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LEAD STORY

GLOBAL MARKET ACCESS

The Influence of Payers and Strategic Solutions to Tackle

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FOREWORD

Dear Patrons,

Let us present you a brand-new Issue of Freyr CONNECT!

Acknowledgements, notable milestones and internal growth. This is what we could conclude about Freyr's journey, for the season gone by. We feel that the season has not just been great, but excellent. How? Below are the self-explanatories.

- Excellence Award at the GHP International Life Sciences Awards 2018
- Crossing 300+ clients' milestone marking a new phase of growth
- US office facility expansion
- A new business centre in Austria
- Official sponsor of the American Medical Device Summit, 2018

For being part of such a remarkable journey since the inception, it's our innate responsibility to share with you the latest, accurate and on-time Regulatory information, market updates for successful compliance and market-entry.

We shoulder that responsibility ensuring that this edition of Freyr CONNECT give you the best of thought leadership on Global Market Access, the influence of payers and strategic solutions to tackle it - as a lead story. Progressing further, this Issue offers various research-oriented articles on mobile medical applications, USFDA expedited programs for serious conditions, eCTD 4.0 and more insights that are currently in focus. We didn't stop there. We made this Issue an exciting amalgamation of fun and business at Freyr.

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

Happy Reading!

Suren Dheenadayalan
Co-CEO

Center of Excellence
Regulatory Strategy

GLOBAL MARKET ACCESS

The Influence of Payers and Strategic Solutions to Tackle

In the era of globalization, being established in a single market is no longer considered to be a beneficial factor for life sciences organizations. With worthwhile investment of time and man power on research and development followed by a keen eye on regional Regulatory procedures for successful compliance and quick approvals, every organization is expected to market their product globally to reach the most needed and to take hold of major market share.

It involves establishing a positive environment that alleviates the product value to the expectations of all the stakeholders. The stakeholders comprise of national and local decision makers, policy makers, related government bodies impacting the medicinal

product users and others who influence the product's position; collectively termed as 'payers'.

Payers are responsible for reviewing a product's cost-effectiveness and therapeutic value and can approve / reject the reimbursement of a part of product development costs. The reimbursement serves as a source of key returns to recover the capital investment for manufacturers. In some countries, the payers are also allowed to negotiate and set limits on pricing of the product. With the capability to influence a product's value in the market, payers can define the future of a medicinal product.

To understand payer's influence in real-time, let us investigate a recent incident. A UK-based major pharma company released a drug with respect to a rare disease whose medical benefits included modest efficacy and was uncertain about long-term safety. The payers in the Europe found that the end result of the drug product did not align with the expected therapeutic value. So, they decided not to reimburse the product development cost.

The case emphasizes the importance of a payer while developing a medicinal product. Unable to earn back the cost of product development, the proprietary owners of the product had to face huge financial losses. Thus, it becomes crucial for the organizations to align with payers' intentions in all the ways possible.

Predominant Challenges of Market Access:

- **Payers' Requirements:** To begin with, companies must understand the implications of the product in the chosen market. Further, they must also interpret the core requirements of a payer and other prevalent challenges and address them with due diligence.

  The payers have become increasingly demanding in terms of value outcome for the end-users. They have an eye on the product's progress and are always on track to know its development and progress. They are shifting towards evidence-based medicine. Not only that they want to understand the product's attributes, but they are also concerned about how the company justifies it's premium pricing. Focus is also on the economic value of the product, which means cost of product must be demonstrated lower in comparison with alternate therapy/therapies. It is solely the company's responsibility to prove that the product brings added-value to the end-users.

- **Competitive Landscape**: Lucrative markets have been competing for a market share from a long time. With alternate medicines for similar diagnosis burgeoning in any given market, companies cannot remain dependent on a single molecule. Additionally, some disease categories have multiple drug choices, leaving it to payers' discretion on competitive pricing. Tracking the competitive pricing continuously and setting a new commercial agenda for their products is also a challenge for manufacturers.

How to tackle the Challenges?

It is clear that the manufacturer, to make a smooth market-entry, should keep the payer informed with the right data at right time. To ensure the same, companies must understand the payer to whom they are catering the data. There are three broad categories that payers are usually grouped into, such as:

- Payers who evaluate clinical attributes such as safety and efficacy
- Payers who evaluate product costs and benefits
- Payers who focus on coverage decisions primarily on cost

Once the payer type is understood, the organizations can step further focusing on the individual needs eliminating other probabilities thereby reducing the overall efforts. Further, it is essential to understand the payers' influence which depends on what they are expecting from the product. The payers' expectations revolve around few key factors:

- core values behind decision making, incentives and evaluation criteria
- quality methods of assessment
- evaluation process and stakeholder engagement
- governing policies and market access mechanisms

Companies must consider following the above-mentioned factors as they make a base to influence payers' reactions. Another major problem lies in understanding how payer will respond to a product profile that doesn't match the physician and end-user requirements. Decoding those details with utmost accuracy require designing and forecasting payer response rather than depending solely on physician's opinions. The companies must assess the customer reaction and market acceptance using more sophisticated analytical methods. Conducting these assessments early in the product life cycle will help to shape a dependable response strategy, thus to shield market entry strategies.

As mentioned earlier, payers have significant control over the pricing and influence the competitive dynamics of market. Decoding perspective of a payer can help manufacturers while communicating the therapeutic value and arrive at a final pricing. In addition, manufacturers should understand a payers' perspectives in several key product-level decisions, such as:

- Value hypothesis development
- Value hypothesis validation
- Evidence prioritization and planning
- Clinical program planning and designing
- Value proposition development
- Payer positioning and messaging
- Pricing and market strategy access
- Life cycle planning and portfolio management

As mentioned earlier, evidence-based medicine (EBM) is one of the primary focuses for payers. Products with complex treatments are often overlooked for intensive clinical data. But products in therapeutic areas with high-priority will be thoroughly scrutinized to establish clear results. To generate such precise evidence, a strategic approach is required while designing clinical trials to collect the data that is answerable to payers' needs. Organizations must increase their focus on quality hypothesis, and they should invest on infrastructure and processes to do the same.

Finally, on a broad level, the company must make certain changes to the procedures that can enhance their market access prospects.

- Internal teams have to develop new techniques and skills to understand the needs of different stakeholders in the regional markets
- Emphasis must be laid on actively learning the changes in stakeholders' needs as part of product management throughout the product life cycle
- Develop a multi-faceted approach along with deep understanding of core areas
- Research and development must expand their thinking beyond the technical clinical performance to cover the stakeholders' willingness to accept the product in global markets
- The company must develop a detailed understanding of cost impact and benefits of product within the regional system
- Regional offices must work closely with the local affiliates
- All parties involved must work together to develop and agree on a common terminology, approaches and working procedures to ensure consistent take on market access
- Induce cross-functional capabilities into the organization
- Market access functions must also be aligned with all key business functions

At each point, the payers' influence has been reiterated and vividly emphasized. The organizations worldwide must turn to understand case-wise payers' needs and make use of more advanced, and sophisticated tools to establish the value of their product. While focusing on product-level changes, it is important that the companies should make some structural changes to bring out positive outcomes for quick and successful market access.

Are you ready for these changes? Consult an expert.

Center of Excellence
Regulatory Labeling

US FDA'S GUIDANCE ON INDICATIONS AND USAGE SECTION OF LABELING

To assist the applicants in drafting the Indications and Usage section of label, FDA has issued a draft guidance: "Indications and Usage Section of Labeling for Human Prescription Drugs and Biological Products – Content and Format," on July 03, 2018.

The purpose of this guidance is to advise the MAH to ensure the Indications and Usage section of the label is clear, concise, useful and consistent across the drug and therapeutic class. Applicants are advised to follow the recommendations mentioned in this draft guidance while preparing a new label or while revising an already approved label.

This guidance has recommendations to include general principles, information to be included, addition of descriptors or qualifiers, inclusion of limitations of use and organizing and formatting of the information in the Indications and Usage section of the label.

Importance of Indications and Usage section in a Label

The Indications and Usage section of a label enables a physician/ healthcare provider to identify the appropriate treatment for the patients by communicating with the approved indication(s) of a label.

Indications and Usage section is meant to provide the disease or condition or manifestation or symptom for which the drug is approved as well as whether

the drug is indicated for the treatment, prevention, mitigation, cure or diagnosis of that disease or condition, including relief of symptoms.

What should the Indications and Usage section contain and how should it be presented?

The Indications and Usage section must:

- Reflect the scientific evidences, accurately
- Be cautiously written to convey the use for which the drug has been shown to be safe and effective
- Use terminology that is clinically relevant and scientifically valid and understandable to healthcare practitioners

The indications, which are clear, concise, straight forward and consistently written, facilitate the indexing of indications in electronic drug data bases. This would assist the healthcare practitioners to easily search the indications in electronic database, thus helping them in quick clinical decision making.

More about Indications:

All indications listed in Indications and Usage section must be substantial evidence of safety and effectiveness based on adequate well-controlled clinical studies. The indications must not be suggested in other sections of the label, if not included in the Indications and Usage section of the label. If a drug is commonly prescribed for an unapproved indication, if such usage is associated with a potential risk or hazard, FDA requires a special warning on the unapproved usage of the drug in Warnings and Precautions section of the label.

Drafting the Indications and Usage section of the label:

The Indications and Usage section of the label should clearly convey the scope of the approved indication along with population in which safety and effectiveness has been established, which should be substantially evidenced by the derived clinical information and ongoing safety studies, if any. Based on the general pharmacological properties of the drug, the indication may be generalized to include the patient population, which are excluded during the clinical phases of the drug (i.e., paediatric, geriatric, pregnant or nursing women). This may be backed up with the ongoing safety evaluation.

Approval of a drug in paediatric population is generally based on the sufficient data in following populations:

- Paediatric population only
- Both adult and paediatric population
- Adults, with supporting data in paediatric population
- One paediatric population that allows extrapolation of effectiveness to another population

In certain circumstances, it may be appropriate to consider an indication for an adult population in an age group broader than the age group that was studied. However, this approach is generally not applicable for paediatric population due to statutory requirements related to paediatric population. For this reason, age group should be included in Indications. Applicants should discuss the scope of age groups for a proposed indication.

Indication Section Elements

The indication section should begin with "Drug-X" is indicated and must include the following elements required as per 21 CFR 201.57(c)(2)(i):

- The disease, condition or manifestation of the disease or condition (e.g. symptoms being treated, prevented, mitigated, cured or diagnosed)
- When applicable, other information necessary to describe the approved indication (e.g. descriptors for the indication mentioned)

Limitation(s) of the use should be mentioned separately in Indications and Usage section of the label. Limitation(s) of use must be mentioned only when awareness of such information is important for medical practitioners to ensure safe and effective use of medicines.

Distribution of information across the labeling sections:

The information which is most relevant to the indication should be mentioned in Indications and Usage section while other information with an elaborated description can be cross referenced in Indication and Usage section.

Updating Indications and Usage section:

The Indications and Usage section must be updated as and when the new information becomes available. The applicants should review the Indication and Usage section regularly to ensure that it reflects the company's position on the mentioned indications.

The principles and considerations discussed above are just a tip of an iceberg. A comprehensive overview of the FDA guidance will be helpful to achieve compliance in drafting the Indication and Usage section of the label. As the guidance is yet to be finalized, consider decoding it with the aid of a Regulatory labeling expert. Act on time. Be compliant.

Center of Excellence
Artwork Pack Management

ARTWORK: IS OPTING FOR "MANAGED SERVICES" THE RIGHT OPTION?

Packaging, labeling and "artwork" are crucial stages of a drug product life cycle, as they are the main safety information sources for the end user. Any mislead in these processes may lead to product recalls.

