic (notification portal)
Japan	Ministry of Health, Labour and Welfare (MHLW)	Consultation (Cosmetics and quasi drugs have the same process)	National Format	Fax
Jordan	Jordan Food and Drug Administration (JFDA)	Registration Required	NA	NA
Malaysia	National Pharmaceutical Regulatory Agency (NPRA)	Notification	National Format	Quest Online System
Mexico	Department of Health- COFEPRIS (Federal Commission for Protection against Sanitary Risks)	Registration Required	NA	NA

New Zealand	New Zealand Medicines and Medical Devices Safety Authority(Medsafe)	Registration not Required	NA	NA
Philippines	Food and Drug Administration	Cosmetic Registration	Online Format	NA
Saudi Arabia	Saudi Food and Drug Authority (SFDA)	Registration Required	eCOSMA Portal	Online
Singapore	Health Sciences Authority	Notification	National Format	Online Pharmaceutical Regulatory Information System (PRISM)
South Korea	Ministry of Food and Drugs Safety (MFDS)	General Cosmetics: Post- market supervision; Functional Cosmetics: Evaluation on safety and efficacy	National Format	Mail or by hand
Taiwan	Taiwan Food and Drug Administration	General Cosmetics: No notification or registration; Medicated Cosmetics: Registration	General cosmetics: National Format; Medicated cosmetics and colorants: National Format	NA
Thailand	Food and Drug Administration Thailand (Thai FDA)	Specially controlled cosmetics (SCC): Registration; Controlled Cosmetics (CC): Notification; General Cosmetics: Do not require approval	SCC: National Format; CC: National Format	SCC: Electronic; CC: Electronic
UAE	Dubai Municipality (DM) and Emirates Authority for Standardization and Metrology (ESMA)	Registration required	NA	NA
USA	US – Food and Drugs Administration	Cosmetics: Voluntary registration OTC: OTC products are developed with drug monographs. If these drug monographs are used, pre-approval is not needed	VCRP	Online or in-person

To assimilate all the factors and tailor a solution for a cosmetic product requires expertise in all these multifarious details. Not only should you be adept in Formulation Review and Product Classification, Safety and Toxicology, Claims Review, Artwork and Labeling Review, Product Information/ Technical File Compilation, and Go-to-market Services; but also, should possess a deep-rooted understanding of regional Regulatory aspects across the globe.

Freyr offers a comprehensive range of services for global Regulatory compliance requirements for cosmetic and personal care companies to ensure their products meet the latest cosmetic safety regulations. With regional offices in USA, Europe and North America as well as in the Middle East and North Africa (MENA) and Asia Pacific (APAC) nations plus a vast partner network spanning 120+ countries, Freyr is uniquely positioned to support Regulatory requirements for beauty and personal care products and to ensure quality, safety, efficacy and Regulatory compliance globally.

Reference Link:

www.businesswire.com/news/home/20170524005627/en/Global-Cosmetics-Market-Reach-390-Billion-2020

MEDICAL DEVICES NEW REGULATORY REQUIREMENTS IN EUROPE

NEW MDR REGULATIONS

Center of Excellence
Global Medical Device Regulatory Services

The new EU Medical Device Regulations (MDR) published by European Commission on 5th May 2017 revamped major portions of EU Medical Device Directive (MDD) raising compliance bars for the Manufacturers of all the classes of devices, Economic Operators and Notified Bodies. The new regulations show a way forward towards the globalization of the medical device regulations which contribute to a high level of safety protection and facilitates easy trade across the borders by the introduction of Unique Device Identification(UDI), general safety and performance requirements, technical documentation, classification rules, conformity assessment procedures and clinical investigations..

The term 'Medical Devices' encompasses a variety of products ranging from simple thermometers which are consumer healthcare products to today's artificial intelligence software programmes for diagnosing diseases using patient test report data. Development of new products to meet the user needs is progressing unimaginably with the advent of digitization, and rapid evolution in medical science innovation giving constricted goals to the Regulatory bodies. With the advent of cases like PIP breast implants, the prevalence for the need of stringent regulations has become the need of the hour.

The overview

"The current Regulatory approach which includes supervision of notified bodies, conformity assessment procedures, clinical investigations and clinical evaluation, vigilance and market surveillance should be reinforced to strengthen further. Also, more provisions should be introduced to ensure transparency and traceability regarding medical devices, to improve health and safety."

Medical Device Directive	Medical Device Regulations
93/42/EEC (MDD)-43 pages 90/385/EEC (AIMD)-20 pages	Regulation EU 2017/745-177 pages Repealing Council Directives 90/385/EEC and 93/42/EEC (MDD+AIMD)
23 Articles, XVII Annexes	123 Articles, XVII Annexes
Total number of rules for classification: 18	Total number of rules for classification: 22

Chronology of Events: Adoption

26th Sep 2012
- EU Commission has released two draft proposals

5th April 2017
- Approval of the counsil petition and publication in Official Journal of the European Union

5th May 2017
- Publication of the regulations (EU) 2017/745-MDR & 2017/746-IVDR

26th May 2018
- 12 Months after EIF, Co-operation among Competent authorities
- MDR (article 102)

26th Nov 2017
- 6 months after EIF, Requirements on Notified Bodies,designation of Competent Authorities and establishment of the Medical Device Coordination Group (MDCG)
- MDR (articles 35–50, 101 and 103)

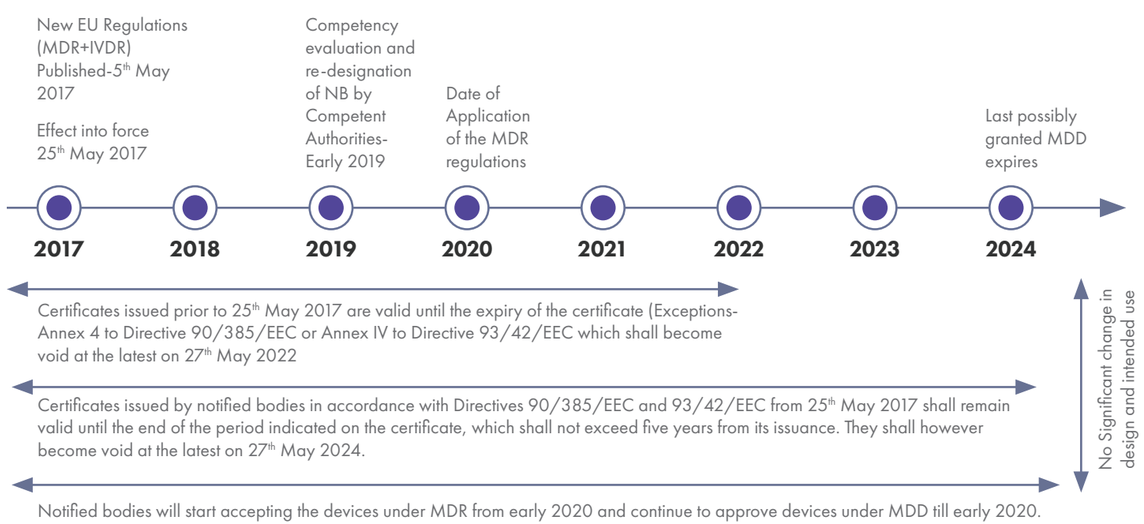
25th May 2017
- The above two regulations Effect in Force (EIF)
- MDR-3 Years Transition Period
- IVDR-5 Years Transition Period

26th May 2020
- Date of Application (DoA) of the regulations

Not before 26th May 2020
- 3 years after EIF and not before 26th May 2020
- 6 months after publication that EUDAMED is fully operational

Not before 26th Nov 2021
- 18 months after publication -EUDAMED is fully functional
- MDR (articles 29(4), 56(5) and 123(3)

Transition Timelines and Validity of Certificates:



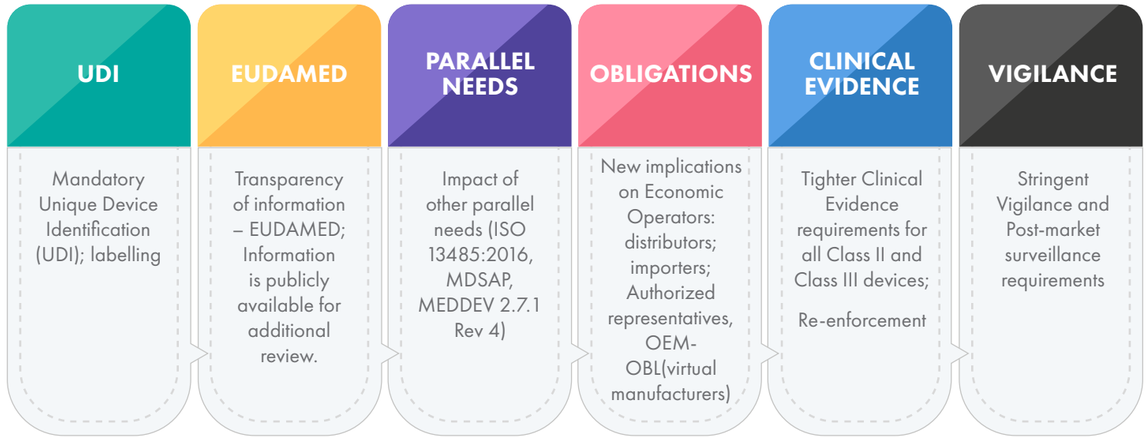
What is in for the Global Manufacturers as per new EU MDR Regulations? Understand the MDR

If your device is currently an accessory to a medical device, products with aesthetic or another non-medical purpose but are like medical devices, borderline products containing medicinal substances, combinational products software products then the new medical device regulations should be evaluated for the classification and up-classification of the device.

The classification and up-classification of the devices has a major impact on the manufacturers, as EU MDR imposes tighter compliance, safety and efficacy requirements. This will have a key role in the finalization of the current and future product portfolio of the manufacturers because of significant cost of compliance. These levels of changes should start from management level making key decisions in management review meetings, deciding the product portfolio for Europe market, assess the impact of the global product approvals and market access based on CE certifications.

Non-compliance to the new requirements with in the stipulated timelines lead to loss of license to operate for your products in Europe.

