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LEAD STORY

Importance of Change Control Mechanism In Tracking Safety Data

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FOREWORD

Dear Patrons,

The pleasure is all ours to bring to you another Issue of Freyr CONNECT - Volume 7, Issue 3.

Wow! What a roller coaster ride it has been for Freyr; not only for back-to-back business wins, but also for:

- **Launching Freyr LABEL 360 – a one-stop labeling solution for all labeling needs**
- **AI Global Excellence Awards 2019 - Best Labeling and Artwork Solutions and Services Provider Lifesciences**
- **GHP International Lifesciences Awards 2019 - Best Full-Service Life Science Regulatory Services Company**
- **Strategic Silver Partnership with OpenText™**
- **Commencing Global Business Operation Center in France**

As we all know, change is an inevitable aspect. When it comes to life sciences, companies must track evolving or ever-changing regulations to update the safety information being communicated to the end user. Emphasizing the need to be effective en route, we are starting this Issue with a key focus on 'The Importance of Change Control Mechanism in Tracking Down the Safety Data.'

In addition, the Issue 3 brings you a combination of insights with respect to the FDA's RTR standards for ANDA, SaMD Classification, GMP Audits, China's Evolving Regulatory Regime, and some of the Freyr's proven cases of OpenText implementation services and a comprehensive coverage of Freyr LABEL 360, a one-stop solution for all labeling needs.

With the end-to-end coverage of Regulatory scenarios of Life Sciences, we do hope that this Issue will help you strategize a right Regulatory path for better and successful global reach out.

Happy Reading!

Suren Dheenadayalan

CEO

IMPORTANCE OF CHANGE CONTROL MECHANISM IN TRACKING SAFETY DATA

The fundamental elements of a core label are its safety and efficacy data. When a product gains momentum in the market, the volume and frequency of its variations/ supplements also increase proportionately. The post-marketing changes are highly critical as they mostly revolve around safety and non-safety updates. Marketing Authorization Holders (MAHs) are responsible for implementing these changes and submitting/notifying them to the Health Authorities (HAs), depending on the type of the change (safety or non-safety). The timelines for the submission/notification vary for both these variation types. If the MAHs miss the submission timelines, it leads to non-compliance, in which case, they are entitled to file deviations.

These challenges are quite common in the industry. However, companies face bigger challenges if they lack in maintenance and tracking of the entire workflow progression in a system. The HAs should have clarity on all the updates received by the MAHs, irrespective of their implementation. The submission timelines for the changes depend on the type of change, safety or non-safety.

As the changes keep accumulating, it is challenging for the MAH to identify the most recent change and its relation to the pending changes. Many HAs around the world are interested to know the worldwide implementation status of safety changes along with changes impacting a specific country. With the increased importance to maintain a central repository, it is essential for the MAH to reconcile worldwide label changes on a periodical basis. Without a central repository, MAHs find it challenging to perform label comparisons for each submission.

Most of the MAHs have global and local Regulatory teams to identify and monitor the change until its implementation. Maintaining a central repository would require effective collaboration and communication between global and local teams. This process, however, is not always smooth as there could be a difference in opinion between the local and global teams on implementing the proposed change(s). The process may get delayed due to such differences, leading to delay in timelines. In such a scenario, it is highly important to have a collaborative tool to maintain a record of this loop in a system which tracks all the dates, right from the time when a change is received by the MAH to the time it's implemented and submitted to the HAs. Unless this level of transparency is maintained, the HAs may not be confident on the integrity the MAH's internal documentation practices.

When Does Safety Data Go 'Unreported'?

Companies may fail to report the safety data on time if they don't have a streamlined process and a system in place, to track and monitor the data. Other factors are not limited to, but include the following:

Lack of Traceability:

With the expansion of products' safety profiles, companies tend to lose control over the data related to targeted countries, population, etc. The FDA has introduced 2D/3D barcoding, serialization, etc., to trace where the drugs reach, who they are administered to and from where they've been dispatched. Though companies are maintaining such kind of data, they lag behind accurate maintenance at all points, before and after their dispatch from warehouses.

Lack of Transparency and Clarity on the Flow of Data:

Changes could be triggered at global or regional levels or they could also be driven by the HAs. In any case, it's important to monitor the workflow progression, irrespective of the trigger point. There should be a mechanism to track the changes in a way that the key milestone dates are captured (the decision to implement, the decision to 'not' to implement, target submission dates, global and local impact assessment dates and so on). It is equally important for the companies to record the reasons put forth by the global/regional teams when a proposed change is rejected or partially accepted.

In addition, companies must also ensure that they have a strong 'notification system' in place to send timely alerts to the target stakeholders. Any delay in the notifications can result in missed timelines and pose further risk to overall compliance.

Here, the whole point is to have a track of data, irrespective of its flows upstream (global to regional) or downstream (regional to global). Furthermore, it is important to track the key milestones in the entire workflow and notify the target teams to ensure timely action is taken.

At present, companies find it challenging to maintain this level of transparency, which leads to less clarity in the data submitted to the HAs.

Regulatory Dependencies:

Countries with lesser or no regulations always depend on other regulated countries for their approvals. This kind of dependency could be for arbitrary reasons (Ad-hoc) or it could be procedural, as in the case of the European countries.