Hence, it is highly important for a manufacturer to contemplate all possible approaches to successfully implement them either in-house or by opting managed services i.e., to contract out. While some companies contract the complete artwork process, others prefer to keep it in-house for confidentiality reasons. But is there really a need for companies to opt for managed services or contract out their artwork processes? Here are some questions that an organization should ask themselves:

- Will it help to gain a competitive advantage?
- Is the outsourcing company experienced with the proven best practices?
- Should the company outsource the entire project or just a part of it?
- Can the organization sustain the cost of the tools and technologies required for artwork?

If your answers are positive, then mostly "managed services" are the best to opt. But before opting, there are a few points which should be scrutinized thoroughly.

Partner Evaluation

With managed services, you may have to provide a vital piece of information about your product to the stakeholders. Hence, it is extremely important to know your contract partner before in hand. You should make sure that the partner is experienced to take up the project and

has been successful earlier.

Quality of Service

The bottom line of giving artwork on contract is to get the work delivered on time adhering to the quality standards of compliance. If the quality of artwork is not up to the mark, it doesn't make any sense. Therefore, the organization must be alert at every step of the process to check the quality not only in terms of delivered outputs, but also the practices the partner is implementing. From artwork to labeling to packaging, every process should be error-free and should be in line with the established SOPs.

After thorough scrutinization of above-mentioned aspects, the next important thing for the manufacturer is to evaluate how beneficial the managed services are for their organization. The manufacturer should look at:

Significant Cost Savings

As discussed above, the main reason to opt for managed services is to reduce the overall cost. It can be the cost incurred in maintaining tools and technologies or accommodating the existing human resources. The manufacturer should evaluate whether the contract can give them the advanced technologies to streamline procedures or does it offer the same what they already possess. If it is the same, then there is no point to give out the contract which will be an added burden.

Focus on Core Business Functioning

At times, due to heavy workload in the organization, the core competencies are ignored. But given that the processes for managed services can save both manpower and time, the organization can focus on core business functioning, i.e., innovation which can be added advantage to competitively differentiate the product in the market.

Simplified Future Processes

Contracting certain processes for expert service providers can simplify the entire product life cycle. For e.g. with the artwork given to an expert managed services provider, the output can be better aligned for future printing and packaging with perfect bleeds and other production aspects. In that way, the overall productivity can be increased throughout the product life cycle for compliance.

Moreover, with the recent trends, approximately 80% of the manufacturers are willing to opt managed services for their artwork processes, amongst which 43% are already reaping the benefits by collaborating with Regulatory Service Providers/Contract Research Organization (CRO) with the world-class design studio. Realizing it beforehand can save a lot of time and money. Be informed. Be compliant.

Center of Excellence
Publishing & Submissions

eCTD 4.0: TAKING ELECTRONIC SUBMISSIONS, A STEP AHEAD

When Agencies were having difficulty in managing and reviewing manual submissions, the eCTD (electronic Common Technical Document) format came to their rescue.

eCTD was introduced as an interface for Regulatory authority transfer of information while considering facilitation of creation, reviewing, life cycle management and archiving of electronic submissions. With continued improvements, even eCTD has evolved many times over the years. In January 2017, the International Council for Harmonization (ICH) updated the Step 4, Adoption of an ICH Harmonized Guideline and implementation of eCTD 4.0 for modules 2 through 5.

eCTD 4.0 is based on the health level seven (HL7) standard called the regulated product submissions (RPS). The RPS standard is intended for broader use as compared to eCTD and beyond life sciences, it could potentially support submissions for medical devices, veterinary, and other regulated products.

The Major changes in eCTD 4.0 are as follows:

1. **Document Reuse**

   With eCTD 4.0, sponsors can reuse a document for another submission unit, submission or application in the same or different context and in other cases too. This is possible as all the documents are assigned a unique ID called Universal Unique IDs (UUIDs) and can be tracked as long as they are present in the agency system. UUIDs are easy to manage as they do not require any central support or maintenance.

2. **Revised Metadata**

   eCTD 4.0 provides provision which

helps to rectify the errors in metadata easily. Users are also allowed to make corrections in previously submitted meta data related to submission types, sequences, operation attributes, manufacturer name etc.

3. Two Way Communication

In the earlier version of eCTD, only sponsors could send eCTD submissions to the agency. With eCTD 4.0, agencies can also revert to the sponsors for issues like request for information as a sequence. However, Japan does not plan to implement two-way communication with eCTD 4.0.

4. Table of Content

As compared to the eCTD v3.2.2, 4.0 does not have a defined table of content or a hierarchical structure which means the files are delivered in a flat structure. To determine the place of any element in the TOC, context of use and keywords are used.

5. eCTD XML

eCTD 4.0 eliminates the need of editing XML stylesheets manually. XML doesn't display a hierarchy in documents, hence, it becomes highly difficult or close to impossible for sponsors to create, read or work on XML stylesheets.

6. Study Tagging Files (STFs)

Study tagging files are used to identify files associated with eCTD Modules 4 and 5 i.e. ICH specific information. The issue with STFs is that they are required in some regions while they are not accepted in specific region. Therefore, to Standardize globally, eCTD 4.0 merged STFs with document groups.

7. Document Groups

To organize multiple documents in a submission, eCTD 4.0 provides a function to group files together based on the nature. This feature is to eliminate the need of STFs in Module 4 and 5. eCTD 4.0 also supports grouped submission. A grouped submission is a single submission unit applied to more than one submission. It is the only business case for sending a Submission Unit with more than one component of submission element.

8. Context of Use

Context of Use allows sponsors to track the specific location where the documents need to be inserted into the CTD/eCTD TOC while presenting in a reviewable structure.

9. Replacing Documents

As compared to the previous version, eCTD 4.0 allows sponsors to replace one document with many and many documents with one, thus, providing flexibility to alter minute details of the documents for life cycle management.

10. Append Life Cycle Operations

Appending already submitted documents was already opposed by many agencies in the past. Hence, here on users won't be able to update the content of already submitted documents but 4.0 does support life cycle operations such as "new", "replace" and "delete".

11. Importance of Metadata

Metadata plays a vital role in eCTD 4.0. It will be used for everything from application type to reviewing status to type of document.

12. Controlled Vocabulary

Controlled Vocabulary is a list of terms allowed for a specific concept. It is important in eCTD as it allows clear communication between systems sending and receiving XML messages.

The main intention behind moving to eCTD 4.0 was to address the new requirements/ improvements/challenges that were discovered during the course of eCTD v3.2.2. Let's have a look at the key enhancements in eCTD 4.0:

- Enhanced control of dossier
- Enhanced identification of information contained within a submission
- Message flexibility
- Support for two-way communication (Regional)

eCTD 4.0 fulfils the main long-term objective of Regulatory authorities to have a globally used standardized electronic message exchange system which is approved and accepted internationally.

Most of the Regulatory Authorities are positive about the impact of eCTD 4.0 and are planning to execute their pilot versions of eCTD 4.0 by 2020. FDA projected that their pilot would begin in the second half of 2018. But now it is likely to start by 2019. In a recent presentation by Health Canada, they stated, "they should be issuing a draft guidance during 2018, for a pilot in 2019 and acceptance in 2020."

Now that eCTD 4.0 is expected to be implemented, it is time for the industry to decode new standards and be ready to execute their pilot projects. It is always good to stay up-to-date and compliant. Be informed. Stay Compliant.

Center of Excellence
Regulatory Intelligence

NAVIGATING THE REGULATORY PATHWAY WITH INNOVATIVE PRODUCTS

Start-ups in the medtech space face many challenges on the way to market, not the least of which is how to prepare for, and comply with, medical device regulations. Here are some points to consider.

Precision medicine, personalised drug therapy, 3D-printed drugs, artificial intelligence (AI), nanotechnology and clinical trial monitoring using mHealth sensors, are some of the cutting-edge technologies advancing solutions for life-threatening diseases.

However, while hundreds of nascent bioentrepreneurs try to turn their new ideas into businesses every year, fewer than 10% are ultimately successful. Those who do succeed face multiple hurdles along the way, including a lack of scientific research data on public forums due to patent right protection, and a partial understanding of Regulatory processes and patterns. Lack of experience in the development stage can mean accurate analysis of processes is not undertaken, which can lead to costly mistakes. Another major challenge is when a drug is in its final stage and ready for the approval process, there may not be enough reliable information on the Regulatory pathways to get it approved by the health authorities (HA).

Established pharma companies have an edge over start-ups, with institutional experience and well-established connections that help them determine the right approach to achieve HA consent. This also helps them to market their products in a timely and profitable manner. For a start-up, however, each step involves trial and error, which can cost time and money. Everything needs to be planned precisely.

Companies have to appraise the latest advances, from manual interventions to AI and Cloud, regarding whether they can be used as a platform to integrate bioscience and computation

in a medical app technology. Then the resulting devices must undergo a series of integrations, tests, and validations. Good Automated Manufacturing Practice (GAMP), including risk-based classification and design specifications, must be taken into consideration to meet the stringent guidelines of the HA.

A major challenge with these medical apps is the lack of guidance on established Regulatory pathways, especially for wearable medical technologies. Innovators wanting to market their products must first review the existing HA Regulatory framework for medical devices to determine the correct pathway. The first step is to assess whether or not the wearable product qualifies as a 'device' under the HA definition.

Like all other medical devices, a mobile app is subject to strict Regulatory requirements. Applicable Regulatory standards typically include compliance to the medical device directive (Directive 92/42/EEC) and the upcoming Medical Device Regulation (MDR), as well as the below standards:

- Software life cycle: IEC 62304 and IEC82304
- Usability: IEC 62366 and IEC 62366-1
- Risk management: ISO 14971
- IT networks: IEC/TR 80001-1 and IEC/TR 80001-2-x etc.

To an outsider, the medical device space looks full of promise. However, like any other industry, it faces its own challenges and uncertainties, both Regulatory and non-Regulatory. These include:

Regulatory challenges

- Compliance with the quality system requires significant investment, in terms of resources and time. This is because the regulations for medical devices set forth detailed requirements for the manufacturer and control of medical devices.
- App manufacturers often overlook or pay little attention to the cognitive accessibility aspects of their content and user interfaces. An app that is easily usable by a younger person may be difficult for an older, or differently-abled, person with specific and unique usability needs related to ageing and/or physical and cognitive impairment.
- A wearable product qualifies as a 'device' based on HA guidance. Many wearable technologies are innovative and may be the first of their kind, and the Regulatory pathway for these devices may not be straightforward.
- Prior establishment of the intended use of the product and intended user population.
- Establishing clinical trials to ensure 'reasonable assurance' of the device's safety and effectiveness.
- Wearable medical technology will bring a number of start-ups under the HA's jurisdiction.

Non-Regulatory challenges

- Transformation of mobile computing devices into secure medical gateways
- Rapid pace of technology change
- Interface between device and wearable/apps
- Cloud and AI
- Increase in global diseases and lack of app-based treatment
- Competition from similar device manufacturers

Despite the challenges, the medical devices sector is set to continue to grow. It has been estimated to reach $342.9 billion by 2021, with a CAGR of 4.6% from 2016 to 2021.

Some actions that medical device start-ups need to address are:

- Establish a clear Regulatory strategy
- Define and document: product user need; a design and development plan, and design inputs
- Establish a design history file (DHF), which contains all design controls, including user needs, design and development plan, and design inputs etc.
- Establish risk management procedure(s); define and document a risk management plan; identify and document product hazards; document and establish a risk assessment and management file; establish document control/record management procedures
- Establish supplier control procedures, create an approved supplier list and maintain supplier files

They should also partner with experts in the field to help them find prospective revenue-generating markets, analyse the product pathway, find product intelligence, forecast the market and evaluate competitors.