Identification of the major compliance requirements



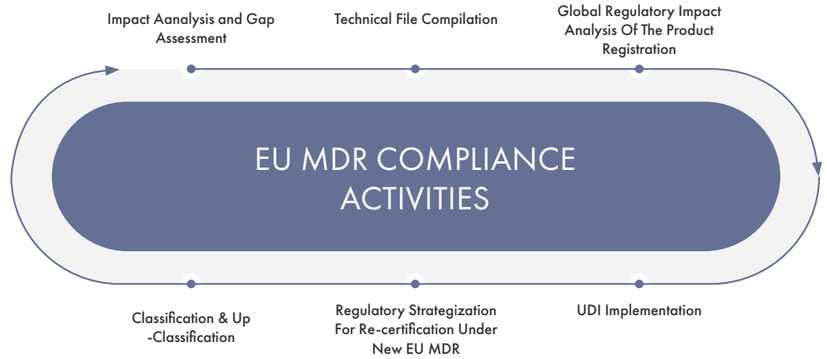
Familiarization of New MDR Terminology:

Medical device co-ordination group (MDCG), General Safety and Performance Requirements, Common Specifications, Unique Device Identification, Virtual Manufacturer.

For products which are newly classified as medical devices as per the new rules, review of the notified bodies will be heightened. New documentation should be made ready for CE certification as per the new regulations for both reclassified and existing products. Some of the key technical documents that should be in place include:

- Risk analysis documents
- Clinical data availability analysis and plan
- General safety and performance requirements
- Common specifications derivation
- All relevant QA SOP's updating
- Performance evaluation tests of the device as per the claims
- Labeling updates
- Alignment to the ISO 13485 requirements for the manufacturing of the product and certification
- PMCF plans

Gap analysis and Strategy finalization for compliance



CLASSIFICATION AND UPCLASSIFICATION

- Classification and Up-Classification of the devices as per new EU MDR classification rules
- Classification of non-medical devices/accessories as per new EU MDR classification rules

IMPACT ANALYSIS AND GAP ASSESSMENT

- Overall Impact assessment of the new regulations on the product (Quality/ Clinical/QMS)
- Transition plan for recertification of devices as per New EU MDR (Including re-classified devices)
- Identification of additional requirements for re-certification as per New EU MDR
- Assessment of OEM/OBL requirements of Technical file (OEM: Own equipment manufacturer; OBL: Own Brand Labeler)

TECHNICAL FILE COMPILATION

- Compilation of technical file as per new EU MDR regulations (Including for the accessories/non-medical/ software devices/high risk)
- Amendment of technical files for software in accordance with requirements for higher risk class
- Gap analysis of consequences of changed Essential requirements and Compilation of safety and efficacy summary

REGULATORY SUPPORT FOR RE-CERTIFICATION UNDER NEW EU MDR

- Identification of Notified Body for certification under New EU MDR
- Certification of new devices under New EU MDR
- Re-certification of existing devices and re-classified devices under New EU MDR
- Regulatory strategy for handling of queries from Notified bodies.

UDI IMPLEMENTATION

- Required for the product right from the submission of application for CE certificate
- Identify the UDI agency for the manufacturer
- Compilation of the UDI requirements for application
- Regulatory strategy on the change of UDI for modifications of the product to manufacturer.

GLOBAL REGULATORY IMPACT ANALYSIS OF THE PRODUCT REGISTRATION

- Regulatory Intelligence on the impact of the re-certification on Global markets where the product is registered based on European Certification
- Regulatory strategy and approach to continue the registration status of the product's active global markets

Despite evolving guidelines and interpretations in the new medical device regulations in UDI, EUDAMED, Medical device co-ordination group (MDCG), General Safety and Performance Requirements, Common Specifications, the new EU MDR imposes adherence to tighter safety and efficacy requirements raising bars for Regulatory evaluation and certification on par with the unimaginable progression of the medical science innovation. Manufacturers should assess the impact of these changes early for R&D, design development and design scale up, manufacturing and commercialization of the products to comply with EU regulations and to continue marketing them in EU.

Reference Link:

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Center of Excellence
Regulatory Labeling

REGIONAL LABELING: THE FORMATS AND REQUIREMENTS IN USA AND EUROPE

Labeling is well-regulated in pharma and life sciences markets across the globe to avoid any deception. This is done with the aim of providing accurate safety information to the patient(s)/end user(s). Keeping in view the serious side effects that some drugs are prone to, their labeling must undergo a thorough scrutiny prior to submitting them to local Regulatory bodies/health authorities (HA) for successful market-entry. The labeling should also be aligned to local HA's framed guidelines to avoid recalls or other lawsuit liabilities.

In addition to various aspects of clinical/regional/global labeling for multiple product categories such as Pharma, Medical Devices, Cosmetics. Nutraceuticals, etc., organizations must also keep track of the labelling systems of various countries/regions for successful compliance. For example, while a lot of countries and regions offer a two-tiered labeling system with patient and consumer information as well as Health Professional (HP) labeling, Canada offers a three-tiered system with detailed scientific information beyond what is included in the "regular" HP labeling.

Below is the detailed information about labeling formats and requirements in major markets like the US and Europe.

US Region Labeling Formats:

- **Physician Labeling Rule (PLR):** The United States Food and Drug Administration's (USFDA's) guidelines for prescribing information is commonly referred to as 'Physician Labeling Rule' (PLR) which applies to human drug and biological products. Its goal is to guide users with the right language about drug usage, other effects and to make it easier overall to access and use such drugs. All NDAs, BLAs, and efficacy supplements submitted after June 30th, 2006 are mandated to conform to this rule. In addition, all NDAs, BLAs, and Efficacy Supplements approved after June 30th, 2001 must be converted to the SPL-PLR (Structured Product Labeling – Physician Labeling Rule) format during a 7-year implementation period.
- **Pregnancy & Lactation Labeling Rule (PLLR):** Recent changes to the USFDA's drug labeling for pregnant and lactating women make prescribing more complex than it used to be, but the information is now far more complete and much more current. The new PLLR has been designed to help prescribers assess the benefits and risks of medication for pregnant and lactating women. In contrast to the old system, the prescribers have used letter categories — A, B, C, D, and X — to evaluate safety precautions.
- **Structured Product Labeling (SPL):** The FDA mandates the filing of product labeling information in the SPL format. Many pharmaceutical developers, therefore, have determined the need for a reliable service provider that will enable their companies to meet Regulatory compliance guidelines without straining their current business practices.
- Depending on the context, Freyr recreates or efficiently utilizes your current labeling content and transforms this readily available content into the required SPL R4 or Physician's Labeling Rule Compliant format..

Europe Region:

For medicines, EMEA and various other national medicine evaluation agencies require certain documents, including the Summary of Product Characteristics (SmPC) and the Patient Information Leaflet (PIL). The packaging and labeling texts should be presented in the official language or languages of the Member States or markets in which the medicinal product is set to be placed. When more than one language is employed, there should be a text available in each individual language, and their contents should all be identical. A manufacturer cannot apply for a drug registration without submitting these relevant documents, and all documents should also be aptly translated and localized for the European or national Regulatory authorities.

Summary of Product Characteristics (SmPC):

The SmPC is a legal document approved as part of the marketing authorisation of each medicine. The SmPC is the basis of information for healthcare professional on how to use the medicine. Its information is updated throughout the life-cycle of the product as new data emerge. The information that can be found in the SmPC includes:

- Essential information for the use of a medicine
- Qualitative and quantitative information on the benefits and the risks
- Information for individualised care
  - Paediatric and elderly population
  - Organ impairment, concomitant disease
  - Interaction with other medicines
  - Genomic factors
  - Pregnancy, lactation and fertility
  - Composition of the medicine: prevention of hypersensitivity and excipients with known effects
  - Information on specific situations
- Pharmaceutical information

Patient Information Leaflet (PIL):

PIL is the European version of the package insert. PILs contain specific information about medical conditions, doses, side effects to give the user information about the product.

- What is the product and what it is used for
- How to use the product
- Possible side effects that may occur
- How to store product
- Further information

To prepare the aforementioned documents for Europe, manufacturers are often challenged with:

- **Culture specific translations and localisation** problems are persistent throughout the region. Guidelines for PIL, differences in PIL usability regulations, differences in expressions, symbols and pictograms established by Member States) must also be considered while translating documents.
- **Multilingual PIL legibility testing:** Each language package leaflet must be written in a clear, comprehensive and legible manner. The patient should be able to understand what is written on it
- **Product Updates:** Legislation changes can be dynamic and not only do they make staying updated with them difficult , but they also complicate matters for manufacturers, who have to go through multiple processes, some times as elaborate as when applying for initial drug approval, requiring detailed translation of all existing documentation.
- **EMEA sets a strict time frame of 20 days** for the submission of the translated versions of all documents. Initial translations must be provided within 5 days after the marketing authorisation is given by the CPMP, the EMEA committee responsible for assessing marketing authorisations. By the 20th day, the final revised versions of the translations must also be provided to the EMEA in their final publishing format.
- **Mistranslations and consequences:** Mistranslations have dire consequences leading to product recall on large scale and product liability lawsuits, both of which result in huge losses to the sponsors / manufacturers while setting back all the progress up until the moment.

In conclusion, no matter which market the manufacturer plans to enter, the labeling document prepared should be able to keep the users / patients informed about the drug usage and ensure their safety, while successfully diagnosing the illness. This makes it essential to not to bypass the rules by any means and mandates strict adherence. In such a scenario to eliminate risk factors, RA experts need to collaboratively work with professional regional Regulatory labeling experts, preferably on a long-term basis. To assist organizations and helping clientele sail through regional markets, Freyr offers specialized labeling services across the globe, availing of a robust affiliate network of 120+ countries.

Center of Excellence
Global Food Supplements Regulatory Services

NIE FEATURES FREYR'S ARUNDHATI KASBEKAR'S THOUGHT LEADERSHIP ON THE NATURAL PRODUCTS INDUSTRY

Transparency in the natural products industry is becoming much more than a business ethic—especially in light of a rise in cases of intentional adulteration of supplements—what some might call a moral imperative. With the natural industry faced with dramatic price spikes from some foreign suppliers, natural companies may well wonder what the future holds regarding internet commerce versus brick-and-mortar (can anyone say Amazon and Whole Foods?). Uncertainty also exists among regulatory prognosticators as to whether the anti-over-regulatory winds in Washington will blow elsewhere, especially in states such as New York and California, which have what many might call a hyper-regulatory, or nanny-state, posture in regards to dietary supplements. Concerns about this, however, are tempered by a general upswing in consumer interest in supplementation along with a growing industry focus on science and innovation. Innovation guru, John Costa, recently wrote that it's possible that innovation is less the elemental magic of creativity and more a function of timing and stimuli carefully injected into a linear process. He said that we shouldn't wait for those eureka moments but, instead, move the process along with well-placed nudges. Here's to more nudges and more science in 2018.