In such cases, the dependent countries need to follow the lead countries for planning their implementation and seeking the HA approvals.

However, if the dependent countries are not informed of approvals or rejections received by the lead countries, their submissions may get delayed and put compliance at risk. Be it an ad-hoc or a procedural dependency, it is critical to report each scenario to the dependent countries on a timely basis. Any delay in these notifications may lead to further repercussions.

In such cases, it's highly important for companies to maintain a record of all the dependent countries and ensure timely notifications are sent to them during the entire workflow.

To deal with the aforementioned challenges, it is necessary to have a comprehensive system which is robust enough to send timely notifications to the impacted countries. It is also important to ensure that the system can be integrated with Regulatory Information Management Systems (RIMS) to identify the impacted countries (distribution) and the dependent countries (in case of Regulatory/procedural dependencies). It should be competent enough to track granular details of all the proposed changes, apart from the key milestones.

Freyr LABEL 360 is one such comprehensive, technology-enabled, single-stop labeling solution. It offers robust change management and implementation tracking across modules and meticulously documents every aspect of every change. It not only supports and stores all the documents related to different modules in the form of versions for future reference but also ensures that they are easily accessible to all the stakeholders, helping the companies to leverage them for compliance validation.

BRINGING YOU, A ONE-STOP LABELING SOLUTION

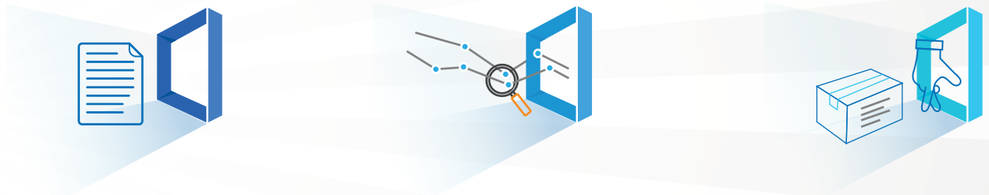
For Comprehensive, and Real-time Content to Carton Traceability

Change is inevitable. If it is in relation to the drug safety data, it should be informed across the channels in real-time for the best of compliance practices and patient safety. To ensure organizations keep track of such safety data and label changes in real-time, **Freyr is delighted to introduce...**

Freyr LABEL360

...a one-stop labeling solution for all the labeling needs

As a comprehensive labeling solution, Freyr LABEL 360 is equipped to address all the cornerstones of a label life cycle right from content to carton such as:



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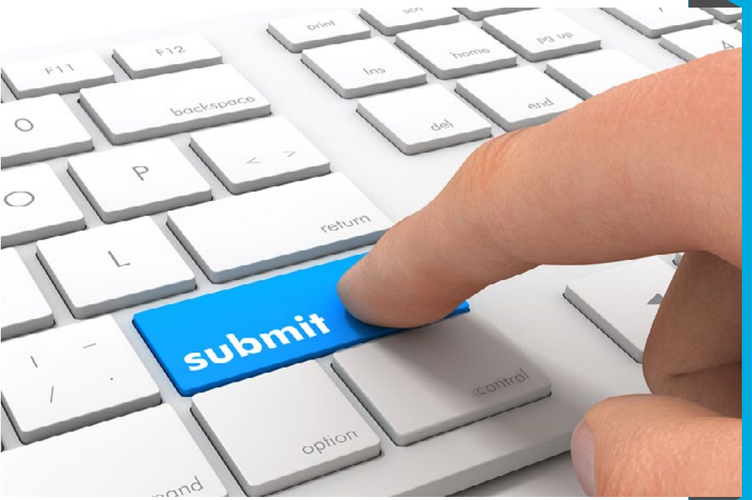
DECODING FDA'S REFUSE TO RECEIVE (RTR) STANDARDS FOR ANDA SUBMISSIONS



Generic drugs are a crucial part of the U.S. healthcare system, making upto 90 percent of all drug prescriptions dispensed in the country. These medicines have saved patients a tremendous amount of money and have paved a path toward more affordable healthcare.

As part of its agenda to speed accessibility of high-quality generic drugs, the United States Food & Drug Administration (USFDA) tentatively approved 190 abbreviated new drug applications (ANDAs) in the 2018 fiscal year (FY2018). Despite this progress, the approval rate for ANDA submissions is said to be lower than expected. In FY2018 alone, the FDA received a total of 1,044 ANDA applications, out of which only 10 percent received first cycle approval.

Though the FDA has laid down clear steps for ANDA submissions, applicants still struggle with the procedural challenges in preparing and submitting their applications. As such, it is important to dig deeper into the process and understand the possible reasons why the FDA may refuse to approve or even refuse to receive (RTR) an ANDA submission.

It certainly is important to be first to market when it comes to launching generic drugs, and sponsors and manufacturers are aware of how critical first-mover advantage is in the success or failure of a product. To improve the likelihood that an ANDA will get through the FDA's review cycle on the very first attempt, it is important for sponsors to submit a complete and scientifically accurate ANDA — issuance of an RTR determination will only add financial burden, delay in market-entry, and increase in market competition. This article will explain the reasons why the FDA issues RTRs and how best can a sponsor prepare an ANDA for success.