This article was first published by
pharmaphorum
bringing healthcare together
www.pharmaphorum.com

References are available at
https://pharmaphorum.com/views-and-analysis/navigating-regulatory-pathway-innovative-products/

Center of Excellence
Global Medical Device
Regulatory Services

US FDA CDRH ANNOUNCES THE PATH AHEAD - 2019

US FDA's Center for Devices and Radiological Health (CDRH) recently announced its plans for publishing the guidance documents for FY 2019. Aligning with the CDRH's vision, the proposed guidance list is focused on the qualitative and quantitative agenda of getting the safe and effective medical devices to the market faster. It is clearly reflecting the inclination to increase the Regulatory efficiencies keeping in mind the public healthcare and safety. The recent announcement comprises of three parts, as listed below:

1. **Priority List or A-list**, as it is named, includes the list of final and draft guidance topics that the CDRH intends to entirely publish next year
2. **B-list** includes the guidance topics that will be published depending on the resource's bandwidth
3. Reconsideration of all the **previous guidance** topics (put together 450, as on date, from last 30 years) and their current relevance and applicability

In this scenario, FDA's thinking at the beginning of the year becomes more significant as it had clearly laid out the high-level agenda with the focus on the following aspects:

Simplification:

FDA intends to reduce the varied and complex CDRH core processes by 80% by 2020. Examples of which are, risk-based framework to benefit-risk framework, Medical Device Single Review Program etc.

Collaboration and Community Focus:

Collaboration and building communities as part of IMDRF for harmonization and better process that can be followed across selected countries. The CDRH also intends to add 10 more collaborative communities by 2020.

Employee Engagement:

CDRH intends to achieve 80% employee engagement level as engaged employees lead to happy workforce that will result in better output and thus enable faster market approvals.

What does the FDA's current thinking include? Let's deep dive into the proposed guidance documents.

Priority List or the A-list

Final A-list Guidance Topics:

- Consideration of uncertainty in making benefit-risk determinations in medical device premarket approvals, De Novo classifications, and humanitarian device exemptions
- Unique Device Identification: Policy regarding compliance dates for class I and unclassified devices and direct marking of inventory
- Breakthrough devices program
- Expansion of the abbreviated 510(k) program: Demonstrating substantial equivalence through performance criteria
- The least burdensome provisions: Concept and principles
- Changes to existing medical software policies resulting from Section 3060 of the 21st Century Cures Act
- Clinical and patient decision support software
- Multiple function device products: Policy and considerations
- Humanitarian Device Exemption (HDE) program
- Requests for feedback and meetings for medical device submissions: The Q-submission program
- The special 510(k) program or the abbreviated 510(k) program to reduce total time for decision

Draft A-List Guidance Topics:

- Content of premarket submissions for cybersecurity of medical devices of moderate and major level of concern
- Surgical staplers and staples – Labeling recommendations
- Nonbinding feedback after certain FDA inspections of device establishments
- Select updates for recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) waiver applications for manufacturers of in vitro diagnostic devices
- Recommendations for dual 510(k) and Clinical Laboratory Improvement Amendments waiver by application studies
- Computer software assurance for manufacturing, operations, and quality system software
- Patient engagement in clinical trials
- Guidance for the content of premarket submissions for software contained in medical devices
- Life cycle Regulatory requirements of medical device servicing (Device servicer vs remanufacturer)
- Guidance on Accreditation Scheme for Conformity Assessment of Medical Devices to FDA-Recognized Consensus Standards (ASCA)

Second-priority or the B-list

Final B-list Guidance Topics:

- Utilizing animal studies to evaluate organ preservation devices
- Unique Device Identification: Convenience kits
- Medical x-ray imaging devices conformance with iec standards
- Replacement reagent and instrument family policy for in vitro diagnostic devices
- Unique device identification system: Form and content of the Unique Device Identifier (UDI)

Draft B-list Guidance Topics:

- Nonclinical testing and clinical considerations for implanted Brain-Computer Interface (BCI) devices for patients with paralysis or amputation
- Continuous ventilators - Premarket notification (510(k)) submissions

Conclusion:

What is in it for the medical devices manufacturers to look at is, the guidance topics would be focused on reducing the time and money for the safe products to enter the USA market. FDA intends to have guidance that supports the product life cycle, while not compromising on the safety and effectiveness standards. And lastly, simplifying and streamlining the market entry approach/process with the support of the stakeholders while keeping in mind the patient centric aspects.

Please get in touch with Freyr to understand these guidance topics and how it might impact your business positively and also align with your business goals.

Center of Excellence
Global Medical Device
Regulatory Services

MOBILE MEDICAL APPLICATIONS:
THE REGULATORY FRAMEWORK IN THE USA AND THE EU

The medical device market is one of the largest industries in the healthcare sector, which has seen significant growth in the last 15 years. Harnessing the benefits of the digital revolution and medical technology, the industry is in a state of continuous transformation. Mobile medical applications (MMA) represent one such transformative invention the industry has provided to healthcare professionals. An MMA is a piece of software that runs on a smartphone and/or other mobile communication device, transforming the mobile platform into a medical device to perform a specific healthcare function.

According to Research and Markets, the global market for mobile health applications is currently valued at approximately $28.32 billion and is expected to reach $102.35 billion by 2023. Complex data analytics and mobile technologies are enabling and driving the integration of mobile devices into the healthcare sector, which in turn are catering to the requirements of healthcare professionals, patients, and general consumers as well. They have also contributed to simpler remote monitoring, better communication, and care coordination among doctors, nurses, and other specialists involved in the diagnosis and treatment of diseases.

Depending upon the functionality, MMAs can be broadly segmented into one of several categories.

Chronic Care Management Apps: These include apps to manage blood pressure, cancer care, diabetes care, mental health, and other illnesses.

Medical Apps: These apps are mainly used by healthcare professionals. Examples include medical education apps, doctor consultation/appointment apps, patient management and monitoring, etc. Clinical decision support systems, which assist doctors/physicians in diagnosing various health conditions, are also categorized under medical apps.

General Health and Fitness Apps: These apps constitute almost 75 percent of MMAs found on app stores. These are related to nutrition, health tracking, fitness, and weight loss, along with wearable technology sensors and other health monitors.

Medication Management Apps: These apps help in keeping track of medicine intake to ensure proper dosing at required intervals.

Personal Health Record Apps: These applications allow patients to store their medical conditions data, history, allergies, etc.

Women's Health Apps: This segment includes apps for pregnancy, fertility, breastfeeding, etc.

Regulatory Framework for Mobile Medical Applications

Currently, there are almost 170,000 MMAs available on various mobile platforms. Of these, only a small percentage (approximately 2-3 percent) resemble the definition of a medical device, thereby requiring approval by the respective Health Authority (HA) prior to public release. While the MMA market is undergoing rapid transformation, the lack of up-to-date and comprehensive Regulatory guidance is creating a challenge for app developers throughout the world. Although major markets like the United States and European Union (EU) have published their regulations, there exists a gray area for mobile medical-oriented application developers. There is ambiguity regarding the conformity of these apps to the regulations. Compared with EU, the U.S. Food and Drug Administration's (FDA) regulations are more detailed and provide better clarification on the criteria for the MMAs to qualify as a medical device.

U.S. MMA Regulations

In September 2015, FDA released a guidance with the name "Mobile Medical Applications," which superseded the February 2015 version. As per the FDA's guidance, MMA is defined as:

"...mobile app that meets the definition of device in section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and either is intended to be used as an accessory to a regulated medical device or to transform a mobile platform into a regulated medical device."

Regardless of the mobile device hardware or platform, consideration of MMA as a medical device is determined by the intended use of the mobile app to cure, prevent, mitigate, and treat a disease. FDA determines the intended use through the examination of advertisements, labeling claims, and oral and written statements by the manufacturer.

FDA considers categorization of MMAs as follows:

- Apps that do not meet the definition of a medical device as per the FD&C Act. The FD&C Act is the legal authority through which the FDA regulates medical devices; it contains provisions and Regulatory requirements that apply to medical devices. FDA does not regulate mobile medical apps that do not qualify as medical devices. Examples: Medical dictionaries and encyclopaedias, educational apps for healthcare professionals and patients.
- Apps that may be medical devices as per the definition but require no regulation by the FDA on account of low potential risk. Most of the general health and wellness mobile applications; for instance, fitness and nutrition apps are subject to enforcement discretion. Examples: Mobile apps that perform simple calculations routinely used in clinical practice such as body mass index and delivery date estimator, patient health record systems, medical device data systems (used to transfer, format, store, convert, and display medical device data).
- Apps that are subject to FDA oversight due to considerable risk to patient safety. Examples: apps that transform the mobile platform into a Class II regulated medical device by displaying radiological images for diagnosis, apps that require an attachment to the mobile device to measure blood glucose levels, mobile apps that wirelessly control computed tomography or X-ray machines.

As a part of the digital health innovation plan in the U.S., the 21st Century Cures Act was implemented in December 2016. The Act came into force to introduce innovative healthcare facilities for patients in a faster and more efficient manner. This Act amended Section 520 of the FD&C Act, resulting in the withdrawal of medical device status for the following MMAs due to their low potential risk to patients:

- Software intended for administrative support of a healthcare facility
- Software promoting and maintaining healthy lifestyle
- Medical device data systems
- Electronic patient record software
- Some of the clinical decision support systems

USFDA Regulations Applicable for MMAs and Software as Medical Device (SaMD)		
	Regulation	**Description**
Final Regulations	**Mobile Medical Applications (MMAs)**	This guidance explains the medical device qualifying criteria for the mobile medical applications.
	Software as Medical Device (SaMD)	An IMDRF (GHTF) document adopted by USFDA to define SaMD.
	SaMD Clinical Evaluation	An IMDRF guidance adopted by USFDA on the clinical evaluation of SaMD.
	General Principles of Software Validation	It explains how the medical device quality system applies to MMAs.
	Off-The-Shelf Software Use in Medical Devices	It details the documentation needed in the premarket submission for medical devices using Off-the-Shelf Software.
	MDDS Rule Federal Register Notice	The document clarifies MDDS classification rules.
	Applying Human Factors and Usability Engineering to Medical Devices	This guidance focusses on user interfaces, display, controls and instructions for use.
	Clinical Performance Assessment: Considerations for Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Approval (PMA) and Premarket Notification [510(k)] Submissions	This document provides guidance regarding clinical performance assessment studies for Computer Assisted Detection (CAD) devices applied to radiology images and radiology device data.
	Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data – Premarket Notification [510(k)] Submissions	The document is for premarket notification (510(k)) submissions for CAD devices applied to radiology images and radiology device data.
	Post market Management of Cybersecurity in Medical Devices	The guidance explains the post market cybersecurity measures to be followed for mobile medical applications.
	General Wellness: Policy for Low-Risk Devices	It defines the criteria for low-risk general wellness applications.
	21st Century Cures Act	This document features the salient features and the implications of 21st Century Cures Act.
Draft Regulations	**Changes to Existing Medical Software Policies Resulting from Section 3060 of the 21st Century Cures Act**	This draft explains information on the effect of 21st Century Cures Act on MMAs and SaMD in general.
	Clinical and Patient Decision Support Software	Contains information on why the medical device status is withdrawn for certain clinical decision support software, post the 21st Century Cures Act.