NIE: What do you feel were the biggest industry issues of 2017, and why?

LeDoux: There were several major issues involving the industry in 2017. The FDA (U.S. Food and Drug Administration) appeared to take a more aggressive role along with the Federal Trade Commission (FTC) in dealing with products they deemed to be adulterated or misbranded. Seizures and fines were levied against several companies and individuals evidencing a renewed interest in achieving compliance with federal laws.

There has also been a proliferation of all things CBD (cannabidiol) but my prediction is that the federal government in actions soon to be forthcoming from the Department of Justice, will begin to reign in what many perceive as some rogue-state activities. Clearly there is room for federal oversight and regulation here, given the obvious concerns over interstate commerce, banking regulations, and other statutes on the books already.

The election of a new president in late 2016 and the resultant executive orders issued requesting reductions in regulations has been significant in our space as well. The delay in implementation of what many perceive as unnecessary changes to label presentations of nutritional facts in foods and supplements is also demonstrative of this bias.

Foreign suppliers raised prices of raw materials, in some cases by over 100 percent. Presumably this was caused by concerns over environmental pollution needing to be controlled in foreign markets such as China, but this was also caused by problems in other production facilities in Germany which suffered from facility interruptions. These price increases are now negatively impacting many suppliers and retailers who have endured price increases without the capacity to pass these along to their customers.

The internet commerce of dietary supplements and natural products is now becoming a game-changer when evaluating business models involving heavy capital expenditures and lease costs for brick and mortar businesses versus virtual companies with reduced distribution costs such as Amazon. The fact that Whole Foods Markets was acquired by Amazon also demonstrates the blurring of commercial lines of contact points with the retail customer.

Mister: Well, I may be a little biased, but I think the launch of the Supplement OWL, the new dietary supplement registry, was one of the most significant events for the industry. It has been well-received in the first few months by product marketers and retailers alike. The Supplement OWL has the potential to be a game-changer by showing our regulators and retailers a new level of transparency about our products and their supply chains.

Beyond the Supplement OWL, the Amarin complaint before the U.S. International Trade Commission (ITC) was a disturbing development this year. Its effort to gain a monopoly on esterified EPA fish oil by declaring it to be a drug was a broadside

attack on accessibility of omega-3 products for consumers. As the year closed, the ITC rejected the complaint but an appeal is in the works. CRN will continue to fight to keep these products widely available as dietary supplements.

And lastly, the direction of the new Trump Administration has recognized that burdensome regulation doesn't enhance public health, but just creates unnecessary costs for compliance. The delay in the label change regulation, the willingness of FDA to engage with industry on new dietary ingredient (NDI) master files, and the realignment of expertise within the agency all illustrate a new—and welcome—approach by FDA.

Emord: A gift to Monsanto, congressional passage of legislation to pre-empt state GMO (genetically modified organism) labeling laws was a great disservice to American consumers and the First Amendment. The Amazon/Whole Foods union invites a potential for a vast expansion in the market reach of select industry products.

Zapp: An ingredient supplier has an interesting perspective when it comes to studying the changes within the industry. In 2017 we found a lot of companies coming to AFS with their challenges in achieving a clean label. While we all know that clean label generally refers to more natural and recognizable ingredients rather than chemical sounding, synthetic, ingredients.

What most people don't realize is that using natural ingredients can be very difficult to formulate with and are not so simple to substitute in current formulations. Therefore, to obtain the same flavors and functionalities as synthetic ingredients, manufacturers need to find the right ingredient options for their products. The biggest hurdle is in solubility and flavor. But with the right extracts, this can be achieved. It is really making clean label products particle.

Another industry issue we are seeing emerge and become more important to manufacturers is sustainability. It is difficult to ignore the planet. Consumers are becoming more aware that, in many cases, where raw materials are sourced, global living conditions are poor and the earth is easily taken advantage of.

For companies like AFS, we recognize this problem and have taken serious steps by creating our own responsible sourcing initiative that includes: sustainable growing, socially responsible sourcing and full traceability. Consumers feel it is their right to know where and how their ingredients are sourced.

McGuffin: There continues to be growing interest by larger companies to expand into the natural health product markets by purchasing brands that have built a reputation for quality and ethical business practices. This is in line with the broader trend of natural health products being adopted by mainstream America.

Some examples of this in 2017 include the purchase of AHPA members Tazo and Pukka Herbs by Unilever and Nestle's purchase of Atrium which owned several brands, including Garden of Life and Pure Encapsulations.

The Trump Administration has provided an opportunity for the industry to request changes to regulations that impact them to reduce burdens on industry while continuing to maintain protection for consumers.

Kreienbrink: The biggest issues in 2017 will remain as challenges for the coming year. These include transparency, quality, and the existence of meaningful, factual scientific efficacy studies

NIE: Companies are drilling down into better processing, better bioavailability, better delivery, essentially better mousetraps. Is this good, and if so, why? Are there no new mousetraps any more?

Lifton: While, on the one hand, everything in nature, or naturals, already exists in some basic form, it is also true that, A, we only have identified a small percentage of what exists and is potentially active, and B, we only understand a small fraction of what we have found actually does, and C, we are finding better and better ways to improve on what we are able to both harvest from nature and harness using science.

And so, as for better mousetraps, a vast majority of the most exciting things in natural products research and development today are happening with proprietary branded ingredients, natural ingredients extracted, processed, mixed, composed or delivered in special, more effective ways.

LeDoux: This is a very interesting development, but points out the value of transparency in sourcing, supply chain processing and finished product development and production. Companies that are willing to invest on the front end of the supply chain and further invest in the science of substantiating the finished product in populations of intended use are assuming leadership roles in the industry. No longer do celebrity endorsements carry the day with the marketing messaging. The FTC has also weighed in here on multiple occasions, and in various selling channels such as multi-level marketing with the erection of some additional commercial guard rails.

The real issue here is that just claiming a better mousetrap is not going to get a "hall-pass" from the regulators or the attorneys general any more. Proof of concept and evidence of benefit conducted in a vigorous scientific method protocol are essential for having a shot at commercial success.

Emord: Contrary to media perception of the dietary supplement industry, it has always been a dynamic, ever-improving industry, providing overall better quality and service year after year. That is due to competition far more than to FDA prior restraints; the latter create anti-competitive barriers to entry and often punish those innocent of causing any actual harm to consumers, those whose only offense is a technical violation of regulation.

Zapp: When it comes to working with botanical ingredients, improvements are necessary to meet the demand for the natural and organic market. One great example is in answering the questions, how do we improve absorption both in finished products and in the body? This process starts by improved research and understanding of how specific compounds within botanical ingredients impact the human body. This leads to improving extraction methods to isolate targeted active compounds, this leads to the need for improved identity testing and verification processes to ensure those actives are really present in the finished product. Trying to improve in all of these areas ultimately leads to new discovery of botanical ingredients that can do more.

Kasbekar: Most of global surveys provide compelling evidence that better mouse traps providing advertisement claims with qualifying language and differentiating levels of scientific evidence can help consumers understand the strength of scientific evidence behind those claims. Moreover, when a visual aid is included, consumers perceive the scientific levels more clearly and have greater confidence in their meanings. Although these surveys suggest that consumers react differently to different advertisement claim levels, it is not yet clear whether consumers understand the variations in the degree of scientific support.

Understanding consumer responses to advertisement and "mouse trap claims" is critical when designing regulations. [The] government's goal is to permit the use of a larger number of, better, easily understood, and up-to-date scientific information on advertising messages to communicate how food choice can affect the health of consumers. Policymakers should therefore try to enact regulations that will ensure that the exact meanings of claims are presented to consumers. Qualitative studies such as focus group interviews may be helpful in identifying more specific disclaimers and effective ways of delivering health messages for food or food components.

NIE: While USDA (U.S. Department of Agriculture) Organic and GMO (genetically modified organism)-free have arguably become much more pervasive and a bit more cost-effective in foods and supplements, there has been a big (perhaps) bigger push for local, especially in the produce aisle. True? If so, is this good or bad? Is local the new organic?

McGuffin: AHPA has observed a growing trend of consumers willing to pay a premium for products made from U.S. domestic and locally produced ingredients. AHPA supports organizations helping farms meet this growing demand and featured two of these groups at the AHPA Botanical Congress. The recent efforts of the Appalachian Beginning Forest Farmer Coalition (ABFFC) and Vermont Herb Growers Cooperative (VHGC) is a testament to the growing demand for locally produced medicinal herbs.

Zapp: Consumer's drive to shop "local" hits on two core values: trust and responsibility. To help align with these values, local really translates to a desire for products to be more accessible, transparent and trustworthy. But this idea of "shopping local" is really misleading as a majority of consumer packaged goods contain ingredients that are sourced from all over the world. Therefore, the real challenge is to bring the values behind "shopping local" to the consumer no matter where the ingredients are sourced for the products they purchase.

Manufacturers should ask themselves, what would it take for our supply chain to be so transparent that consumers can feel that same trust and idea of responsibility no matter where their ingredients come from? Sure, any respectable supplier should have a FSVP (food safety verification program) in place, which will provide some of that ground work.

However, consumers are really saying, "Show me, don't tell me!" Show me who is growing these ingredients as if they were my local farmer. Show me how both the environment and the local people are being cared for so that future generations can benefit from the same ingredients I am benefiting from today. That is true transparency. That is the true value of "local."

Lifton: Organic and natural have become very big and very important for the industry and for consumers.

Local, as in locally sourced ingredients and produce, has become a buzzword, that is true. And when "local" means supporting farmers, growers and communities, as in sustainable, then I think there is real muscle behind the mantra.

That's one of the reasons we've become involved in the Organic & Natural Health Association, because we're committed to the real power and promise of naturals, not just the words. LeDoux: With the Millennial market calling for non-GMO and organic products, it is clear that the demand exists for these products. The challenge is in achieving and maintaining certification of these claims. Consequently, there is now an undeniable trend for local source production of foods, and this speaks to the tribalization of our culture which has been a mega-trend in consumer behavior for the last 10 years.

Kreienbrink: This is true. Local is certainly a positive but can be very confusing to the consumer. What is local? If you live in Chicago and you're eating fresh vegetables from California in the middle of January, is this considered local? Marketers are stretching the limits and meaning of the term "local."