An Introduction To Refuse To Receive (RTR)

Put simply, RTRs which apply both to ANDAs and to prior approval supplements (PASs) to ANDAs (required when making a major manufacturing or other change to a previously approved ANDA) indicate that FDA does not consider the submitted information to be substantially complete. When an ANDA is submitted to the FDA, the agency evaluates each application to ensure that it is complete and contains all the required information as per the section 505 (j) (2) (A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and doesn't contain any deficiency as described in 21 CFR 314.101 (a) and (e).

An FDA reviewer can determine that the application is not complete and ready for review, and thus refuse to receive it, based on:

- Inadequate stability data
- Incomplete response to screening deficiency
- Inadequate dissolution data
- Qualitative (Q1) and quantitative (Q2) dissimilarity from the innovator drug
- Response to screening deficiency delayed beyond the prescribed time limit

There are two milestones in the ANDA submission when the agency decides the necessary action to be taken by the applicant with respect to RTR:

- The submission of an application to FDA
- FDA accepting the submission and initiating the application review

Both stages are governed by their respective rules (like stability duration, justification for impurities, missing application form for initial submission, and not responding within 7 calendar days/not fulfilling the FDA requirements during screening deficiency), and applicants must clearly understand the acceptance criteria. If it is ignored, it may lead to application rejection.

The table below shows the number of ANDAs submitted and the number of those the FDA refused to review from FY 2016 through FY 2018.

RTR Scenarios: Major And Minor Deficiencies

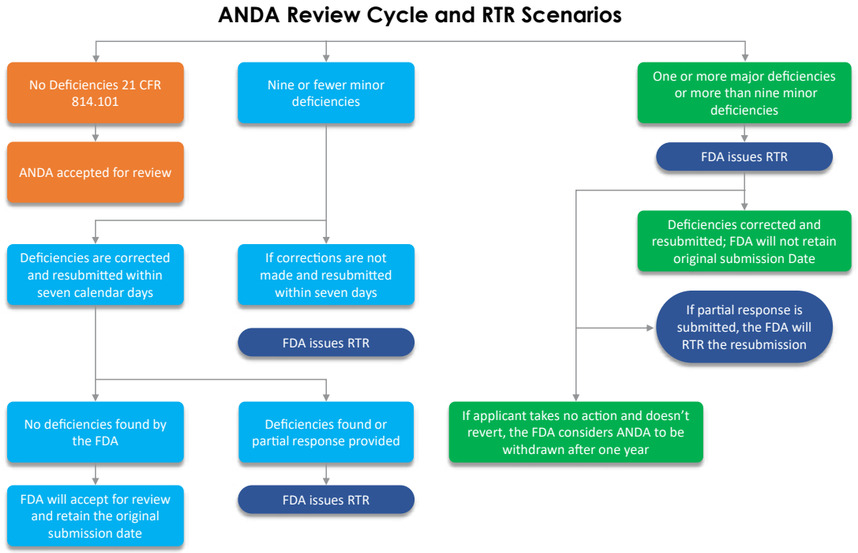
When an ANDA is submitted for review, the FDA will determine if the application is complete from a high-level view. The FDA will check for any missing details, highlight deficiencies (both major and minor), and mark if any corrections are necessary. To ensure an application is correctly completed and filed, it is important to understand the differences between major and minor deficiencies.

- **A major deficiency** is one that the FDA considers "significant" in nature, such as some found in 21 CFR 314.101 (d) and 314.101 (e). If a major deficiency is identified, FDA will RTR the ANDA.
- **A minor deficiency** is one that the agency considers less critical in nature and can be remedied easily. If the ANDA contains fewer than 10 minor deficiencies, the FDA will notify the applicant via phone, fax, or email and give them seven calendar days to correct these deficiencies or amend the ANDA. If the deficiencies aren't corrected within seven days or additional deficiencies are found, the agency will issue an RTR.

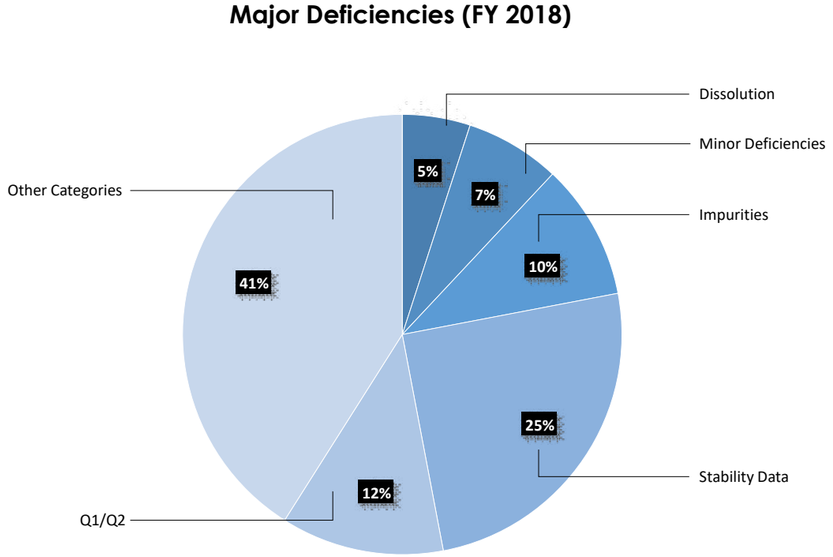
ANDAs Submitted vs RTRs Issued by FDA Fiscal Year

	FY 2016 (Oct.2015-Sept.2016)	FY 2017 (Oct.2016-Sept.2017)	FY 2018 (Oct.2017-Sept.2018)
ANDAs Submitted	852	1306	1044
ANDAs Received RTRs	246	142	127

The figure below shows the FDA's process for reviewing ANDAs and issuing RTRs, depending on the number and type of deficiencies found.