EU MMA Regulations

The EU's definition of a medical device is similar to that of the U.S.'s. The Regulatory process applies only to those MMAs that meet the EU definition of a medical device. As per EU Medical Device Regulation, the definition of a medical device is:

"Medical device means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- Diagnosis, prevention, monitoring, treatment or alleviation of disease;
- Diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;
- Investigation, replacement or modification of the anatomy or of a physiological process;
- Control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means."

In July 2016, the European Commission issued a guidance "Qualification and Classification of Standalone Software" to assist the app developers in qualifying their software as a medical device. In EU, health-related apps, generally known as mHealth apps, are categorized as:

Medical Apps: Generally used in prevention, diagnosis, and treatment of diseases (CE certification is required for these apps).

Non-Medical Apps: Related to fitness, lifestyle, and well-being.

At the national level, several EU member states such as France, Spain, Germany, and Italy are participating in developing the guidance for MMAs to provide clarification on the European Commission guidelines. To expand mobile capabilities in the healthcare sector, app developers in EU should also take into consideration the latest General Data Protection Regulations (GDPR), which were scheduled to come into effect on May 25. These regulations are expected to have several implications on personal data security and data privacy. They also require all app developers processing users' personal data—either EU-based or not—to strictly adhere to the latest GDPR policy.

Conclusion

Regulatory authorities in the EU and U.S. are diligently working on creating overarching policies for MMAs. The ideology behind the regulations for MMAs in the EU and U.S. is almost similar, but the FDA is, by far, further along in developing guidance in a detailed manner. In this environment of technological transformations, it is crucial for HAs to maintain updated draft regulations that strike a balance toward ensuring safety and efficacy, while promoting innovation.

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References are available at
https://www.mpo-mag.com/issues/2018-06-01/view_columns/mobile-medical-applications-the-regulatory-framework-in-the-us-and-the-eu/

Center of Excellence
Global Medical Device
Regulatory Services

MEDICAL DEVICES REGULATORY PRIORITIES IN INDIA

The Indian device market is among the top 20 across the globe and is the fourth-largest market in Asia. Its market value is approximately USD $5.5 billion, with an expected growth rate of 15 percent CAGR.

This market has witnessed continuous transformation over the past two decades. Before the New Economic Policy (1991), it was dominant in domestic manufacturing circles.

Later, it transformed into an import-driven market. Prior to 2006, the medical device sector in India was unregulated; that era ended in 2006, when the Central Drugs Standard Control Organization (CDSCO) notified 15 medical devices for which registration is required.

In solidarity with the Make in India program, the CDSCO published the new Medical Device Rules, 2017, which came into force on Jan. 1, 2018. Prior to implementation of the Medical Device Rules, 2017, notified medical devices were regulated as drugs (pharmaceutical products) in India under the Drug and Cosmetic Act, 1940. Therefore, it was required to distinguish medical devices from pharmaceutical products. Secondly, there was an urgent need to provide a more conducive environment for local manufacturers to set up industries in India.

Finally, the Ministry of Commerce and Industry issued a public procurement in 2017, and identified the Department of Pharmaceuticals as a notified agency.

The new rules have been formulated to promote domestic manufacturing and to regulate import and manufacturing in the region. Currently, multinational companies occupy approximately 75 percent of sales in the Indian medical device market. The new regulations follow the GHTF (Global Harmonisation Task Force) guidelines and are in consonance

with these rules' risk-based classification. In addition, inspections by notified bodies have been introduced in the new medical devices rules. In this article, we highlight some of the key points for a better understanding of the Medical Device Rules, 2017.

Classification

In consonance with global regulations, the new rules introduced a risk-based classification system. The CDSCO classifies these devices and publishes the list of classified devices from time to time on its website. Importers and manufacturers are required to follow the classification list to classify their devices. If the classification is higher in GHFT countries, then a higher grade of classification will be considered.

Table 1: Device Classification System, per Medical Device Rules, 2017

Type of Device	Risk involved	Examples
Class A	Low-risk	Nasopharyngeal Catheter, Surgical Dressings
Class B	Low-moderate	Intravenous Catheter, Disinfectants
Class C	Moderate-high	Bone Cement, Bifurcation Stent
Class D	High	Copper T, Cardiac Patches

Quality Management System (QMS) Assessment

Per the new rules, a new procedure of "third party conformity assessment and certification'" through Notified Bodies has been introduced. The notified body can perform a QMS assessment at manufacturing sites for Class A and Class B devices. Upon request, the notified body also can support CDSCO for Class C and Class D medical devices' manufacturing site QMS assessments. The accredited list of notified bodies then will be displayed by CDSCO on its website. In case of foreign manufacturers, CDSCO may also require an inspection of the overseas manufacturing site, either by in-house CDSCO inspectors or by any notified body.

Registration

The new rule is going to make it compulsory to obtain manufacturing and import licenses for all devices. All the applications for manufacturing and import licenses are processed through an online portal, SUGAM — an online licensing system that belongs to the Ministry of Health and Family Welfare.

The State Licensing Authority (SLA) will regulate the Manufacturing License for Class A and Class B devices, whereas Class C and Class D license application will be presented to the Central Licensing Authority (FSSAI). A Quality Assessment Report (QAR) must be submitted for Class B, Class C, and Class D devices, along with an application for a manufacturing license. In contrast, a QAR for Class A medical device needs to be submitted within 120 days from the date of grant of Manufacturing License.

In case of an Import License, a license for manufacturing or distribution is a prerequisite. Foreign manufacturers should appoint an authorized Indian agent to hold the license and carry out post marketing surveillance (PMS) activities, as well as distribution of medical devices. Import Licence applications for all classes of medical devices are to be presented to the Central Licensing Authority.

In contrast to the Manufacturing Licence, an Import License does not require a QAR, but the Central Licensing Authority may inspect the foreign premises, if required. To make the new guideline even more stringent, it is now mandatory to submit the complete Technical File and Import License application to the Central Licensing Authority, and every Indian agent will be responsible for the PMS activities within the country. Multiple Import Licenses for the same product, by different Indian agents, are possible under the 2017 rules.

All licenses granted are perpetual unless they are cancelled. In order to retain the license, one is required to pay license retention fee every five years. The Indian government has made special note of the inevitability of timelines, and rationalized the time required to grant a license.

Table 2: Timeline to obtain Manufacturing/ import Licence for medical devices

Class/ Timeline	Manufacturing Licence	Import Licence
Class A	45 Days	Within 9 Months
Class B	140 Days	
Class C	150 Days	
Class D	150 Days	

Clinical Investigation

The Medical Device Rules, 2017 changed the clinical trial scenario for an investigational medical device from a four-phase trial — like those for drugs, per Schedule Y — to a two-phase trial. The two phases will be divided into pilot clinical investigation (Exploratory Study) and pivotal clinical investigation (Confirmatory Study). In addition to this, PMS also is compulsory after gaining marketing approval for the device. However, for an Import License of a medical device without any predicate device in India, clinical investigation would not be required if a Free Sale Certificate (FSC) has been issued by a competent authority from Australia, Canada, Japan, the United States, or member states of European Union.

Additionally, "Substantial Equivalence" to a predicate device for medical devices (except investigational medical devices) has been introduced in the new rules. In case of invitro diagnostics, "Clinical Performance Evaluation" will be part of the Regulatory requirement. Further, no prior approval of a clinical trial is

required for academic clinical trials, provided the data generated is not used for obtaining manufacturing and import license.

Labeling

It is mandatory to follow labeling requirements according to specifications outlined in the new rules. In addition to this, the Indian government also has made it mandatory to follow the Legal Metrology (Packaged Commodities) Rules, 2011. Moreover, the Unique Device Identification (UDI) number for each device must be mentioned on the label, effective January 2022.

Recalls

The Drug and Cosmetic Act fails to obligate the manufacturer or importer to withdraw the product from the market. Per the new rules, the manufacturer or importer must recall any product that is dangerous or harmful, and they are required to provide a reason for the recall.

Public Procurement Order (PPO)

To improve ecosystem for domestic manufacturers, Government of India (GoI) brought draft guidelines for PPO. These rules cover tenders valued at 50 lakhs or less for the public procurement of medical devices. The determination of local content cost shall be based on manpower and country of origin of material (direct component). The Government proposed a formula to calculate local content:

D= (A/C)*100

(C=A+B)

D= Percentage of Local Content

C= Total Cost

B= Cost of Imported component

A= Cost of Domestic component

Table 3: Minimum local content in domestic medical devices fixed by the GoI

Category of Medical Device	% of Local Content
Medical disposables and consumables	50%
Medical electronics, hospital equipment, surgical instruments	25%
Implants	40%
Diagnostic Reagents/IVDs	25%

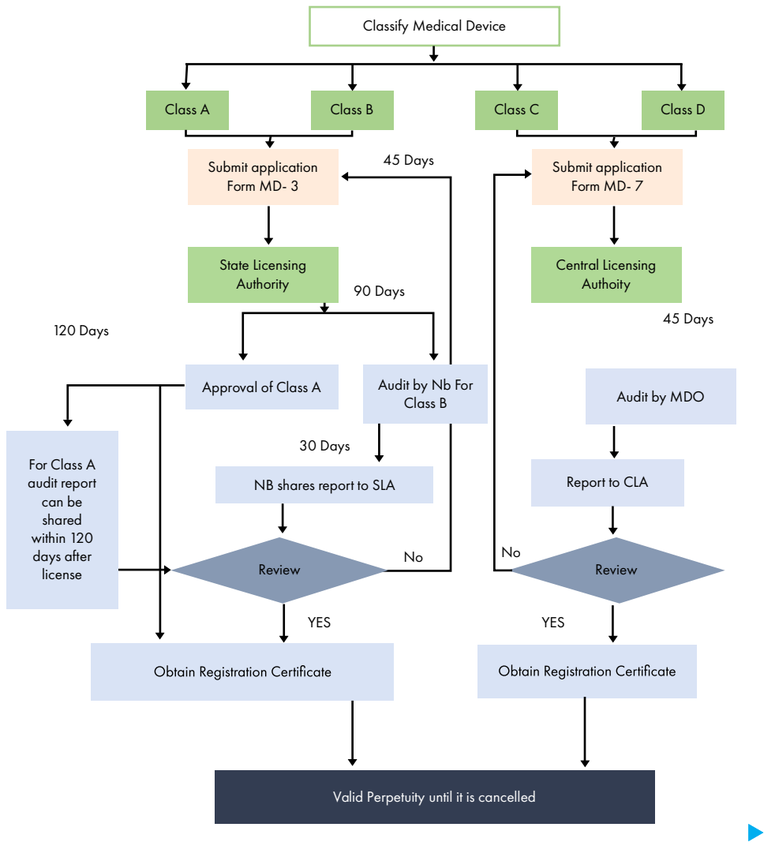
Table 4: Requirements for approval of product

Regulatory Compliance	Class A	Class B	Class C	Class D
QMS	Yes	Yes	Yes	Yes
Risk Analysis Report	Yes	Yes	Yes	Yes
Device Master File	Yes	Yes	Yes	Yes
Biocompatibility		Yes*	Yes*	Yes*
Animal testing			Yes*	Yes*
Clinical Data			Yes#	Yes#