Kasbekar: Is local the new trend like new organic? Yes, it is, but let's bear in mind that this is not totally new. During the pre-globalization era, our way of living was primarily local produce and local consumption. With globalization and efficient supply-chain infrastructure, we now have access to a variety of global products in a competitive market with better prices. While it is certainly a great advantage, we also have to face challenges such as longer shelf life requirements, unwanted preservatives and ingredients that need to be regulated and monitored closely to avoid health risks and frauds.

I believe in increasing awareness of organic operations that demonstrate protecting natural resources, conserving biodiversity and using only approved substances.

At the end of the day, the responsibility lies

with consumers to make the right choices based on scientific evidence, their personal beliefs [about] ecological issues, price points, food and health needs."

NIE: While calcium may be an old standby, magnesium has been attracting a great deal of interest over the last several years, but is the industry doing a great job in making a case to consumers as to why we need to supplement with this heart-healthy mineral? If this is a problem, what would the lesson be?

LeDoux: Amazingly, the consumer knowledge of the role of magnesium is limited, even though the established and ample body of science concerning bone mineralization shows convincing evidence that calcium is best metabolized in the presence of magnesium, vitamin D and other micro-minerals such as boron. The economic question here is how does a company achieve a satisfactory return on investment of marketing messaging for what essentially is a commodity business?

Lifton: There's a lot we can do to overcome the commoditization of magnesium and its bad rep. Magnesium is just one of many examples where both absorption and tolerability can be a challenge, too. Sucrosomial Magnesium, which we offer, is a highly bioavailable complex of magnesium hydroxide providing elemental magnesium derived from the crystal-clear waters of the North Sea and which is encased in a liposomal-like structure, helping consumers to avoid the diarrhea and nausea that are sometimes experienced with conventional magnesium ingredients.

Emord: The greatest impediment to dissemination of truthful information concerning the health benefits of magnesium (as well as all other vitamins and minerals) remains the FDA. The FDA's evidence based system of review for health claims manipulatively truncates the universe of reviewable scientific evidence to such an extent that credible, science-backed claims continue to be suppressed long after the U.S. Court of Appeals in Pearson v. Shalala ordered otherwise. Rather than favor disclosure over suppression, FDA continues to favor suppression over disclosure.

NIE: Industry organizations have endorsed GMPs (good manufacturing practices) for botanicals, which is good, but this year has also been a banner year for kratom sales and adulteration with undeclared drug ingredients, such as sildenafil. What are we doing right? What do we need to do better?

Mister: Companies across the industry are embracing what some have said for years: you can't "test" quality into a product at the end; quality is the result of attention paid throughout the supply chain. The adoption of good agricultural practices and cultivation practices, and the increased focus on identity and purity throughout processing and manufacturing are evidence of that recognition. Quality issues that used to result from inadvertent errors or carelessness should be greatly reduced with this new paradigm. However, kratom, adulteration with sildenafil, and the introduction of selective androgenic receptor modulators (SARMs) all illustrate another reality: that some companies will intentionally ignore the law and put their consumers at risk.

As 2018 rises, all responsible companies should recommit to drive these outliers from the industry by refusing to deal with companies who market these products. ABC's new program urging firms to destroy illegal ingredients when they receive them is one good way to start.

LeDoux: The recent proclamation from the FDA commissioner on this matter involving kratom is welcome. The presence of adulterants or APIs (active pharmaceutical ingredients), which are undisclosed in botanical blends is essentially criminal behavior and needs to be prosecuted to the fullest extent of the law. This means the FDA and ICE/Homeland Security need to tighten the border entry points, increase random raw material testing, seize offending products and fine exporters and importers once evidence of criminal intent to create adulterated products has been established. This is a case begging for more enforcement versus more regulation.

Kasbekar: While there have been a number of FDA-enforcement actions in 2017 leading to recalls, the number of hospitalizations due to food-based illness has not reduced. The records indicate that every year, 130,000 people in the U.S. are hospitalized with a foodborne illness, and out of them, 3,000 people die. A new report from the Department of Health and Human Services' Office of the Inspector General raises some red flags about the FDA inspections program. Overall, the report concludes that the FDA "consistently failed to conduct timely follow-up inspections to ensure that facilities corrected significant inspection violations." And in 17 percent of the cases, the FDA did not conduct a follow-up inspection at all. Also, in some instances where inspectors found significant violations, the FDA took no enforcement action.

The creation of [an] oversight group within the FDA called SCORE, which stands for strategic coordinated oversight of recall execution, has played a critical role in thousands of product recalls that FDA oversees each year.

FDA should continue to adopt creative ways of expanding public notification of recalls that may affect the most vulnerable consumers, including the very young and elderly.

NIE: Hemp madness is alive and well, in this case CBD oil. The FDA does not seem to be a fan of CBD as an ingredient in supplements, salves, balms and other non-medical delivery forms, correct? With a murky landscape of IND filings and some companies throwing in the towel, others are digging in their heels. Where do you think we will, or should, net out on CBD?

LeDoux: My opinion is that CBD oils have remarkable benefits, but they need to be

produced under strict GMP guidelines and federal oversight of the FDA. This "wild-west," state's rights approach is leading to a myriad of problems which can significantly and negatively affect users given the real potential of variability in finished products in terms of purity and potencies. There are multiple reasons that the federal government needs to oversee this in terms of production, licensure, distribution and regulation and that is what I believe is going to happen in the not too distant future.

Emord: As with all ingestible products, the standard needs to be the Paracelsian Principle of Harm. If CBD at the dose recommended produces adverse physiological effects, it is properly forbidden by the FDCA (Federal Food, Drug and Cosmetic Act) but only at that dose level and above.

NIE: Way back when, mom and pop retailers were very worried about Whole Foods and Wild Oats stores opening up near them, but in many cases, net, general interest in natural went up and mom and pop sales stayed steady or even grew as a result. Now Whole Foods is again on the radar, in this case with Amazon. Now Kroger's sales are surging—is this a halo effect again or something else? What does the whole Amazon/Whole Foods thing mean for the industry short term and long term?

Kasbekar: Amazon's acquisition of Whole Foods is not merely an expansion into the grocery business. I believe it is going to fundamentally change the way consumers buy and receive food. Amazon is following a market opportunity for [a] value vacancy that can be exploited through a digitally enabled business model.

While groceries are not new to Amazon, this acquisition is the company's first significant investment in the industry. Despite Amazon Fresh, the grocery sector is one of the last large retail sectors where Amazon does not have a significant share. At the same time, the food-delivery market represents a significant revenue opportunity.

Amazon has made its fortune by selling products at prices most competitors can't match while driving revenue through membership programs and other services.

In the short term, Amazon doesn't have to operate at a profit as other grocery retailers do. In the long term, if Amazon operates the fresh groceries business at a very low margin, while driving profitability through its Prime membership and cash from other areas, many grocery chains won't be able to compete.

LeDoux: A rising tide lifts all boats. The challenges here are remaining relevant to your consumer base. If you are running a small store or small chain, what makes you locally essential for your community? Is it education? Is it carrying locally produced products? Is it providing a value proposition that is larger than just having fair pricing? Amazon's purchase of Whole Foods is really an endorsement of brick and mortar for local communities in terms of a centralized shopping experience. At the end of the day, the consumer wants to buy their natural products where they buy their canned goods, paper goods and household cleaners, because it is all about convenience. There is a reason that Walmart is the largest grocer in America today.

McGuffin: It is likely too soon to assess the full impact of this acquisition, but it is part of an increasing trend of large companies buying ethically focused brands that have built a reputation of providing high quality products that promote consumer health and wellbeing. These acquisitions also provide an opportunity to enhance both brands by combining their strengths. It can be a tenuous balance, but other companies have walked this line successfully in the past.

NIE: Where did we as an industry wind up with the whole ODI (old dietary ingredients) list process?

Mister: I think it's too soon to assess how FDA's efforts to create an ODI list will net out. If the FDA process only gives "safe harbor" to those ingredients already widely recognized as "old," will it be worth the trouble? What we are seeing is a new openness at the agency to try and resolve the outstanding issues around NDI (new dietary ingredient) notifications. The industry needs to reach resolution on these issues because achieving a predictable and certain process for bringing new ingredients to market is desperately needed. The climate of uncertainty around NDIs will stymy innovations. Hopefully 2018 will provide strong progress in this regard.

LeDoux: I think the ODI list process was part theater and partly an exercise in regulatory discretion. The likelihood of a list being adopted by the FDA of pre-1994 DSHEA (Dietary Supplement Health and Education Act of 1994) usage for dietary ingredients is remote at best, but the NPA just published for purchase a fairly seminal and exhaustive compilation that should withstand regulatory scrutiny should a dietary ingredient found there be challenged for suitability by regulators.

Kasbekar: We at Freyr, as a regulatory consulting company, have begun [advising] our customers about creating a risk-based analysis that entails compiling a list of every dietary ingredient in their products and then evaluating these ingredients. A detailed assessment based on the following questions is presented to the client for this purpose:

- Does this ingredient meet the definition of dietary ingredient?
- Is there adequate documentation for this ingredient's ODI status?
- Has the product undergone a manufacturing change?
- Does some food supply exemption apply, and if so, has the ingredient been chemically altered?
- Has my supplier submitted an NDI notification or is there a GRAS (generally recognized as safe) affirmation?

No matter which way the list is analyzed, the objective is to have a picture of the company's current exposure and an understanding of steps to take to minimize potential risks. This will help locate ingredients that may require an NDI notification so that a company can

be fully prepared to submit a notification if it is determined to be ultimately necessary for regulatory compliance.

While the past year has not provided greater insight into the long-term effects of the 2016 NDI Draft Guidance, it has been helpful to have the time to digest the revisions and strategize future compliance.

While there is no sign as to when the FDA will finalize the NDI Draft Guidance, the industry [...] has started to determine how it will comply when the decision rolls out. It is expected that there will not be any major changes in the final guidance, so the best step is to begin planning now to minimize potential pitfalls.

NIE: What are your big predictions for 2018, in terms of category growth, specific supplements and ingredients, challenges and opportunities at wholesale and retail?

Mister: 2018 promises increased growth and acceptance of dietary supplements for promoting better health. The industry will make a strong case for allowing recipients of SNAP (Supplemental Nutrition Assistance Program) benefits to purchase a multivitamin with those benefits. This platform will allow us to raise awareness of the realities of nutrient insufficiencies, particularly among low income Americans, and the role supplements can play in alleviating them.