The pie chart below depicts the distribution of major deficiencies by type in FY 2018:



Deficiencies In Abbreviated New Drug Application

This section provides an example of deficiencies, organized by module of the Common Technical Document (CTD), that could lead to an RTR.

MODULE 1

Minor Deficiencies:

- Incomplete Form FDA 356h, such as:
  - Field 11: Full chemical name not provided
  - Field 20: Patent certification is inconsistent with the patent certification provided in Module 1.3.5.2
  - Field 28: Establishment information does not match with the facilities information provided in Modules 3.2.S and 3.2.P
  - Field 29: Typo in drug master file (DMF) number or failure to list all the DMFs referenced in module
- Basis for submission 21 CFR §314.94(a)(3)
  - Failing to provide the appropriate basis of submission — designated reference listed drug (RLD) and reference standard (RS; if applicable) currently listed in the Orange Book
  - If an ANDA suitability petition is required, failure to provide the docket number or FDA's correspondence approving the petition
- Labeling (Module 1.14)
  - eCTD: Legibility of draft and RLD container labels
  - Failing to provide the proposed container and carton labels for each strength and each packaging configuration (container size)
  - Failing to provide the RLD container and carton label for each strength

Major Deficiencies:

- Unsigned Form FDA 356h
- Failure to submit Form FDA 356h

MODULE 2

Minor Deficiencies:

- Provide separate PDF and Word documents
- Missing summary data tables in module 2.7
- Failure to provide the certificate of analysis for each strength of the RLD
- Failure to provide the exact location of the long-term storage stability (LTSS) study reports and data (Table 10), along with working hyperlinks to respective information

Major Deficiencies:

- Inadequate dissolution studies, lacking:
  - Minimum of 12 units
  - Use of FDA-recommended test media
  - ½ tablet dissolution for modified-release products with functional score marks
- General deficiencies of in-vitro dissolution (Table 5)
  - Not conducted on 12 units
  - Not conducted on all strengths (test vs. RLD)
  - Not conducted in all test media

MODULE 3

Minor Deficiencies:

- Lack of legibility in documents/data
- Failure to translate non-English content into the English language
- Failure to follow the ANDA checklist
- Missing batch reconciliation and label reconciliation information
  - Executed batch reconciliation tables don't include theoretical, actual, and packaged yield
  - Yield is not expressed in dosage or product units (e.g., number of tablets and bottles, number of vials, etc.)
- Potential impurities not listed in tabular format as per FDA recommendation

Major Deficiencies:

- Failure to demonstrate Q1/Q2 sameness for sterile drug products, ophthalmic, and otic solutions to the RLD
- Lack of justification for unknown/unspecified impurities
- Not providing method validation/verification reports
- Inconsistent functional scoring configuration with RLD
- Lack of compliance with inactive ingredient database (IID) limits for excipients for solid orals/parenterals/

ophthalmics/otics/topical drug products

- Lack of justification (supporting data and information) for impurities (specified identified or specified unidentified) where proposed acceptance criteria (AC) percentage exceeds qualification threshold (QT) or identification threshold (IT), respectively
- Proposed AC percentage exceeds QT or IT percentage, as applicable
- Failure to provide stability data on two discrete API lots for each strength of drug product, and on a minimum of three drug product batches of each strength
- Failure to provide six months (180 days) of stability data with a minimum three time points
- Accelerated and long-term stability studies
- Intermediate studies for all three batches of the specific strength if accelerated stability study shows significant change or failure of any attribute
- Failure to submit worst-case scenario and non-worst-case stability data related to container orientation
- Lack of verification for all stability start and pull dates

Consequences of an RTR

When the FDA issues an RTR, it is communicating to the sponsor that their ANDA has effectively not been "received," and it returns 75 percent of ANDA fee already paid by the applicant. As the result of an RTR, sponsors face the following ramifications:

- Loss of 25 percent of the ANDA fee
- Loss of original submission date
- Loss of market exclusivity period (180 days) in the case of NCE-1 submissions
- Delay in product launch

If the applicant submits required information and material to correct the deficiencies, the FDA is all open to consider (if found substantially complete) the new and corrected version of ANDA. Upon such new submission, however, the applicant needs to pay the total ANDA submission fee, accordingly. The date of the revised submission will be considered as the new application date.

The applicant can request the FDA for a reconsideration, if the applicant disagrees with the major deficiencies identified and notified by the agency. Then the ANDA applicant can provide the relevant supporting information and material to the FDA and request for reconsideration. If the FDA does not agree even after submission of the supporting information, the applicant can request for a teleconference with the Agency for further evaluations. If the reconsideration issue remains unsolved, the applicant should refer to 21 CFR 314.103 and guidance for industry Formal Dispute Resolution.