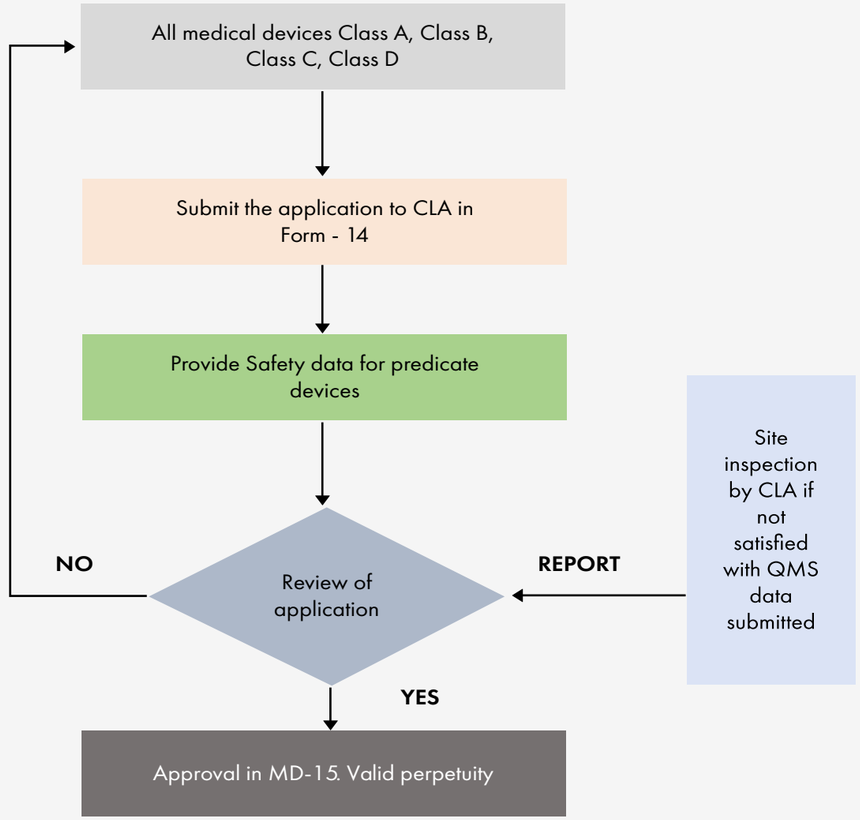
#Only for Investigational devices

*Only for Invasive devices

APPROVAL PROCESS FOR MANUFACTURING LICENSE



APPROVAL PROCESS FOR IMPORT LICENSE



Conclusion

The Medical Device Rules, 2017 have many attractive features that encourage the medical device sector in India. By introducing a single online portal, the registration process has been streamlined. An audit by the notified bodies will further increase the manufacturing quality of devices. A change in clinical trial requirements will encourage the innovation of new medical devices. The regulations will thus encourage domestic manufacturing and increased scrutiny of Import License documents.

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References are available at

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Center of Excellence
Regulatory Medical Writing

US FDA EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS

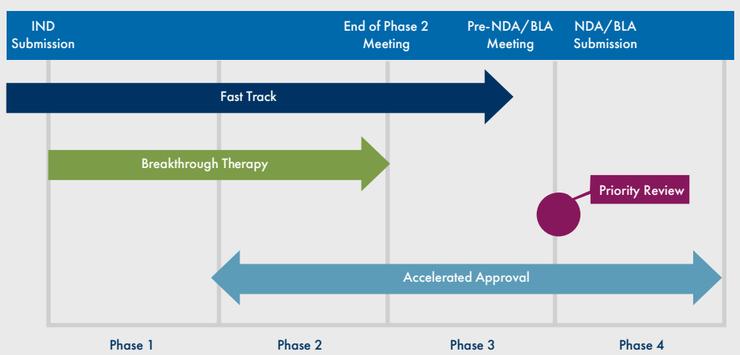
Overview of Expedited Programmes: An FDA Perspective

Introduction

Speeding the availability of drugs that treat serious diseases is in everyone's interest, especially when the drug is a first available treatment of choice or if the drug has advantages over existing treatments. The FDA has developed 4 distinct and successful approaches to make such drugs available as rapidly as possible. A process of FDA expedited programs are shown in Figure 1.

1. Fast Track Designation
2. Breakthrough Therapy Designation
3. Accelerated Approval
4. Priority Review Designation

Figure 1
FDA Drug Approval Process



FDA has a history of applying the philosophy underlying 21 CFR, Part 11, subpart E (accelerated approval of biological products for serious or life-threatening illnesses) to drugs for rare diseases through use of the Agency's expedited programs. FDA recognizes that certain aspects of drug development that are feasible for common diseases may not be feasible for rare diseases and that development challenges are often greater with increasing rarity of the disease. FDA will continue to apply flexibility in these situations to address challenges posed by each disease. Expedited programs are described below:

Fast Track Designation

Fast track designation is a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and to fulfil an unmet medical need. The purpose is to get essential new drugs to the needy patient at the earliest.

Determining whether a condition is serious is a matter of judgment, but generally is based on whether the drug will have an impact on factors such as survival, day-to-day functioning, or the likelihood that the condition, if left untreated, will progress from a less severe condition to a more serious one. Acquired immune deficiency syndrome (AIDS), Alzheimer's disease, heart failure and cancer are obvious examples of serious conditions. However, diseases such as epilepsy, depression and diabetes are also considered to be serious conditions.

An unmet medical need is a condition whose treatment or diagnosis is not addressed adequately by available therapy. Unmet medical need includes but not limited to:

- Where there is no available therapy;
- Where there is available therapy: When available therapy exists for a condition, a new treatment generally would be considered to address an unmet medical need, if the treatment:
  - › has an effect on a serious outcome that is not known to be influenced by available therapy
  - › shows an improved effect on a serious outcome
  - › has an effect on serious outcome in patients who are unable to tolerate or fail to respond to available therapy
  - › can be used effectively with other agents, where available therapy cannot be combined with other therapy
  - › provides comparable efficacy to available therapy by avoiding serious side effects
  - › has comparable safety and efficacy to available therapy but has a documented benefit
  - › addresses an emerging or anticipated public health need, such as a drug shortage
- Where the only available therapy was approved under accelerated approval and clinical benefit has not been verified post-approval

Benefits

Fast track designation must be requested by the Sponsor, it can be initiated at pre-IND, end of phase 1/end of phase 2 meetings during the drug development process. FDA will review the request and make a decision within 60 days based on whether the drug fulfills an unmet medical need in a serious condition. Once a drug receives Fast track designation, early and frequent communication between the FDA and Sponsor is encouraged throughout the entire drug development and review process. The frequency of communication assures that questions and issues are resolved quickly, often leading to earlier drug approval and access to patients. A drug that receives fast track designation is eligible for some or all of the following:

- More frequent meetings with FDA to discuss the drug's development plan and ensure collection of appropriate data needed to support drug approval
- More frequent written communication from FDA (i.e., the design of the proposed clinical trials and use of biomarkers)
- Eligibility for Accelerated Approval and Priority Review, if relevant criteria are met
- Rolling Review, Sponsor can submit completed sections of its Biologic License Application (BLA) or New Drug Application (NDA) for review by FDA, rather than waiting until every section of the NDA is completed before the entire application can be reviewed. BLA or NDA review usually does not begin until the Sponsor has submitted the entire application to the FDA

Breakthrough Therapy Designation

Breakthrough therapy designation is a process designed to expedite the development and review of drugs that are intended to treat a serious condition or life-threatening disease and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s). To determine whether the improvement over available therapy is substantial is a matter of judgment and depends on both the magnitude of the treatment effect, (which could include duration of the effect), and the importance of the observed clinical outcome. In general, the preliminary clinical evidence should show a clear advantage over available therapy. Breakthrough therapy designation applies to the drug (either alone or in combination with other drugs) and the specific use for which it is being studied. The term drug refers to the combination of two or more drugs, if the combination is the subject of the breakthrough therapy designation or

request. When appropriate, FDA may grant designation to the development of a new use of an approved drug.

For purposes of breakthrough therapy designation, clinically significant endpoint generally refers to an endpoint that measures an effect on irreversible morbidity or mortality (IMM) or on symptoms that represent serious consequences of the disease. A clinically significant endpoint can also refer to findings that suggest an effect on IMM or serious symptoms, including:

- An effect on an established surrogate endpoint that typically would be used to support traditional approval
- An effect on a surrogate endpoint or intermediate clinical endpoint considered reasonably likely to predict a clinical benefit (i.e., the accelerated approval standard)
- In rare cases, an effect on a pharmacodynamic (PD) biomarker(s) that does not meet criteria for an acceptable surrogate endpoint, but strongly suggests the potential for a clinically meaningful effect on the underlying disease (in such cases a sponsor should provide evidence supporting the use of the PD biomarker) i.e., the extent of understanding of the disease pathophysiology, the time course of the drug's effect on the biomarker, and whether the biomarker is on a causal pathway of the disease process
- A significantly improved safety profile compared to available therapy (i.e., less dose-limiting toxicity for an oncology agent), with evidence of similar efficacy

Benefits

Breakthrough therapy designation is requested by the Sponsor. If a sponsor has not requested breakthrough therapy designation, FDA may suggest the sponsor to consider submitting a request if the Agency thinks the drug development program may meet the criteria for breakthrough therapy designation after reviewing submitted data and information. The remaining drug development program can benefit from the designation.

Ideally, a breakthrough therapy designation request should be received by FDA no later than the end-of-Phase-2 meetings if any of the features of the designation are to be obtained. Because the primary intent of breakthrough therapy designation is to develop evidence needed to support approval as efficiently as possible, FDA anticipates that Breakthrough Therapy designation requests will rarely be made after the submission of an original BLA or NDA or a supplement. FDA will respond to Breakthrough Therapy designation requests within 60 days of receipt of the request.

Breakthrough therapy designation approaches may be especially useful in studies related to rare diseases. For example, single-arm trials may be an important option in rare diseases with well-understood pathophysiology and a well-defined disease course.

Accelerated Approval

The accelerated approval provisions of Food and Drug Administration Safety and Innovation Act (FDASIA) in section 506(c) of the FD&C Act provide that FDA may grant accelerated approval to: a product for a serious or life-threatening disease or condition-upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than IMM, that is reasonably likely to predict an effect on IMM or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. For drugs granted accelerated approval, post marketing confirmatory trials are required to verify and describe the anticipated effect on IMM or other clinical benefit.

The accelerated approval pathway has been used primarily in settings in which the disease course is long, and an extended period of time would be required to measure the intended clinical benefit of a drug. For example, accelerated approval has been used extensively in the approval of drugs to treat a variety of cancers and AIDS where an effect on tumor growth or viral load can be assessed rapidly, but demonstrating an effect on survival or morbidity generally requires lengthy and sometimes large trials because of the duration of the typical disease course.

For purposes of accelerated approval, a surrogate endpoint is a marker - a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit. Likewise, an intermediate clinical endpoint is a measure of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on IMM.

Using surrogate or intermediate clinical endpoints can save valuable time in the drug approval process. For example, instead of having to wait to learn if a drug actually extends survival for cancer patients, the FDA may approve a drug based on evidence that the drug shrinks tumors, because tumor shrinkage is considered reasonably likely to predict a real clinical benefit. In this example, an approval based upon tumor shrinkage can occur far sooner than waiting to learn whether patients actually lived longer. The Sponsor will still need to conduct studies to confirm that tumor shrinkage actually predicts that patients will live longer.

Where confirmatory trials did not verify clinical benefit, FDA will generally terminate the requirement. Approval of a drug may be withdrawn, or the approved indication of the drug changed, if trials fail to verify clinical benefit or do not demonstrate sufficient clinical benefit to justify the risks associated with the drug.