Developing research on nutrigenomics and individualized medicine will help us better understand unique nutrient requirements and lead us toward more individualized supplement regimens. Probiotics will continue their growth, along with overlooked nutrients like choline, iodine and magnesium. And lastly, even as the scrutiny from states attorneys general may be waning, private class action litigation directed at the industry will continue. Fortunately, several influential courts have signaled that they will require evidence of real harm to allow these cases to move forward.

Zapp: Complex flavors [are] on the rise—in foods and beverages, we have had noticed a number of manufacturers requesting more complex flavors, like turmeric. Generally, the ayurvedic tastes of India tend to be on everyone's radar and ingredients like ginger and turmeric are heavily sought after right now in new product development and R&D.

As food changes and adopts more of a clean-label footprint, the landscape of supplements is slowly evolving to follow suit. Many large sports nutrition and supplement companies are now requesting organic ingredients to "green-up" their labels. Especially in sports nutrition, labels used to be dominated by hard to pronounce branded ingredients: "the more the better." Today, we are seeing products being developed in this space with fewer, but more specific ingredients. Organic tends to be a big emphasis and we can expect that to continue in 2018.

Kasbekar: The industry is constantly trying to introduce a variety of products catering to different customer segments. For example, there is an increasing demand for the vegan variants of nutraceuticals targeting the global vegetarian population. Omega-3s, traditionally extracted from fish, have been developed with vegan variants obtained from algae and flaxseed oil. There are also surveys that emphasize the increasing demand for vegan-based protein supplements.

I believe some of the niche segments such as anti-aging, energy boosting, skin care, digestive care may continue to grow in 2018. There are predictions for high growth in categories such as fortified water, fortified noodles, sports and energy drinks, etc.

LeDoux: I think 2018 will see the advent of CBD regulations at a federal level. I think that Congress will be more receptive to the role of supplements in disease prevention or management, and the value of having supplements and healthy foods as a component of the WIC (Women, Infants and Children) and SNAP programs for people in need. Furthermore, I think more and more large companies of all sorts will be making investments in this space and increasing consolidation because the consumer demand is real and growing.

Challenges that remain will be spotty enforcement of economically adulterated goods, or "supplements" with undisclosed APIs that are illegal per se, and the industry needs to hold the regulatory agencies accountable for enforcement.

I also think there will be some changes involving anti-doping of athletes, enhancement of concussion prevention protocols in contact sports such as football, and more work done on providing supplements to the fastest growing segment of the population, namely the aging Baby Boomers, who remain influential and affluent as they head for their sunset years.

Lifton: In terms of challenges, intentional adulteration of dietary supplement formulas and ingredient mixes has become a big problem where we need much more enforcement in 2018, not more regulation.

Plus we need a better argument to counter the anti-supplement narrative than "Drugs are much more dangerous than supplements."

As we double-down on self-regulatory initiatives and support agency efforts to make the marketplace completely inhospitable, and even hostile, to the bad actors operating on the periphery of the industry, we must do a better job—and here's the opportunity—of spreading new, science-backed messaging to get the word out on the ability of dietary supplements and functional products to improve health and make life better for so many people.

Reference Link:

This article was published in Nutrition Industry Executive
https://www.freyrsolutions.com/freyr-in-media/nie-features-freyrs-arundhati-kasbekars-thought-leadership-on-the-natural-products-industry

Center of Excellence
Publishing & Submissions

HEALTH CANADA'S REVISED VALIDATION RULES FOR REGULATORY TRANSACTIONS IN THE eCTD FORMAT

Stakeholders seeking information about Health Canada's revised validation rules regarding eCTD (Electronic Common Technical Document) Regulatory transactions, would be pleased with this bit of information, intended to assist them in the preparation of Regulatory transactions in the eCTD format. These revised rules also carry forward the good work done by previous guidance documents and add to the information provided in the Guidance Document: Preparation of Drug Regulatory Activities in Electronic Common Technical Document (eCTD) Format as well as specifications for the regional administrative module (Module1) of the eCTD standard defined in Guidance for Industry: Creation of the Canadian Module 1 Backbone (eCTD) and the International Conference on Harmonization (ICH) Electronic Common Technical Document Specification (Version 3.2.2).

Health Canada has been providing validation reports only for Regulatory transactions that failed previous validations and this has been happening since June 2016. Prior to sending their eCTD Regulatory transactions to Health Canada, participants are now expected to validate such transactions and correct any failings, warnings and errors. As of February 1st, 2018, Health Canada will be validating Regulatory transactions in eCTD format using the Canada eCTD - Profile 4.3. Profiles can be updated by the Regulatory authority without further notice.

To know more, reach us at sales@freyrsolutions.com

eCTD PILOT FOR CLINICAL TRIAL REGULATORY ACTIVITIES - EXTENSION

DECEMBER 19TH, 2017 | OUR FILE NUMBER: 17-114361-659

Health Canada is announcing an extension to the eCTD pilot for clinical trial Regulatory activities in electronic common technical document (eCTD) format. The objective of this extension is to provide further opportunity for sponsors to participate in the pilot project, thus enabling more comprehensive experience using eCTD format for clinical trial regulatory activities, for both Health Canada as well as external stakeholders.

Since June 1st, 2016, Health Canada has stopped accepting paper copies of clinical trial Regulatory activities and their related transactions. The accepted format for these transactions is "non-eCTD electronic-only"; the Guidance Document, Preparation of Drug Regulatory Activities in "Non-eCTD Electronic-Only" Format contains detailed information on filing Regulatory activities or transactions in this format.

With the exception of Regulatory activities filed as part of this pilot project, Health Canada currently does not accept clinical trial Regulatory activities in eCTD format. This pilot will assist Health Canada and sponsors to further assess the feasibility of accepting clinical trial Regulatory activities in eCTD format without jeopardizing performance standards. Lessons learned and experiences gained will be used to determine broader acceptance of clinical trial Regulatory activities and transactions in eCTD format.

Sponsors are encouraged to participate in this pilot project. All requests to participate in the pilot will be assessed and participants will be selected based on the requirements below. Further instructions on how to submit clinical trial Regulatory activities in eCTD format will be provided to the participants at a future date.

Who can apply for participation in the eCTD Pilot for Clinical Trials Regulatory activities?

a. Prior to expressing an interest to participate in this phase of the pilot, sponsors must ensure they have one or more Clinical Trial Applications (CTAs) or eligible Clinical Trial Application - Amendments (CTA-As) with either a 7 day administrative or a 30 day default performance standard, to be submitted during the period of September 1st, 2017 to March 31st, 2018.

b. Sponsors must commit to the following requirements, if selected to participate in the pilot project:

   - All transactions provided during the pilot must be sent via the Common Electronic Submissions Gateway (CESG); no other form of transmission will be accepted.
   - The first transaction in eCTD format can be:
     - A CTA, with a 7 day administrative or a 30 day default performance standard; or
     - A CTA-A, with a 7 day administrative or a 30 day default performance standard, in eCTD format where the initial CTA or CTA-A has been filed after June 30th, 2016.
   - Once a participant has filed a Regulatory activity in eCTD format, all additional information and subsequent Regulatory activities/transactions [CTA-A, CTA-Notification (CTA-N), Pre-CTA Consultation meeting (Pre-CTA) and Clinical Trial Site Information (CTSI) Forms] must also be filed in eCTD format. Participants must not convert back to "non-eCTD electronic-only" format.
   - Participants must provide responses to clarification requests in eCTD format as per the Regulatory timelines.

How to apply for participation in the Clinical Trials eCTD Pilot

a. Sponsors interested in participating must express their interest by providing:

   - A written request to participate in this phase of the pilot, via email to eReview@hc-sc.gc.ca, with the subject heading "Clinical Trial eCTD Pilot".
   - A plan listing the CTAs intended to be filed in eCTD format during the period September 1st, 2017 to March 31st, 2018, including the following information:
     - Brand Name, Medicinal Ingredient and/or the Drug Code Name
     - Intended Indication
     - Month of intended filing
     - Protocol Number (if known)
     - Lead Directorate/Bureaux (if joint review)

b. Sponsors currently participating in the pilot can update their existing list of planned CTAs and CTA-As at any time.

To know more, reach us at sales@freyrsolutions.com

Center of Excellence
Regulatory Affairs

THE REAUTHORIZATION OF GDUFA AND ITS EFFECT ON DRUG REVIEW PROCESS

The United States Food and Drug Administration's (FDA's) generic drug program is short of resources. As the generic drug applications and the foreign facilities developing those drugs have grown in number, the staff have been unable to take measures to keep pace with that growth.

Following negotiations between the FDA and generic drug industry, the Generic drug user fee program (GDUFA 1) was developed and submitted to Congress for approval, which enacted it as part of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA).

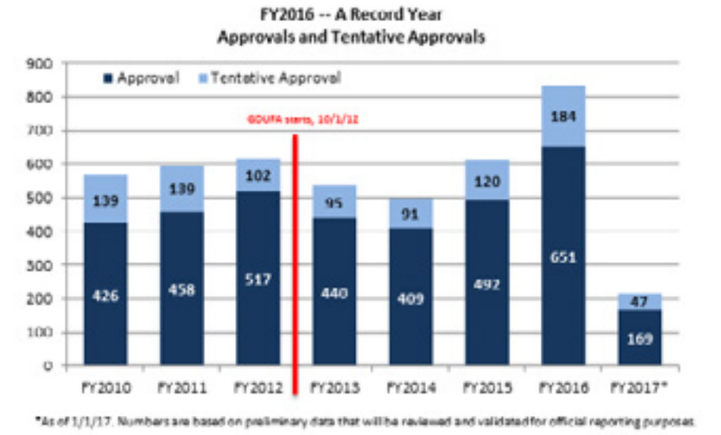
The industry has agreed upon funding a portion of FDA's drug review activities of the Generic Drug User Fee Amendments (GDUFA) program from 2012 to 2107. During this period the FDA, has in turn, agreed to improve the performance goals, like timebound review of applications (a certain % of them). FDA has also significantly cut down the review time for new products, without giving up on its standards of safety, efficacy, and quality of new drug products prior to their approval.

The GDUFA program's success shows the collective efforts put forth by the FDA, the industry and other stakeholders who worked for the best results. This has led to expanded access to affordable generic medicines. Among all the generic drugs approved so far by the FDA, approximately 25% were approved only in the last four years with the efforts of the GDUFA, which also does not compromise on the quality of those drugs.

After a modest beginning, the generic drug industry has grown to be a large force in healthcare. Till date, FDA has met / exceeded all GDUFA review goals including goals set for original Abbreviated New Drug Applications (ANDAs), ANDA amendments, Prior Approval Supplements (PAS), and controlled correspondence. In FY 2016, FDA has approved 835 ANDAs. These were the maximum FDA approvals ever in one year. FDA's previous high was 619 in the FY 2012.