Conclusion

There have been several guidance documents issued by the FDA elaborating on the requirements for ANDA filing suitability. In addition, the FDA has published Q&A documents answering questions they have received from industry on these topics. In this current environment of information accessibility, an RTR for an ANDA can be easily avoided. However, it is important for product development, quality, and Regulatory professionals to understand every aspect of the FDA's guidance related to their product and generate necessary data for a high quality ANDA submission for successful and quick review and approvals.

References

- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/anda-submissions-content-and-format-abbreviated-new-drug-applications
- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/anda-submissions-refuse-receive-standards-rev2
- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/anda-submissions-refuse-receive-lack-justification-impurity-limits
- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/andas-stability-testing-drug-substances-and-products-questions-and-answers
- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/controlled-correspondence-related-generic-drug-development
- https://www.fda.gov/media/107325/download
- https://www.fda.gov/media/107637/download

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References are available at

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SOFTWARE AS MEDICAL DEVICE (SaMD) THE CLASSIFICATION AND REGULATORY APPROACH

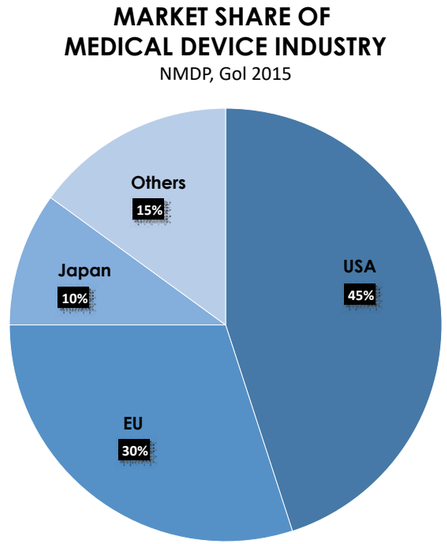
Technological advancement has created novel ways of diagnosing illnesses. 3D printing brought down prices for prosthetics, implants, and surgical training. On the other hand, Machine Learning and Artificial Intelligence revolutionized diagnostic methods to make them cheaper and more accurate.

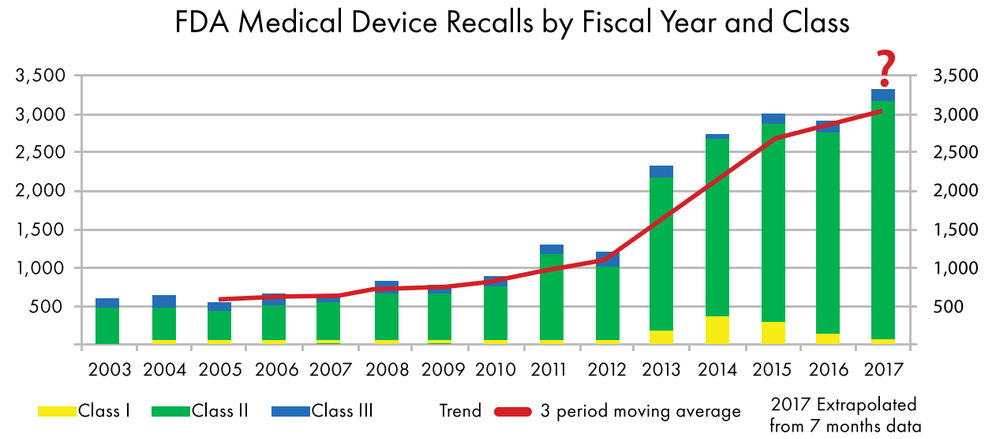
Software-based diagnostic equipment is as the best and most qualified specialist and is improving itself continuously. Software-based medical equipment is expected to outperform the best of human-beings both for patient care as well as diagnosis and treatment.

It is not surprising therefore that (SaMD) has seen a tremendous rise in adoption and development. The global market for SaMD is expected to reach an estimated $342.9 billion by 2021. It is expected to grow beyond the developed markets like the U.S., the EU and Japan. The following chart shows the market share in various regions in 2017:

SaMD and the Need for Regulations

From a Regulatory perspective, guaranteeing safety associated with SaMDs is becoming increasingly challenging for device manufacturers. The following graph shows recalls of medical devices in the U.S. alone. At least 80 percent of these are estimated to be software-based devices.





SaMD and the Need for Regulations

From a Regulatory perspective, guaranteeing safety associated with SaMDs is becoming increasingly challenging for device manufacturers. The following graph shows recalls of medical devices in the U.S. alone. At least 80 percent of these are estimated to be software-based devices.

As seen from the graph above, approximately 2600 medical devices were recalled from 2010 to 2014 in the U.S. and the graph keep moving upwards. To understand the Regulatory space for SaMD, it is important to understand its recent history. It started in late 1990s and early 2000s. Most Class II and Class III devices were integrated with in-built software. As software became robust, its role in medical devices became more prevalent. By late 2000s, software started playing an important role in medical devices and was being used to treat and diagnose underlying pathologies. This shift in increased use of software brought with it the risks associated with automation and clinical decision making and started attracting the eyes of global health authorities(HAs).