Priority Review Designation

Prior to approval, each drug intended for marketing in the United States must go through a detailed FDA review process. In 1992, under the Prescription Drug User Fee Act (PDUFA), FDA agreed to specific goals for improving the drug review time and created a two-tiered system of review times – Standard Review and Priority Review. A Priority Review designation means FDA's goal is to act on marketing application within 6 months (vs 10 months for standard review). A Priority Review designation is intended to direct overall attention and resources to the evaluation of applications for drugs that treat serious conditions and FDA determines at the time of NDA, BLA, or efficacy supplement filing whether the proposed drug would be a significant improvement in the safety or effectiveness of the treatment, prevention or diagnosis of a serious condition(s) when compared to standard applications. Significant improvement may be demonstrated by the following examples:

- Evidence of increased effectiveness in treatment, prevention, or diagnosis of condition;
- Elimination or substantial reduction of a treatment-limiting adverse reaction;
- Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes; or
- Evidence of safety and effectiveness in a new subpopulation.

FDA decides on the review designation for every application. However, an applicant may expressly request priority review as described in the Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics. Priority review designation does not affect the length of the clinical trial period. FDA informs the applicant of a Priority Review designation within 60 days of the receipt of the original BLA, NDA, or efficacy supplement. Designation of a drug as "Priority" does not alter the scientific/medical standard for approval or the quality of evidence necessary. A comparison of FDA expedited programs is presented in Table 1.

Table 1 - Comparison of FDA Expedited Programmes

Type of FDA Program	Fast Track Designation	Breakthrough Therapy Designation	Accelerated Approval Pathway	Priority Review Designation
Definition	Fast Track is a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and to fulfil an unmet medical need.	A process designed to expedite the development and review of drugs which may demonstrate substantial improvement over available therapy.	The FDA initiated this program in 1992 to allow faster approval of drugs for serious conditions that fill an unmet medical need. The faster approval relies on use of clinical/surrogate endpoints.	A Priority Review designation means FDA's goal is to take action on an application within 6 months.
Reference	Section 506(b) of the FD&C Act, as added by section 112 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) and amended by section 901 of the FDASIA of 2012	Section 506(a) of the FD&C Act, as added by section 902 of FDASIA (2012)	• 21 CFR part 314, subpart H • 21 CFR part 601, subpart E • Section 506(c) of the FD&C Act, as amended by section 901 of FDASIA (2012)	Prescription Drug User Fee Act (PDUFA) of 1992

Type of FDA Program	Fast Track Designation	Breakthrough Therapy Designation	Accelerated Approval Pathway	Priority Review Designation
Qualifying criteria	• A drug that is intended to treat a serious condition AND nonclinical or clinical data demonstrate the potential to address unmet medical need OR • A drug that has been designated as a qualified infectious disease product[1]	• A drug that is intended to treat a serious condition • AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies	A drug that treats a serious condition AND generally, provides a meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (ie., an intermediate clinical endpoint)	• An application (original or efficacy supplement) for a drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness OR • Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505A[2] OR • An application for a drug that has been designated as a qualified infectious disease product[3] OR • Any application or supplement for a drug submitted with a priority review voucher[4]
When to submit request	• With IND or after • Ideally, no later than the pre-BLA or pre-NDA meeting	• With IND or after • Ideally, no later than the end-of-Phase 2 meeting	The sponsor should ordinarily discuss the possibility of accelerated approval with the review division during development, supporting, for example, the use of the planned endpoint as a basis for approval and discussing the confirmatory trials, which should usually be already underway at the time of approval	With original BLA, NDA, or efficacy supplement
Timelines for FDA response	Within 60 calendar days of receipt of the request	Within 60 calendar days of receipt of the request	Not specified	Within 60 calendar days of receipt of the request of original BLA, NDA, or efficacy supplement
Features	• Actions to expedite development and review • Rolling review	• Intensive guidance on efficient drug development • Organizational commitment • Rolling review	• Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably • Other actions to expedite review likely to predict a drug's clinical benefit	Shorter clock for review of marketing application (6 months compared with the 10-month standard review)[5]
Additional considerations	Designation may be rescinded if it no longer meets the qualifying criteria for fast track[6]	Designation may be rescinded if it no longer meets the qualifying criteria for breakthrough therapy[7]	• Promotional materials • Confirmatory trials to verify and describe the anticipated effect on IMM or other clinical benefit • Subject to expedited withdrawal	Designation will be assigned at the time of original BLA, NDA, or efficacy supplement filing

Abbreviations: BLA = Biologic License Application; FDA = Food and Drug Administration; FDAMA = Food and Drug Administration Modernization Act; FDASIA = Food and Drug Administration Safety and Innovation Act; FDCA = Federal Food, Drug, and Cosmetic Act; IMM = Irreversible morbidity or mortality; IND = Investigational New Drug Application; NDA = New Drug Application; PDUFA = Prescription Drug User Fee Act.

[1] Title VIII of FDASIA, Generating Antibiotic Incentives Now (GAIN), provides incentives for the development of antibacterial and antifungal drugs for human use intended to treat serious and life-threatening infections. Under GAIN, a drug may be designated as a qualified infectious disease product (QIDP) if it meets the criteria outlined in the statute. A drug that receives QIDP designation is eligible under the statute for fast track designation and priority review.

[2] Any supplement to an application under section 505 of the FD&C Act that proposes a labeling change pursuant to a report on a pediatric study under this section shall be considered a priority review supplement per section 505A of the FD&C Act as amended by section 5(b) of the Best Pharmaceuticals for Children Act.

[3] See foot note (1) above.

[4]Any application or supplement that is submitted with a priority review voucher will be assigned a priority review. Priority review vouchers will be granted to applicants of applications for drugs for the treatment or prevention of certain tropical diseases, as defined in section 524(a)(3) and (a)(4) of the FD&C Act and for treatment of rare pediatric diseases as defined in section 529(a)(3) of the FD&C Act.

[5]As part of its commitments in PDUFA V, FDA has established a review model, the Program. The Program applies to all new molecular entity NDAs and original BLAs, including applications that are resubmitted following a Refuse-to-File action, received from October 1, 2012, through September 30, 2017. For applications filed by FDA under the Program, the PDUFA review clock will begin at the conclusion of the 60-calendar day filing review period that begins on the date of FDA receipt of the original submission.

[6]A sponsor may also withdraw fast track designation if the designation is no longer supported by emerging data or the drug development program is no longer being pursued.

[7]A sponsor may also withdraw breakthrough therapy designation if the designation is no longer supported by emerging data or the drug development program is no longer being pursued.

To summarize, there is always an unmet medical need in the society and there is an effort across the world to address the unmet medical need. FDA has developed 4 distinct expedited strategies (Drug approval processes) to achieve this objective without jeopardising patient safety. Though the assurance on safety and efficacy is not comparable to that of classical pathways, the benefits from these approaches outweighs the risks in accelerating approval of drug molecules. These FDA strategies are designed for the benefit of patients and society. In addition, these strategies provide a great opportunity to the innovator to get their new pharmacophore approved in shorter time and in a much economic way. Both fast track and breakthrough designations are designed to speed up the drug development. Fast track assets can obtain a rolling review which allows the FDA to review completed sections of a New Drug Application rather than waiting until the entire application is complete for review. Breakthrough designation requires clinically significant endpoint that measures an effect on irreversible morbidity or mortality. Priority review shortens FDA review time from 10 months to 6 months. This review designation is determined at the time of a Biologics License Application, NDA, or efficacy supplement submission. Accelerated approval pathway is suitable in scenarios where the disease course is long, and an extended period would be required to measure the intended clinical benefit of a drug. Thus, these approval processes present an opportunity for drug developers and investors to take a speedier path to drug approval. These approval processes will facilitate any type of applications, specifically for the drugs used for rare diseases (orphan drugs). In-order to utilize this opportunity, an innovator should have very strong hold on the understanding of several aspects namely, etiology, disease progression, chemistry of the molecule, efficacy and safety profile, etc. along with a sound Regulatory knowledge. A well placed technical and Regulatory team can successfully take up the case and criteria for each designation and classify the drug in apt Regulatory approval pathway. In our experience, a mix of opportunities, knowledge and strategies are required to file expedited designations. It is also evident that the poor presentation of the case will fail to attain an opportunity of expedited review processes.

References are available at

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf. May 2014.

http://www.xcenda.com/Insights-Library/HTA-Quarterly-Archive-Insights-to-Bridge-Science-and-Policy/HTA-Quarterly-Fall-2016/Rapid-Access-in-the-US-UK-and-France-How-Do-the-US-Expedited-Programs-for-Serious-Conditions-Compare-to-EAMS-and-the-ATU/

Center of Excellence
Global Cosmetics Regulatory Services

REGULATIONS FOR SELLING FRAGRANCE IN THE MIDDLE EAST

As demand for fragrances in the Middle East continues to grow, Roshini Raj explores the fragrance industry's Regulatory framework across the region

Fragrances and perfumes are essential oils (made using traditional processes) and alcohol-based synthetic solutions (obtained via modern industrial processes) applied to enhance body odour. The Regulatory bodies of various countries define them based on regional understanding and their intended use. For example, the US Food and Drug Administration (USFDA) perceives fragrances that are intended to be applied to a person's body as cosmetics. In the Middle East, they are termed as only 'perfumes'. It is necessary for manufacturers to understand these regional differences before planning their market entry into a targeted region/country. Today, people perceive perfumes and fragrances as less of a status mark and more of a necessity. Increased income and spending capabilities have supported this trend and are driving product usage fervently, creating an opportunity for many internationally recognised fashion brands to claim a market share, attracting both the uber-rich and commoners alike. Destined to reach millions of lives, perfumes and fragrances are subject to stringent evaluation for safety and efficacy. Manufacturers are required to establish products' quality as per the standards laid out by domestic regulations in individual regions/countries and are responsible for carrying out post-market surveillance for any adverse reactions on the user end. The Middle East, with its huge demand for fragrance, exhibits caution to ensure consumer safety. For a manufacturer wanting to gain a market stake in the region, the onus lies in their understanding of the Regulatory frameworks and procedural challenges, and practicing compliance throughout.

> **"In the Middle East, the Regulatory focus is on product safety and a recognised risk management system."**

Across the globe, the Middle East region is among the largest consumers of fragrances and perfume products. Market growth in the region is second in the world, behind only Latin America. With a traditional inclination towards perfumes and a rapid income surge, the region offers immense potential for global manufacturers of fragrances and perfume products to tap into.

In the Middle East, the Regulatory focus is on product safety and a recognised risk management system for the safe use of fragrance ingredients to ensure there is no risk for the consumer or the environment.

These parameters are regulated by various bodies including The Fragrance Foundation Arabia and the Emirates Authority for Standardization and Metrology (ESMA). All these regulations are in line with global standards in the perfumery industry. All the fragrance products must therefore match with international standards before the product launch. Across the Middle East, different markets perceive fragrances and perfumes differently. Here we list a few:

KINGDOM OF SAUDI ARABIA (KSA)

KSA is the biggest perfume and fragrance market in the Middle East. It does not provide separate regulations for fragrances and perfumes; instead it recognises them under cosmetics and personal care products. With no specific definition for perfumes and fragrances, suppliers and importers of fragrances and perfumes in the KSA should adhere to the usual regulation applicable to cosmetics as the final rule.

> **"With a traditional inclination towards perfumes and a rapid income surge, the region offers immense potential for global manufacturers of fragrances and perfume products to tap into."**

UNITED ARAB EMIRATES (UAE)

UAE declares fragrances and perfume products to be a sub-section of cosmetics and personal care products, defining them as "any perfume or perfumery product offered for sale, such as musk, dehn al oudh, incense and other perfume types, which emits a pleasant odour so that it can be used as a perfume". ESMA is the competent authority in the UAE for regulating such products, while the Emirates Conformity Assessment Scheme (ECAS) will assist in the testing and certification for registration of conformity to compliance requirements of products manufactured and imported into the country. According to ESMA, fragrances and perfume products are divided into five categories based on the percentage of perfume in the solution. The percentages and relevant names are:

- **Concentrated perfumes** are solutions with a minimum of 20% perfume and their product compound in it
- **Perfumes or extracts** are solutions with 15-20% perfume and their product compound in it
- **Eaux de parfum** are solutions with 8-15% perfume and their product compound in it
- **Eaux de toilette** are solutions with 4-8% perfume and their product compound in it
- **Eaux de cologne** are solutions with 1-4% perfume and their product compound in it.