The review of "first generic" ANDAs was formerly delayed, since lawfully they could not be filed until after four or five years after the innovator drug was approved. But the potential of generic drug competition in the market has led to increased pace of process, and beginning October 2014, these ANDAs received goal dates in accordance with GDUFA I. The agency's efforts for expedited review has resulted in increased revenue from sales of these products.

Before the GDUFA enacted, barely 1 % of ANDAs cleared the first review cycle compared to the current 9% which was a result of the modern drug program. Increased number of applications led to increased official status and to cope with additional incoming demand, the business process was reengineered by hiring and training over 1000 employees on an integrated informatics platform.



FDA is currently facing the following challenges for approval of ANDAs:

- Number of review cycles
- Volume of applications – Contrary to FDA's assumption of 750 ANDA submissions per year, it received in the range of 1000 to 1500 ANDA submissions per year.
- Several factors can delay timely consumer access to less expensive generic medicines. These factors include:
  - inappropriate use of statutory requirements regarding single-shared system Risk Evaluation and Mitigation Strategies (REMS) to delay generics entry to the market
  - delaying or denying generic companies' access to reference listed drug products, thereby preventing organizations from conducting studies required for approval
  - misuse of FDA's citizen petition process to block generic approvals

As the GDUFA must be reauthorized every five years, on August 18th, 2017, the President signed the bill reauthorizing GDUFA through September 30th, 2022. To meet the GDUFA-II goals, FDA implemented the following changes:

To further hasten the approval process for priority submissions, Priority review would be available for submissions that the FDA considers to be public health priorities pursuant to CDER's Manual of Policies and Procedures (MAPP) 5240.3 Rev.4, Prioritization of the Review of Original ANDAs, Amendments and Supplements, as revised (the CDER Prioritization MAPP) in the GDUFA II program.

In the final year of GDUFA I, all ANDAs receive a review goal of 10 months. In GDUFA II, standard ANDAs would continue to be reviewed within 10 months of submission. But priority ANDAs would be reviewed within eight months of the submissions. To help ensure that the more aggressive eight-month timeline could be met for each priority review, the applicant would have to submit a pre-submission facility correspondence (PFC) listing all the facilities, which will require the FDA inspection at least two months prior to the date of ANDA submission.

GDUFA II – Faster Review of Priority ANDAs

- GDUFA I: All ANDAs must be reviewed within 10 months
- GDUFA II Proposal: Priority ANDAs must be reviewed within 8 months
- Front end: FDA identifies and communicates deficiencies in "real time"
- Back end: Applicants can correct deficiencies
- Increase odds of approval in current review cycle
- The number of cycles to approval to be reduced
- Increase overall rate of approval
- Concept drawn from PDUFA

The eight-month priority review goal, which is the shortest time possible, was agreed upon by both the FDA and the generic drug industry. The FDA needs to inspect one or more manufacturing facilities before approving the ANDA applications. Since not all facilities are located within the US, the overseas facility reviews take more time given the travel-specific reasons. The process can be expedited by providing all required data of the facility in advance of the inspection to plan the inspection process accordingly.

Pre-ANDA Program Enhancements:

A pre-ANDA meeting program has been setup to clarify the Regulatory expectations for prospective applicants, to reduce the review cycles, especially for complex products. This helps the applicants develop more definitive submission and increases the efficiency and effectiveness of the review process.

For complex products, it is expected that the GDUFA II pre-ANDA program would establish three types of meetings such as:

- Product development meetings, wherein FDA would provide targeted advice concerning an ongoing ANDA development program. These are Pre-submission meetings, which would give applicants an opportunity to discuss and explain the content and format of an ANDA before it is submitted.
- Mid-review-cycle meetings, which would occur post-submission. After the last key review discipline has provided deficiencies, it would help the applicants to discuss existing concerns and further actions.
- FDA issued a guidance concerning the pre-ANDA program, setting forth meeting policies and procedures. In addition, the Agency intends to establish metric goals for product

development and pre-submission meetings.

GDUFA II would direct the Agency to establish metric goals for FDA to issue product-specific guidance for non-complex products. They intend to identify the methodology for developing generic drugs and generating evidence needed to support generic approval. They help companies develop ANDAs that will meet FDA's Regulatory expectations. In addition, the pre-ANDA program is expected to enhance controlled correspondence, Regulatory Science, the Inactive Ingredient Database, and Safety Determination Letters.

ANDA Review Program Enhancements:

- Expand frequency and scope of communications
- Collaboration with applicants in "real-time"
- More opportunities to correct deficiencies in current review cycle
- Reduce number of cycles for approvals
- Increase overall rate of approvals

After submission of ANDA under GDUFA II,

- Initially, FDA determines whether an ANDA is sufficiently complete to permit a substantive review. If it finds sufficiency, then FDA "receives" it within the meaning of the statute.
- FDA would aspire to make these receipt determinations within consistent deadlines.
- Roughly around the mid-point of the review, the FDA provides the deficiencies, which will keep going on a rolling basis.
- Unlike GDUFA I where many deficiencies were communicated at the very end of the review, in a Complete Response Letter, which was too late for the applicant to fix them, GDUFA II does "real time" communications to give applicants more opportunities to correct deficiencies in the current review cycle and avoid repeated cycles.
- To support product launches and business planning that could improve access to generics, Regulatory Project Managers (RPMs) would provide review status updates and certain other types of notifications.
- The Agency would also establish new technical procedures to facilitate approval of tentatively approved ANDAs at the earliest lawful approval date
- The FDA issues a Complete Response Letter if it finds deficiencies in an AMDA preventing the approval, and GDUFA would also provide teleconferences after receiving CRLs to clarify about the deficiencies identified

Simplifying and streamlining the operation, GDUFA II aligns all ANDAs and their amendments in a single line, consolidating review goal scheme.

Drug Master File (DMF) Review Program Enhancements: DMFs consist confidential information about facilities, processes, or articles used to manufacture, process, package, or store drugs. They support approval of ANDAs and are often submitted by API manufacturers that sell to ANDA sponsors. The commitment letter that accompanies GDUFA II contains five significant DMF review program enhancements.

Enhanced infrastructure and analytics enacted by GDUFA II, would increase transparency and accountability. They would, further strengthen program management and resource use. FDA would develop internal capacity to enable improved productivity and performance through regular assessment and progress towards GDUFA II goals and transparent, efficient administration, allocation and reporting of user fee resources. Additionally ,an independent third party would evaluate the program, to assure quality.

To enhance performance, monthly, quarterly and annual reporting of GDUFA program would be introduced which would enable Congress, industry and other stakeholders to compare and evaluate the overall performance of the program.

Modification of User Fee Structure:

The number of applications can vary each year and for stability of program, user fee must be predictable as the number of generic drug facilities and ANDA sponsors is limited. To have a stability between both, annual program fees structure is proposed by FDA and the industry, wherein firms that sponsor approved ANDAs would pay annually.

On a whole, the newly proposed GDUFA II agreement has major reforms that will resolve foreboding challenges, especially the likes of multiple review cycles which make both applicants' and FDA's work inefficient to review through the ANDAs repeatedly. The proposed changes increase the chances pf approval in the first cycle, making the process more efficient, saving time and also thus reducing costs to the generic medicine consumers.

Assessing User Fees Under the Generic Drug User Fee Amendments of 2017

(GDUFA-II)

GDUFA II has been implemented from October 2017, and accordingly, changes were made to the structure of the GDUFA user fee program soon after:

GDUFA-II authorizes the collection of following types of fees:

1. ANDA filing fees
2. Drug master file (DMF) fees
3. Facility fees
4. The GDUFA program fee will be allocated among three tiers of application holders:
   - Small (companies with 5 or fewer approved ANDAs)
   - Medium (companies with between 6 and 19 approved ANDAs)
   - Large (companies with 20 or more approved ANDAs)

FY2018 User fee rates

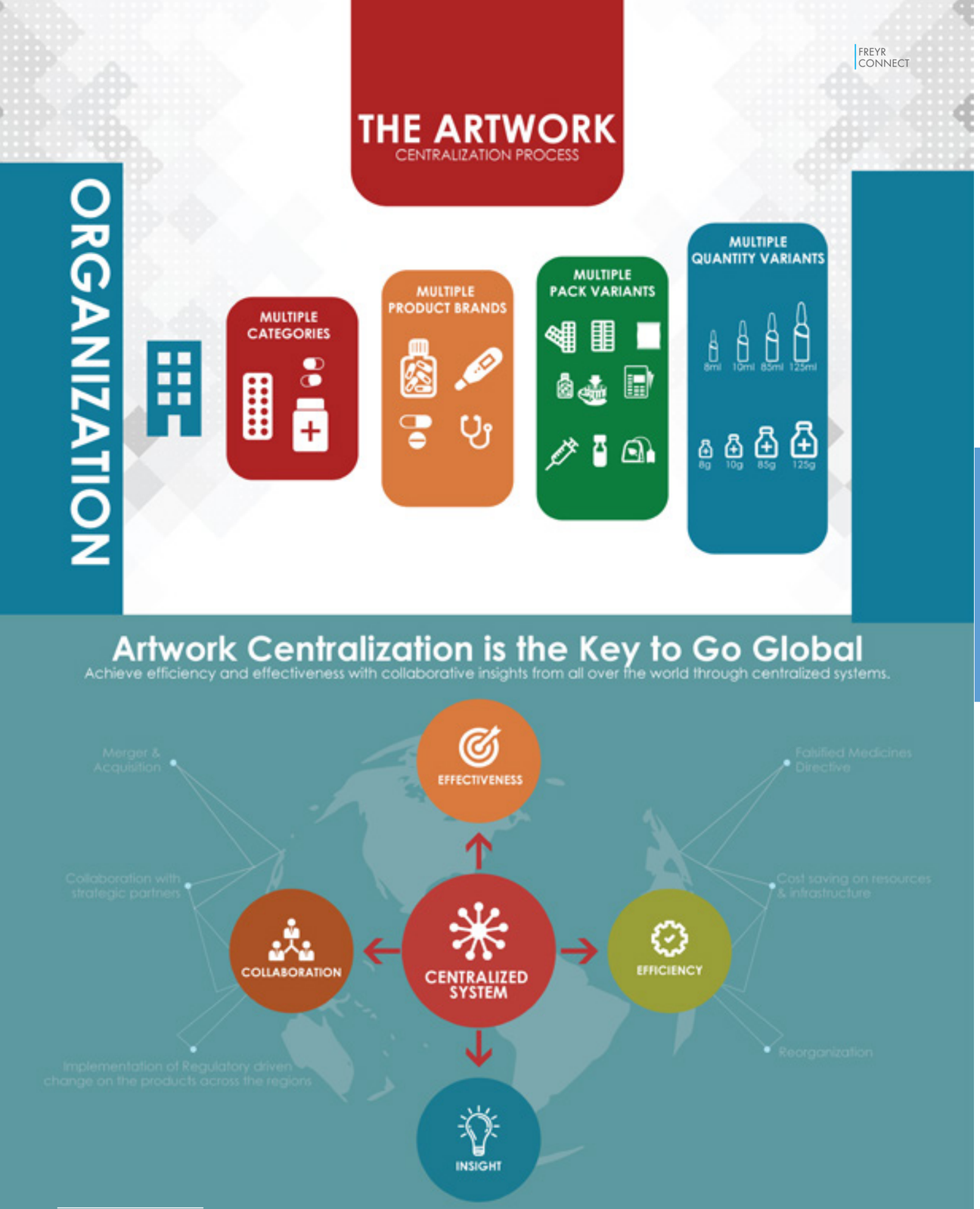
Fee Category	Fee for FY 2018
Applications	
Abbreviated New Drug Application (ANDA)	$171,823
Drug Master File (DMF)	$47,829
Facilities	
Active Pharmaceutical Ingredient (API)-- Domestic	$45,367
API—Foreign	$60,367
Finished Dosage Form (FDF)-- Domestic	$211,087
FDF—Foreign	$226,087
Contract Manufacturing Organization (CMO)-- Domestic	$70,362
CMO—Foreign	$85,362
GDUFA Program	
Large size operation generic drug applicant	$1,590,792
Medium size operation generic drug applicant	$636,317
Small business operation generic drug applicant	$159,079