Landscape

As the SaMD market acceptability is increased, the FDA and other HAs needed to bring in some regulations. In 2013, the International Medical Device Regulators Forum (IMDRF), a voluntary group of global medical device regulators came together to define and standardize regulation of SaMD. The Software as a Medical Device Working Group (SaMD WG) is an outcome of their discussion. The key function of this group is to develop, guide, and support innovation and to ensure timely access of safe and effective SaMDs. The working group collaborated and defined a framework for classification, and the clinical evaluation of SaMDs.

However, the rapid advancement of software often surpassed WG's definitions and classifications. Some latest tools or technologies didn't fit into any of the quantified definitions, making it difficult to regulate these devices. This is something that HAs still trying to overcome.

Software as Medical Device - Current Trends

The primary challenge in regulating SaMD is that the range of devices has gone beyond the oversight of a medical professional. Wearable devices that monitor daily health of a person is an excellent example of this. Without proper medical supervision, most buyers depend on the device to know their health status. In such cases, it is necessary that these devices are correct and do not cause any risk to the wearer and must alert them on time, so that they can get immediate help.

As software devices get more accurate, the areas of their application have been increased. 2017 alone has seen a number of innovative devices like Abbott's CardioMEMS™ and BrainScope Company, Inc.'s BrainScope® One (The Galien Foundation, 2018). These devices monitor heart failures and brain waves to monitor sleep patterns. While these are great innovations, they needed to be regulated to ensure the public safety.

Medical Devices Classification

To appropriately declare any medical device to the HA, the manufacturer must first classify the device. A device can be classified as low, medium and high risk based on its risk, invasiveness, and the manufacturer's claims. Official definitions of risk and invasiveness are broad and can get muddled even further since SaMDs have entered the arena.

Freyr has worked on several such cutting-edge technology-based medical devices and has helped companies with necessary Regulatory assistance from device classification to market entry. Freyr is successful in assessing Regulatory requirements and executing challenging projects in record time. Freyr maintains a focus group in different verticals and regions and is ready to take up complex projects anytime.

In our recent project, we helped an established software company to enter the SaMD market for the first time. This company developed a software that addressed a niche demand for diagnosing underlying pathological conditions. The software aimed to diagnose a patient's condition with no human intervention. It would use inputs like scans and images and would interact with other established 510(K) medical devices to get the clinical decisions. This software was designed to have the competency and reliability of an experienced medical practitioner. It could make decisions at a speed that humans cannot make. The output from this system would help a seasoned practitioner make an informed decision about the treatment plan. This software was novel and could be patented, so the developers wanted to release as little information as possible.

Freyr had to decide how to approach the project with these constraints and the first thing the team did was to define the details that could be shared about this project. After a few rounds of discussions, the company agreed on releasing the following details:

- The software would use Machine Learning to read, analyze and present the data in a way that can be easily interpreted by a medical practitioner.
- The data from the software would be uploaded, analyzed in a cloud based unit or in a local stand-alone computing unit.
- In case of the data being uploaded to the cloud, the cloud-based system would have proper security, data protection and compliance for the territory in which the product is deployed.
- As a stand-alone tool, the software would only be a data storage and retrieval unit and wouldn't do any other computational tasks.
- The software itself could be deployed in multiple ways; on-premise, on-cloud or in combination of the both. In all these scenarios the technology is same.
- The cost and extent of control over the output for the medical practitioner or the end user may vary based on the type of deployment.

The challenge was that there was no history of devices of this kind in the market in the known clinical space. Nothing similar had undergone regulation or classification. The software was complex, and the tasks it was performing were sensitive enough to be posing risk to the patients. However, it was not invasive and would not pose any direct physical threat to patients. The classification of such a device was challenging.

Freyr's Approach

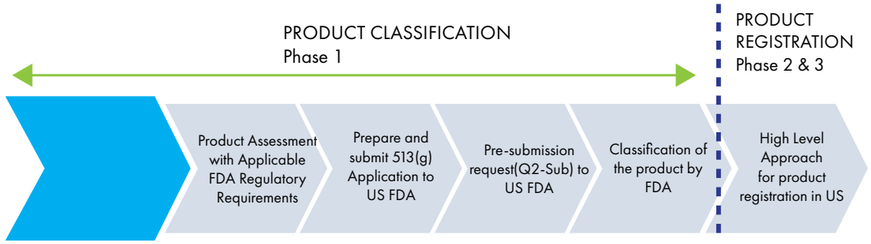
After decoding and analyzing all the aspects of the issue the team at Freyr decided 'to take a phased approach and not addressing the entire issue at one go.' The phases include:

- Product Assessment (brief) including the technical aspects
- Liaising with the authorities for the classification

In the first phase, Freyr collated product details, classified them according to the HA mandates in the U.S., and the EU. Freyr then liaised with the respective HA and to get confirmation on the classification that would be used for the software. Once this was done, Freyr began the work for the next phase to give a high-level Regulatory approach for product registration.

This paper will limit its scope to discussing Phase 1, so all details are given requisite attention.

Classification Approach for the U.S.