The supplier (as manufacturers are referred to by the UAE authority) must ensure the following safety and quality requirements to conform to Regulatory

compliance:

- The supplier must refer to the terms laid down by the International Fragrance Association (IFRA) for the presence of any prohibited, restricted and specific ingredients in the manufacturing of fragrances and perfume products
- The supplier shall test the products for safety and quality using an accredited laboratory and must provide documentation of the results
- In case the supplier observes the presence of any allergens beyond the threshold limit of 0.001%, they shall declare the same (in labeling and packaging). Labeling and packaging requirements that are consistent with the regional law must be applied by the supplier. The common requirements are:
- The supplier shall comply with packaging and labeling requirements in the Gulf Standard (UAE.GSO ISO 22715:2008)
- All information shall be visible, legible and declared in clear Arabic and English languages
- Pictures and illustrations which are inconsistent with the prevailing social customs and values in the UAE shall not be used, nor any religious phrases
- The supplier shall not claim any medical benefits for their perfumes or products
- In compliance with quality and safety standards, the supplier shall declare the observed allergens on the label

The supplier holds responsibility for providing any required additional documentation when and if required, and for maintaining all records for submission. The product supplier is granted the below depicted Emirates Quality Mark (EQM) once ESMA finds compliance with all regulations are in place. It grants conformity to products that are compliant with such standards, manufactured by organisations with an effective quality management system.

However, local municipalities such as Dubai have placed additional restraints to scrutinise companies. So, more filtering may be imminent for suppliers.

Usually, the KSA and UAE registration certificates for fragrances and perfumes are perceived as the gold standards by most of the other countries in the Middle East. Often, no additional requirements are called for other countries in the region. Even if required, the manufacturer must provide as per the regional health authority standards.

LANGUAGE FOR LABELING OR ARTWORK

The labeling requirement should comply with the regulations of the Gulf Standard Organization. With regard to GSO 1943:2016, the name of the product, its trademark, the name and address of the manufacturer or distributor, the country of origin, the content of product and the date of manufacturing, both on primary and secondary packaging, are required in English and/or Arabic.

The name of the product, usage and warning/precautions instructions and storage instructions for safe use shall be presented in both Arabic and English language on the product label. These are some of the mandatory requirements in the Middle East before the registration of perfume products.

If compliant, the product supplier is granted the Emirates Quality Mark (EQM)

To conclude, the perfumes and fragrances industry in the Middle East is constantly evolving. Currently, the UAE and Saudi Arabia are leading the fragrance markets in the GCC. Because of the rise in people's economic status, increased beauty consciousness and a rise in spending on cosmetics, many of the large and medium-sized perfume and fragrance companies are eyeing Middle East market entry. From a Regulatory perspective, it is predicted that in future there will be no trade secrecy for perfume formulas.

With great opportunities lying ahead, it would be safe to say that the perfumes and fragrances market is burgeoning and constantly growing in the region. But, before stepping into the region, manufacturers must clearly evaluate their Regulatory priorities and ensure compliance is thoroughly met with authoritative market intelligence for a smooth market entry.

> **"Usually, the KSA and UAE registration certificates for fragrances and perfumes are perceived as the gold standards by most of the other countries in the Middle East."**

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References are available at

https://www.cosmeticsbusiness.com/news/article_page/Regulations_for_selling_fragrance_in_the_Middle_East/143432

CASE STUDY

Regulatory Strategy and 510(k) Submission Services

Center of Excellence
Global Medical Device
Regulatory Services

CLIENT

Mid-Size Medical Device Company

GEOGRAPHY / LOCATION(S)

India

FUNCTION(S)

Regulatory Submission

SERVICE(S) / SOLUTION(S)

Regulatory Strategy Development and Implementation [510(k) compilation]

THERAPEUTIC AREA(S) / INDICATION(S)

Wound Dressing :Stops moderate to severe bleeding

PRODUCT(S)

Medical Device

BENEFIT HIGHLIGHTS

- Timely compilation and submission of 510(k)
- 100% quality of compliance
- Timely Regulatory strategy for guiding the product registration process
- 100% quality compliance of technical documents required for 510(k)
- Timely compilation and submission of 510(k) with minimum queries from the agency

Business Imperatives

- The client has an advanced class of wound dressing products that stops severe bleeding quickly and provides an active mechanical barrier to the wound site
- These products have various variants –Emergency, Vascular, Military and Dental
- The client had planned for product launch in the 3rd quarter of 2017 and reached out to Freyr for development of strategy and successful registration of 510(k) with the US FDA

Challenges

- The product had two prescription indication for wound healing
- Client has changed the indication in the middle of the project, which in turn led to re-work of the deliverables
- Biocompatibility testing data was not sufficient to prove substantial equivalence data between client product and predicate device
- Raw material had no GRAS number approved by the US FDA
- Vendor for sterilizer was not registered under “device establishment” requirement
- SOPs were not in-line with 510(k) submission requirements
- Packaging labels were not updated in-line with the US FDA packaging requirements

Freyr Solutions & Services

- Assisted the client for understanding the Regulatory strategy for submission of two indications together in one 510(k) as bundle-up submission
- Provided awareness on getting vendor registered and raw material supplier registered parallelly as it is important while importing the product post 510(k) clearance
- Performed in-depth gap analysis on the requirement of 510(k) submission for the US FDA against the data availability
- Based on the available information and gaps identified, aligned with the client and suggested to perform additional testing
- Regulatory templates prepared to include the Regulatory submission information related to 510(k)
- Compiled, written and reviewed all technical documents for usability in 510(k)
- Assisted client to identify gaps on present content on carton , label and IFU and updated the label in-line with guideline and in comparison to predicate device
- Listed all SOPs required as supporting for 510(k) clearance
- Created template and written missing SOPs/ updated available SOPs

Infographic

MARKET-ENTRY FOR COSMETICS IN THE EUROPE AND THE 3-STEP PROCESS

Apart from above mentioned compliance pre-requisites, manufacturers should follow a right-from-the-first-step approach to make a successful market-entry of their cosmetic products in the Europe.

WHERE SHOULD YOU START?
CONSULT AN EXPERT.

+1 908 483 7958
sales@freyrsolutions.com

A MAN WITH MANY SUCCESSFUL EQUATIONS

Sridhar Gunda
-Chartered Accountant

Excellence is walking that extra mile, whatever may come! Some does this so meticulously that none can feel the burden of walking towards achieving it. With an unquestionable commitment towards solving the organization's many monetary equations, once such persona Freyr has been working with is Sridhar Gunda – a true professional behind Freyr's many successful proposals, agreements and achievements. With due respect to his busy schedule, and after many failed endeavors to catch him even for a minute, below is what we could decode about his views on the status quo of Freyr's success and his secret code of humility.

As we spoke to him...

Hi Sridhar. At the very outset, thank you and your team for all the efforts during month end, during proposals, closures and for periodical insights on EPF/Investment best practices. We mean it.

Fundamentals are clear. Risk & reward go hand in hand. The best practice should be linked to the respective individual's self-appetite [Not by way of selecting a method of Investment].

I feel everyone must explore and find the meaning and difference of surplus money / excess money where in each Individual can easily define the "Investment best practices" for themselves.

Though not into the core functioning of the organization, Finance, as a department, has always been the backbone and frontrunner for growth. Is it due to the state of Isolation, the department works in? Or any systematic approach that drives the phenomenon? Let us learn the success formula.

I feel Finance Department is not the only core function for the organization, success formula for organization's growth is equally linked with all the functions.

Whether an individual / department / organization, everyone must look at success as a journey, not as a destination (He quotes emphasizing the need for a common goal among organization).

Being meticulous in the last minute can be exhaustive for Finance professionals. What inspires you to conform to this field and lead successfully?

It is just a coincidence that I came to this planet Earth on 01st Apr – where in compliance clock for a financial year starts for every organization in India, where in Finance professional must go through in that path.

"Gunda sir is so humble," is what we were told when inquired about you. What drives you to interact with people so humbly, irrespective of their position?

I am really unaware about this [What people see in me as being humble]. But, being humble generally leads to better communication resulting in a better work performance for both parties. So, there is no room for position.

With the tenure you have spent with Freyr and with the closures you have been tracking, we believe you are the most reliable person to speak about the growth of Freyr. Could you please let us (the new lot) know how fruitful our future is going to be with Freyr?

It is going to be very 'bright'.

From an eagle's point of view, do you see any wastage (any kind of liability i.e. holding us back) in our organization? If any, what do you suggest us to use them effectively and be cost-effective?

There is no scope for wastage, when everyone does good & stays effective about themselves and for the organization.

Be good. Never try to prove that you are good.

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

There are many – I cannot limit to one.

Could you please let us know the unknown Sridhar Gunda in a single word?

Never tried to define myself. I would request you to pass on this question to the Directors.

What's the funniest query you have received from an employee related to pay structure or any finance related aspect?

NIL

Lastly, what's your take on recent fall down of Mutual Funds? On a lighter note, when can we score the century per a litre of petrol?

Mutual funds - I always believe, we get what we think.

Petrol 100 - very soon.

If Julia Roberts can find love here, we can at least find our lost peace!

NATURE, BEAUTY AND BALI

A BLISS TO THE EYE

Do you remember the scene from Eat, Pray, Love, the green rice paddies of Ubud(Bali) on her cycle? Or the one where she visits the spiritual healer, Ketut Liyer? Or where she sat meditating right by the beach to find her inner balance? Well, ever since I watched that movie, all I wanted was to visit Bali (Indonesia) and fall in love with its intrinsic beauty just like Julia Roberts. I can recollect frames of her roaming around the roads of Bali amidst greenery, wishing, that someday I get to experience the adventure that is Bali. Recently, I got the long-awaited opportunity to visit Indonesia. Even though I was there just for four days, I fell for Bali and I fell really hard. I don't think I'd be able to forget that exhilarating experience ever. But where do I start? So, let me tell you my version of Eat, Pray, Love, with a pinch of bliss and cultural heritage.

Ah, Bali, thou natural beauty and art a bliss to the eye.

We planned our vacation in the month of June which we thought was perfect for us and experienced as expected the cool weather with occasional showers of rain. We took our flight (Thai Airways) from RGIA, Hyderabad, to Denpasar, the official airport of Bali, with a layover of four hours in Bangkok. The in-flight services of Thai Airways are exceptionally good. Their staff is really welcoming, and they have amazing food and entertainment units on board.

Denpasar Airport

Imagine your flight touches the runway and all you can see is water on both sides. Yes! That's the first sight of Bali. The runway of Denpasar international airport is right in the middle of the Bali sea and it is just mesmerizing. From the airport, we took a cab to our villa, The Flintstones, in Canggu. I know what you are thinking on "The Flintstones." A stone house with stone furniture! Well, it

was just like that! Finally, when we were done praising the

Flintstones Villa

beauty of the villa, we had hopped onto the rented bikes and went on to explore Canggu and Kuta.

Canggu and Kuta

Canggu is basically a coastal village of Bali which is majorly famous for lavish resorts, villas and black sand beaches. Roaming around Canggu made me realize the beauty that simplicity holds. The houses in Canggu are inspired by Balinese heritage and the environment is rich with greenery.