Some important aspects in which GDUFA-II differs from GDUFA-I are summarized below;

- Applications submitted by State and/or Federal government entities for non-commercial drugs do not incur fees under GDUFA II.
- In GDUFA II, the Prior Approval Supplement (PAS) fee is eliminated which will have a significant impact on any generics manufacturer considering major post-approval changes to their drug products or related manufacturing processes.
- Facilities manufacturing both API and Finished Dosage Form (FDF) will pay only the FDF fee according to GDUFA II.
- Annual facility fee is incurred for a pending or approved ANDA, where even if the submission is pending approval the sponsor may have in GDUFA I, which has been altered in GDUFA II to incur a fee only after the ANDA is approved.
- Within the FDF facility category under GDUFA II, The CMOs (Contract Manufacturing Organizations), which are independent facilities contracted by ANDA sponsors will pay only one-third of the annual fee paid by firms that manufacture generic products at facilities which they themselves or their affiliates own.
- GDUFA II, allows to withdraw the ANDA before it is received for filing by the Office of Generic Drugs – and entails a 75% refund, both of which are not availed in GDUFA I.

Conclusion

The concept of a human drug user fee has revolutionized the drug review process in the United States since it was adopted 20 years ago for prescription drug products, allowing the FDA to speed-up the application review process without compromising the Agency's high standards. User fees offer a strong example of what can be achieved when FDA, industry and other stakeholders work together on the same goal. User fees provide a critical way for leveraging appropriated dollars, ensuring that FDA has the resources needed to conduct reviews in a timely fashion. The reauthorization of GDUFA will allow FDA to build upon the demonstrated success of these programs.



INDUSTRY EVENTS

Upcoming Event

With an aim to radically redefine the Regulatory solutions and services landscape, Freyr strives to decode various industry perspectives from different geographies. The only way we get to do this is by meeting industry professionals and thought leaders across the world at renowned events.

Freyr is one of the sponsors for:

GCC Pharma Regulatory Summit 2018

14th-15th March 2018

Dubai, UAE

Past Events

Freyr is glad to be a part of renowned industry events. We are delighted to come across many industry leaders and their thought leadership on various industry best practices related to Medical Devices in MENA, Artwork Packaging etc. region and across global markets.

The Arab Health Exhibition and Congress

Jan 29th to Feb 1st, 2018

Dubai International Convention and Exhibition Centre.

MEDLAB Congress 2018

Feb 5th to Feb 8th, 2018

Dubai, UAE

Annual Pharmaceutical Packaging and Labeling Forum

Dec 4th to Dec 6th, 2017

Hilton Philadelphia City Avenue, Philadelphia

LEADERSHIP STORY

THE BUSIEST & THE BUZZIEST

RAGAVENDRAN BABU

Sr. Manager - Publishing Services

Are leaders made or born? Probably the oldest of debates has a conclusion here. From leading a team to a position of managing a Center of Excellence (Publishing and Submission) and making it one of the busiest and the liveliest in the entire organization, not only showcases his dedication to the responsibilities he has been assigned, but depicts his innate capabilities at being one of the most cheerful, exhilarated and go-getting managers of his times at Freyr. Ladies and Gentlemen, let us bring you the ever-busy and most importantly an ardent fan of Thalaiva, Mr. Raghavendran Babu, Sr. Manager, Publishing services. As we get in conversation with him for this Leadership CONNECT, we discovered some interesting things, which all Freyrians should also know. Here are some excerpts...

The Global platform is shifting towards electronic and online submissions. Do the merits outweigh the demerits?

Yes, definitely. Because most of the countries are shifting from older formats like NeeS and Paper to Regulatory submissions in eCTD format. Emerging markets like Australia, Thailand, South Africa and GCC Region are moving fast towards eCTD. Even the lesser known markets are adapting to this trend. This is because of the merits of the eCTD format.

Paper format has a lot of challenges - storing data; sending hardcopy to authorities; maintaining documents as per Regulatory standards etc. It is difficult to retrieve information in such cases.

On the other hand, electronic submissions greatly outweigh as per these challenges and adds significant value when it comes to maintaining life cycle in electronic version. It enables easy retrieval and review of information. It offers safety and integrity due to its validation alerts. The entire history of changes is available for communication with authorities. Review comments and questions can be added and answered in one location. Modules in electronic versions avail reusability of existing data, globally, for submitting the same data to authorities irrespective of region with necessary changes. The electronic submission simply reduces the fatigue of submission and makes it easier than ever.

Do you think that Publishing and Submissions as a service, is saturated, given the long history of its existence in the market? Yes/No – How can you say so?

No. The Publishing and Submissions service is not saturated. Rather, in fact, it has a great scope to grow than it is today, offering more opportunity and space for the industry to thrive.

There are new products with multiple categories entering the market. They require proper validation to enter various time zones and regions. This calls for new health authority requirements from the agencies. The current guidelines and procedures are dynamically altered to make the products, transparent, safe and efficient by the day. Constant updates and new versions require sponsors to stay compliant with these changes. This keeps the hunt for new information on. Add to this, new countries are also adapting creating more and more opportunity. So, I would strongly say, Submissions as a service is not saturated and in contrary moving ahead as an evolving and growing market.

The dynamic nature of your work requires you to remain on your toes all the time. Sudden requests, time-critical deliverables, and being meticulous always. How do you keep up with that pace?

(With a grin...) Actually, I perform better under pressure. It is one of those things that keeps me going.

"When you clear the airs of difficulty, there is an opportunity lying around."

Planning the work, time and work-load management, and regular meet up with project members, helps me handle the work seamlessly.

What approach do you employ among your team to achieve harmony at work?

Notice the little things and appreciate. Socialize regularly, which happens pretty well at Freyr. I practice an open-door policy and have remained open to suggestions from team mates irrespective of their positions. I have always given my team additional roles and responsibilities and have noticed that it helps them learn and be prepared for unforeseen occasions. It helps them to be trained to handle the difficulties of issues which were not projected as part of mitigation handling.

Work and life, where does one end and where does the other begin? How do you find that amicable balance?

Being a service provider, we are expected to remain alert and available always. But then again, when we have offs and holidays, I see to it that I make the most out of it. Thus, we can say, work-life balance has not at all been easy.

At work, I often use the experience of previous cases to make similar situations easy to tread. But then again, there is always something different and difficult coming up. So, I keep up an attitude of taking them as opportunities which keeps the work amicable. On time deliveries can be tough (says thinking of some of his upcoming deliverables) but managing data at the last moment and all is something that keeps the interest in this work alive. So, no qualms about it.

How is your journey at Freyr? From the days of leading a team to managing a CoE?

Lots of learning experience. Everyday new things and lot of challenges. My communication skills have improved by leaps and bounds. I have learnt situation-handling, people management, customer management and a lot more. It also keeps the journey interesting.

If you were to quote someone on leadership/anything, who would it be and what would be the quote? Why?

"A pessimist sees difficulty in every opportunity; an optimist finds an opportunity in every difficulty." – Winston Churchill

This quote remains very close to my heart and has always influenced my work.

And also, Thalaiva Rajinikanth! Why not? I grew up watching his movies and am his fan to this day. He has, in a subtle way, moulded me. No quotes in particular though.

You are passionate about

Travelling, visiting various places, experiencing diverse cultures, and learning new languages. Especially the Western Ghats region. Trekking in those hilly areas is one of my favourite activities for travelling.

Interesting things you do apart from work

Sports and games, especially Chess. I played chess at district level. Carroms too, won a cup at Freyr! At times, badminton. You can say, I am pretty much an indoor person when it comes to sports and games.

Raghav as a family man: Serious/ jovial

I have to confess, I act a bit serious with my wife. But the rest of them find me jovial. (adding a smirk)

What would you do, if you had absolutely none for company. No TV, devices, and family?

Reach out to friends. Catching up with them is one activity I find warm and cosy apart from daily skirmishes of life.

FREYR CONNECT

CLIENT VISITS

It was a great honor to welcome a multi-million pharmaceutical company at Freyr to oversee the ongoing projects for Labeling and discuss the future perspectives for Medical Writing services.

Client delegation met Freyr's core group to discuss business aspects aligning with ANDA dossier preparation & publishing. The client also explored other capabilities on Artwork and Labeling during the visit.

SEIZE THE MOMENTS

The age-old adage that "a happy workforce is a productive one" is a business philosophy that rings true even today. To cultivate a sense of camaraderie and team spirit among our employees, Freyr Clubs – a group of fun enthusiasts - organized varied fun-filled activities throughout the last quarter. Here are a few glimpses of the fun-packed events for you to relive the moments again.