Step 1- Product Assessment:

FDA maintains a product classification database by using keywords that are close to your device or by looking up other devices that are like yours; a product code and the regulation number for the device can be identified. Most Class I devices are required to comply with Quality Systems Regulation (QSR) and Class II and III devices must meet the FDA's QSR.

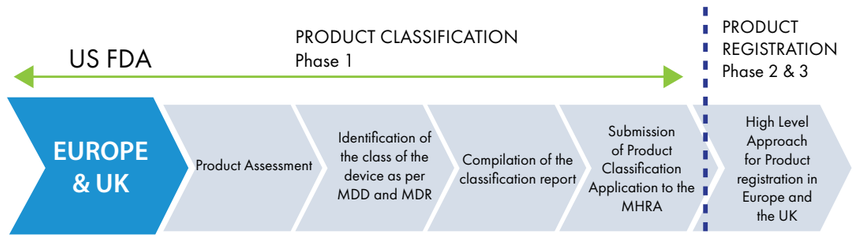
Step 2 - Submitting a 513 (g):

In case of innovative Class II and Class III devices, clinical trials are often required. The manufacturer will be required to submit a 513 (g), if there is no product code and regulation number that matches the novel device. FDA will then respond and clarify the classification applicable to the device.

Step 3 - Pre-Submission Request:

The medical device company will need to prepare a pre-submission request to the FDA. The FDA provides feedback and advice on next steps. These kind of discussion, always help in establishing accurate data to meet the FDA requirements and help in getting faster approvals.

Classification Approach for the UK and the EU



Step 1 - Product Assessment:

Europe's Medical Device Directive classifies most medical devices into four broad categories; invasive, non-invasive, active, and special rules. They are also segregated based on risks that they could pose to the patients:

- Class I – Low risk
- Class I – Low/Medium risk
- Class II a – Medium risk
- Class II b – Medium/High risk
- Class III – High risk

Step 2 - Identification of the Device Class as per MDD and MDR:

Based on the intended use and other technical details, device Class will be identified as per the Medical Device Directive (MDD) and the new Medical Device Regulation (MDR). Europe's new MDR is expected to bring significant changes to the way medical device manufacturers bring their devices into the European market, and how they prepare for compliance throughout the product's life cycle. As a medical device manufacturer, one has three years from May 25, 2017 for MDR transition. Within this timeframe, manufacturers are required to update their technical documentation and processes to meet the requirements of the new regulation.

Step 3 - Compilation of the Classification Report:

A classification report is compiled with all the relevant details that need to be submitted to the MHRA for the classification of the product. Once a manufacturer clearly defines their products' classification as per the regulations, the report should be prepared.

Step 4 - Submission of Product Classification Application to the MHRA:

MHRA reviews the product classification report submitted and provides the classification of the product. Based on the classification of the product and novelty of the device, Freyr has designed a Regulatory approach for CE certification of the product.

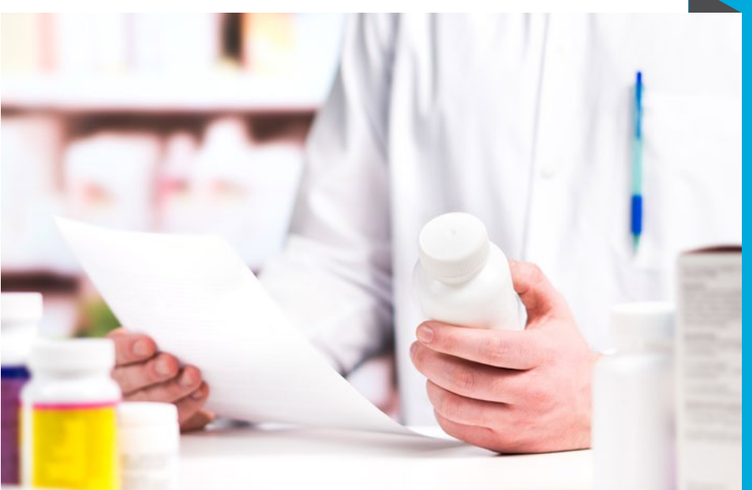
Conclusion

Fryer's team prepared a product classification report specifying the classification of the product for the countries in the scope, along with the methodology for classification as per applicable Regulatory guidelines and the high-level approach for product registration. After the submission of product classification application, Freyr provided a bird's eye view of product registration requirements and process. For more details on the process and advice on product classification from our experts, please get in touch with us at **sales@freyrsolutions.com**.

References

- FDA. (2017, December 12). Software as a Medical Device (SaMD). Retrieved January 17, 2018, from U.S. Food & Drug Administration:
- https://www.fda.gov/MedicalDevices/DigitalHealth/SoftwareasaMedicalDevice/default.htm
- Hoorn, J. &. (2017). Here Comes the Bad News: Doctor Robot Taking Over. International Journal of Social Robotics, 1-17.
- Joshua R. Dix, S. R. (2017). What's Behind Medtech's Recall Epidemic? USA: MDDIOnline.
- Lucintel. (2016). Growth Opportunities in the Global Medical Device Market by Application Type. Global: Research and Markets.
- Menlo Park Software. (2017). FDA Medical Device Recalls by FY and Class. USA: Menlo Park Software.
- Sethi. (2017). Medical Devices Regulation in USA, EU and India. Pharmaceutical Regulatory Affairs: Open Access, 1-9.
- T. Lueddemann, S. S. (2016). Experimental evaluation of a novel ISO 14971 risk management software for medical devices. SICE International Symposium on System Integration (SII). Sapporo, Japan: IEEE. doi:10.1109/SII.2016.7843992

WHAT IS A PRIVATE LABEL?