While Canggu is mirror of the Indonesian culture, Kuta is more western. It is the hap and happening place in Bali. One can also say that Kuta is a surfers' paradise. Every year, thousands of surfers from all over the world visit Bali, specially Kuta, to surf. Right from beginners to people who effortlessly punt a 360, you can spot all kind of surfers here. So, we also tried our luck at surfing, but never mind! With a pale effort, we chilled at the beach, enjoyed our sunset in peace and recharged ourselves for the next day.

All of us woke up with full energy as we had a whole day of fun planned ahead. And without wasting much time, we left for the adventure that had awaited us at Nusa Dua and Uluwatu.

Nusa Dua

Nusa Dua is located in the southern part of Bali and is highly famous for its beaches and water sports. Therefore, we decided to have some fun with water sports. We reached our destination to enjoy Flying frog, Para-sailing and Underwater walk, the three famous water sports.

It was the first time I was attempting water sports and I am so glad that I did it. I mean, it was super-duper fun! First, we tried "flying frog", where they hang you on a rubber flap in mid-air. Crazy, isn't it? There after we did para-sailing. I know we have para-sailing in India too, but the view! At Nusa Dua, you can actually see the sea in two different colors. The one where water sports are allowed is more in the shade of turquoise, but if you move your eyes further towards the horizon, the water turns to darker shade of green. The next sport was underwater walk, where you go right to the bottom of the sea and walk amidst corals and school of fishes. The experience of walking under water is absolutely surreal (Zindagi na milegi dobara feels!). It's like the current of water is whispering "Carpe diem" in your ears.

Uluwatu

After water sports, we headed to Uluwatu or Pura Luhur Uluwatu, which is considered to be an auspicious temple of Bali. It is one of the six temples among the spiritual pillars of Bali. The temple is situated 70 meters above sea level on a steep cliff. Even though only locals are allowed inside the temple, tons of tourists visit the temple just to see the splendid sunset from the cliff. Standing on the cliff, you get lost looking at the horizon and listening to sound of waves splashing at the bottom of the cliff. If that isn't the beauty of nature, then I can't describe what is it.

In spite of a short trip, we saved an entire day just for Ubud because if Julia Roberts can find love here, we can at least find our lost peace!

Ubud

Ubud is said to be the cultural capital of Bali and I couldn't agree more. Be it the houses or artefacts or temples, you can see a glimpse of Balinese culture everywhere. It is truly the soul of Bali. For us, the first halt in Ubud was at a silver ornaments showroom, Chez Monique. Bali is widely famous for its gold and silversmiths. The showroom also had a workshop where you can see how intricately the silver work is done. And as every other girl would behave, I went gaga over the collection of jewelry they had and spent more than I should've.

Our next destination was Ubud's famous coffee plantation, Teba Sari Bali Agrotourism. I don't drink coffee but the idea of experiencing the harvest of coffee intrigued me. So we went inside the farm and we came to know that the highly famous Kopi Luwak is actually made of coffee beans which comes out of civet cat! Even though my initial reaction was that of disgust, going forward I realized that the civet cat actually

feeds on the best coffee seeds and since it can't digest it, it passes it as whole. The beans are then collected, roasted and grinded. The farm offers almost 15 types of coffee and tea as samples for you to savor your favorite one and buy them. If you are a coffee person, go for Kopi Luwak and if you are a tea person, like me, go for Rosella tea (it's one of a kind!). Oh, did I mention there was a cliff swing too?

Description: Teba Sari Bali Agrotourism

After trying all the coffee and tea, we headed to the streets of Ubud. And honestly, I was stunned! There is art in every corner of Ubud. I have never seen such artefacts and sculptures anywhere else. Wherever you see there are lamps, dreamcatchers, sculptures, souvenirs, paintings, Balinese wooden artefacts, bags and what not. The place was filled with eye pleasing entities. So after all the shopping, we walked towards our next stop which were rice terraces. The rice terraces are the prized possession of Ubud. They contribute equally to the agriculture and beauty of Bali. Take a nice walk through these terraces and you'll know what I mean. Also, there are several cafes located just by these terraces where you can sip your coffee and appreciate nature at its best.

Rice Terraces

Since, we had seen enough of the nature side of Ubud, it was time to explore the artistic side of it. So, we finally decided to treat ourselves with an evening of cultural appreciation of Bali with Kecak Dance. In Bali, there isn't a single place where you cannot find the mention of "THE" famous Kecak dance. Originated around 1830s, Kecak is performed by 40+ men chanting "cak" in harmony. The Kecak dance form is a portrayal of the epic Ramayana; it's a theatrical depiction of the abduction of Sita by Ravana and how Rama saved her. They say that the dance is a form of gratitude to the Gods for their blessings on us. Being there in middle of the Balinese tradition, one thing that struck me the most was the amount of energy that the art form produces. It's huge and enthralling! It was nothing like I have ever witnessed before. At the end of it, all you feel is rejuvenated and happy. Such simple emotions that we miss out in day-to-day life.

Kecak Dance

Our flight back to Hyderabad was around noon. So instead of rushing our way through multiple sites, we decided to chill at a beach café in Denpasar. And it turned out to be one of the best moments of the trip. We sat right by the beach under the huge umbrellas. Sipped the mocktails, glancing at gushing waves. With the drizzle to its addition, in tranquility, we couldn't realize that three hours were passed by. It was like resting in our own fortress of solitude!

Denpasar Beach

Oh, Bali, you are so beautiful! You scored your name on my heart and it is going to stay forever and ever. That's what I murmured as I was about to leave Bali. Those four days were the most refreshing days of my year. And I am sure the serenity of Bali will pull me back soon to explore the places that I missed. I guess what they say about Bali is undoubtedly correct.

"Bali is more than a place. It is magical."

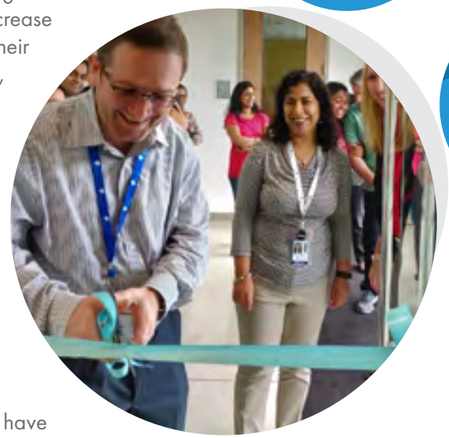
FREYR MARKS
THE NEW PHASE OF GROWTH

With New Office Set Up in Austria and Facility Expansion in the USA

To lead a step towards serving the clients better, Freyr takes all the pleasure to mark its new phase of growth with new office set up in Austria and Facility expansion in the USA.

USA Office Expansion

Reflecting the significant growth of our client base and the need to increase our pace in catering to their Regulatory requirements, Freyr's office expansion in the USA marks its commitment to both the clients and internal staff .



We are happy to share with you that on successfully completing 4 collaborative years with us, our valued client partners from Otsuka Pharmaceuticals have inaugurated the facility. Nothing could make us happier.

Austria Office

European Life Sciences market is expanding quick and fast, so do the client Regulatory requirements to enter the market. To ensure clients reach every possible destination in the Europe, Freyr opens a new business centre in Jordangasse 7/12, 1010 Vienna, Austria.

With the third business centre in the Europe, Freyr stands as a strong and leading Regulatory partner for customers to mark their success in the region.

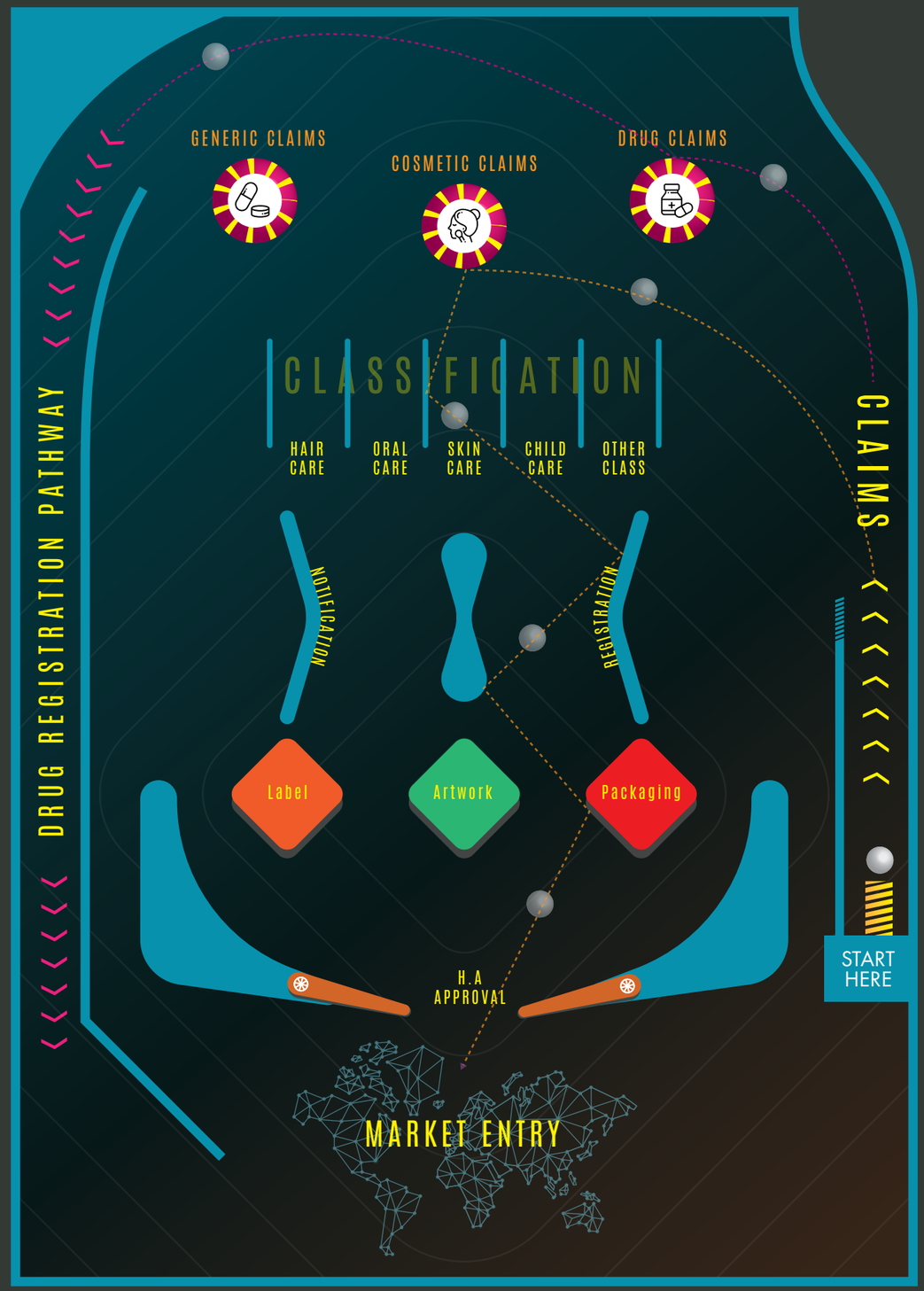
"This is really a new phase of growth at Freyr. On one side, **we are expanding locally**, and on the other side, **we are growing globally**. With these new establishments in the USA and Austria, we not only aim at offering our clients the end-to-end Regulatory services even in the most challenging situations, but we ensure our commitment in unbroken to push the boundaries for our clients' global market-entry," said Suren Dheenadayalan, CEO, Freyr.

Comic

WIN OVER THE GAME OF COMPLIANCE

With Right Classification and Pathway, Right from the First Step

Center of Excellence
Regulatory Affairs



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