ENJOY THE SNAPSHOTS.

FREYR
CONNECT

Book Club

Ethnic Day

Fitness Challenge

I4Farmers Airtel Marathon

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TURKISH DELIGHT: THROUGH THE LEGACY OF ISTANBUL

> **IF YOU REJECT THE FOOD, IGNORE THE CUSTOMS, FEAR THE RELIGION AND AVOID THE PEOPLE, YOU MIGHT BETTER STAY AT HOME.**
>
> *– JAMES MICHENER*

But we have not. As a family, we are avid travellers who believe that there is no greater teacher and no greater learning than travelling. We love travelling by road and have journeyed to most parts of India by road. This time, though, due to time constraints (just 4 days in hand for travel), we decided upon Turkey. The final choice was between Marrakesh and Istanbul and the latter finally won due to logistics.

Let me admit, I had heard a lot about Istanbul before, but nothing prepared me for the fabulous country that I was going to experience. Istanbul really has something to offer for every traveller, of every age. Here's a quick run-through of our itinerary and the wonderful places we visited during our four-day stay.

We certainly saw Istanbul with our eyes wide open; there were too many sights to see and we wanted to savour everything! The delicious food, the delightful customs, fascinating amalgam of religions; and the supremely warm and gracious people. Istanbul is sheer MAGIC!!!

A land of adventure, romance and history. Where two continents meet. Where the warmth of the East seamlessly merges with the ethos of the West. Where I want to go back soon to explore the unexplored.

DAY 1

Sultan Ahmet– On our first day, we drove right into the heart and soul of Istanbul. A busy hub buzzing with activity. The Sultan Ahmed Mosque, simply called 'Sultan Ahmet' is a historic mosque and a popular tourist site which continues to function as a mosque even today. In and around the Sultan Ahmet, there are more conversation spots, eateries and must-see tourist attractions.

The Blue Mosque, as it is popularly known, was constructed in the early 17th century and contains Ahmed's tomb, a madrassah and a hospice. It's a spectacular sight! Hand-painted blue tiles adorn the mosque's interior walls, and at night the mosque is bathed in blue as lights frame the mosque's five main domes, six minarets and eight secondary domes.

It is believed, that the Blue Mosque is a symbol of religious tolerance and secularism. It represents peace and hope.

We also visited the lovely Hagia Sophia another popular tourist site in Istanbul, which is located adjacent to the Blue mosque. One of the world's great buildings, the cathedral of Hagia Sophia, A UNESCO World heritage site, is an architectural marvel dating back to the Byzantine Empire. It was once a Christian church, when Istanbul was Constantinople. That was around the 6th century AD. Over time, it was made into a mosque and is now a museum.

DAY 2

The Topkapı Palace, the largest and the oldest palace in the world to survive to modern times. It was our first visiting spot on the second day. The palace is located directly behind the Hagia Sophia, and was built on the same spot where the acropolis of the ancient Greek city of Byzantium once stood. This palace was said to be the heart, brain and nerve centre of the Ottoman Empire. Topkapı Palace is also a part the Historic Areas of Istanbul, and is a UNESCO World Heritage Site.

Straight from the historic to the largest and oldest canopied markets in the world. We moved to the Grand Bazaar, a meandering maze of 61 covered streets, filled with approx. 4000 shops and number of peddlers along with a charming array of goods. The grand bazar in Istanbul reminded us of the Indian bazars. Walking through the market, taking in the fragrances of food, spices and perfumes is a heady experience. It signalled for a cup of the famous Turkish coffee and Turkish snacks at one of the many quaint roadside cafés.

The hamam. Visiting Istanbul cannot be complete without visiting the authentic, historic hamam; a public bathhouse. We visited the Cemberlitas Hamam, which is said to have offered one of the most quintessential bathing experiences in the late 1600. It was designed and built by a renowned Ottoman architect. As one of the oldest Turkish hamams in Istanbul, Cemberitas is revered and therefore a popular haunt for relaxing, steaming, and bathing. It is exemplified by its tranquillity, practicality, and simple elegance throughout its design. Cemberlitas features a massive central dome, which is especially beautiful when the sun is shining and then the interior lights up magnificently and heats up the gobektasi, a huge, hot stone slab on which visitors can lie down and soak in the warmth.

DAY 3

The Basilica Cistern, which we visited on Day 3 was an absolute delight. It is the largest of several hundred ancient cisterns that lie beneath the ancient city of Istanbul.

Built in the sixth century by the Byzantine emperor Justinian as a place to store fresh water for his palace and nearby buildings, the reservoir was rediscovered a thousand years later when a scholar named Petrus Gyllius visited what was then Constantinople. In 1545, he found the secret: a gigantic subterranean cistern, beautifully carved and replete with carved Medusas, the Basilica and several other similar cisterns which actually took care of all the all water needs of Constantinople. They're marvellously engineered and beautifully carved. The cistern is also known for its filmy venture in the 1963 James Bond film 'From Russia with Love'.

Taksim Square- Fanning out from Taksim Square with its Republic Monument, Taksim is a busy nightlife, shopping and dining district. Vintage trams trundle along Istiklal Caddesi, the city's main pedestrian boulevard, which is lined up with 19th century buildings housing international shopping chains, movie theatres and cafes. A dense web of side streets contains bars, antiques shops, and rooftop eateries with Bosphorus views. We walked around, shopped, ate and enjoyed the impromptu shows of musicians and magicians.

DAY 4

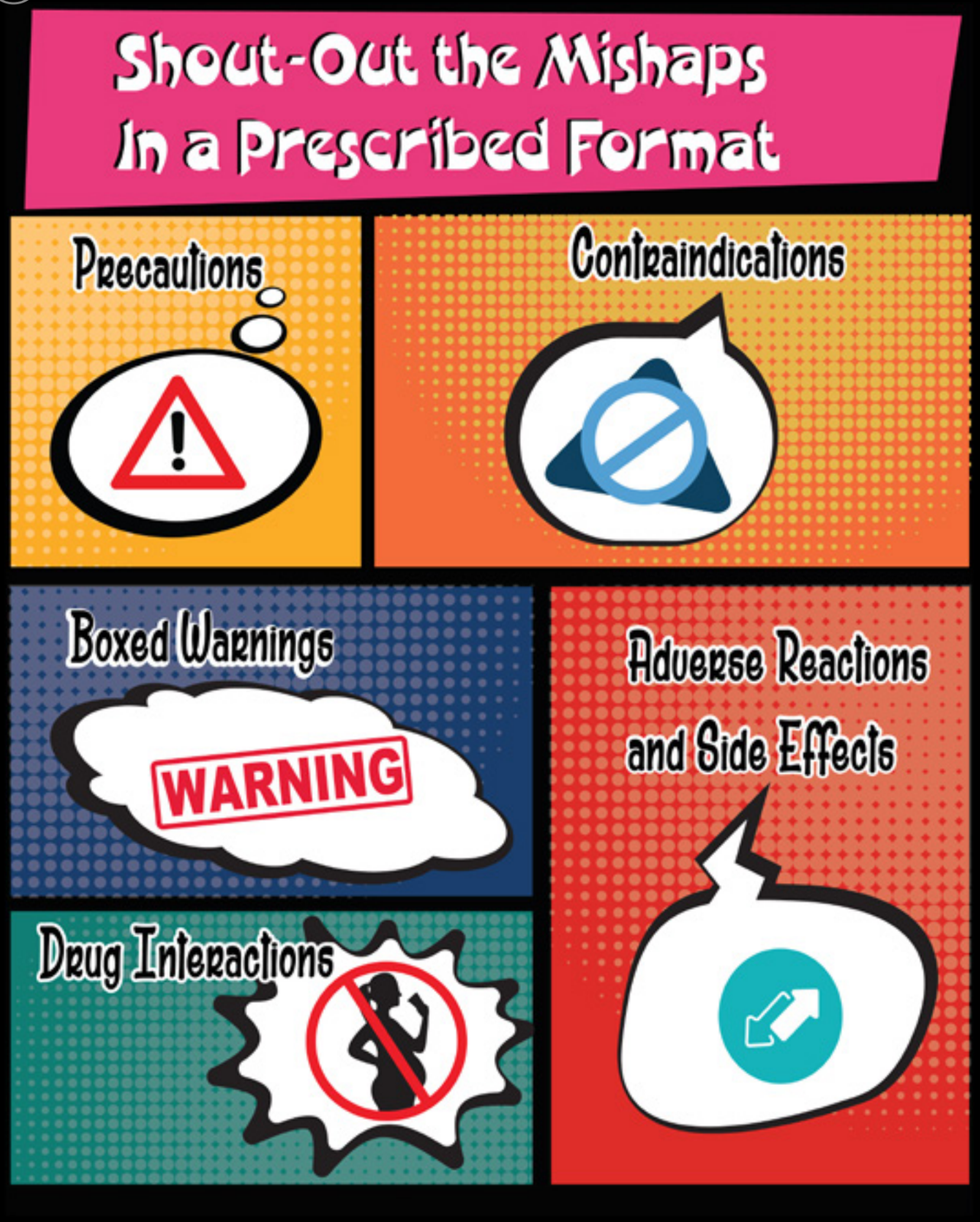
The final day in Istanbul went through museum-trotting and savouring Istanbul's history. The Istanbul Archaeology Museums is a group of three archaeological museums and is one of the must-visit places. This is the city's top museum attraction and it should be high on the list of things to do for history-loving tourists.

The Whirling Dervishes marked the end of our 4-day visit to Istanbul. It was a fitting finale, satiating the mind and the spirit. The whirling dervishes played an important part in the evolution of Ottoman high culture. From the 14th to the 20th Century , their impact on classical poetry, calligraphy, and the visual arts was profound, while music was perhaps their greatest achievement. In their work, the chanting of poetry, rhythmic rotation, and incessant music create a synthesis, which according to the faith, induces a feeling of soaring, of ecstasy, of mystical flight.

From a mystical flight to a flight back to reality. Istanbul in four days was everything we asked for...and then some more. Back home with an innate wish to see and experience other places in Turkey, soon.

REWARDS & RECOGNITIONS

Freyr conducted the Rewards & Recognitions for Quarter 2 to acknowledge employee efforts towards meticulous implementation of projects and successful accomplishments. The rewards were handed over to employees who went an extra mile in different categories like Target Oriented Performance, Critical Incident Performance, Deadline Meeting Performance, Innovative Performance, and Client Appreciated Performance.



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