When a product is manufactured by one company but sold and distributed under the brand name of another company, it is known as a private label product. Private labels have evolved to overcome some of the challenges faced by the manufacturers such as lack of resources, monetary deficit or heavy workload. Alternatively, they are also useful when a company wants to manufacturers according to custom requirements without investing into in-house resources. In life sciences industry, these companies are called "private label distributors (PLDs)".

If a company is distributing a product under its private label, they are not required to register under the concerned health authority. But they have other responsibilities to fulfil, in case of drug products:

- PLDs are required to obtain the National Drug Code (NDC) for the drug to be distributed.
- PLDs are required to obtain labeler codes for their products. If any changes are made to the code, PLDs need to update the information immediately.
- PLD labeler codes must be used by manufacturers for listing the products.

Advantages of Using Private Labels

- **Ease of Control** – Since the manufacturing process is outsourced to a third party, it offers an end-to-end control to the private labeler over the entire process. It also provides control over the cost involved in the process.
- **High Customer Loyalty** – Successful private labels serve as a booster for greater customer loyalty and help increase the brand value as well.
- **Competitive Edge** – Private labelers are well equipped with the competitive scenario of the market which provides them an edge over other distributors.
- **Profitability** – With all the factors of production under control, the PLDs can control the level of profits managed by distributor.

Although private labels help in increasing the brand name of the product, if not done right, may lead to unforeseen contingencies. To know more about private labels and how they can help your business, reach out to us at sales@freyrsolutions.com.

CHINA AND THE EVOLVING REGULATORY LANDSCAPE

The Chinese pharmaceutical industry has been lagging behind in terms of drug development and bringing new products to the market. In this article, we discuss the changes that the National Medical Products Administration (NMPA) of China is making to existing policies and we share our perspective on guidance documents that have been released to streamline the Regulatory procedures for market access.

China has become a business powerhouse for many pharmaceutical companies. To make the Chinese market more accessible the National Medical Products Administration (NMPA) of China, formerly known as the Chinese Food and Drug Administration (CFDA), took a step forward and changed several Regulatory guidelines and frameworks. The aim was to harmonize drug development and clinical trials execution, and by joining hands with the International Council for Harmonization (ICH), they framed the Regulatory changes which came into effect in August 2015. But what made the NMPA change the regulations and what challenges were faced by organizations under previous Regulatory scenarios?

Market-entry Challenges and Remediation

China has been considered a challenging market to enter due to the following issues:

- Quality gaps between locally and internationally manufactured products
- Longer timeframes for review and approval of new drugs
- A huge number of applications awaiting approval

To address these challenges and promote structural adjustments, procedural transformations, and policy upgrading plans and to see the marketed products align with the international standards in terms of efficacy, safety, and quality, the State Council of China shared its opinions on amending and reforming the review and approval systems for drugs and medical devices in 2015. Some of its key practical aims included the following:

- Eliminating the existing backlog of registration applications
- Establishing and enhancing the quality of generic drugs
- Creating a regional framework that encourages R&D of new drugs in line with global standards
- Increasing transparency in review and approval processes

With the proposed changes and their impact on Regulatory procedures, the modifications/reforms in China have had a positive effect on drug development,

which reduced approval timelines for Investigational New Drugs (INDs) and New Drug Applications (NDAs) and also reduced delays in sanctioning drug approvals as compared to the U.S. and the EU.

Reforms that Took Place

With an aim to encourage more drug manufacturers to enter the market and expedite the drug approvals, China has restructured the Regulatory system with the following reforms:

1) Increasing the Number of Drug Reviewers

Recruiting more drug reviewers has had a significant impact within the Chinese Centre for Drug Evaluation (CDE). It has not only resulted in reducing review timelines but has also increased the number of approvals. For NDAs submitted in 2014, 2015, or early 2016, the approval time was relatively longer (between 15 to 40 months with an average review and approval time of 21.4 months). For NDAs submitted at the end of 2016 or early in 2017, the approval timeline was much shorter (between two to 10 months with an average of 6.8 months).

There has also been a comprehensive investigation of all the priority reviewed INDs and NDAs projects submitted in 2016 and 2017, and the approval timeline appears to be shorter than the previously approved applications. The reports show that it took an average of 10 months for CDE to accept the dossier and approve the INDs and NDAs submitted in 2016 and it took just 6 months for review for the INDs and NDAs submitted in 2017.

These Regulatory modifications, such as increasing the number of drug reviewers, has helped the NMPA reduce the turnaround time when compared to the US Food and Drug Administration (FDA) approvals. Prior to the modifications, time taken for approvals was 85 months and post-modifications it is just 28.3 months. The lag time for drug approvals in China when compared to the European Medicines Agency (EMA) has similarly changed, with an average lag time of 84.3 months prior to the modifications and 30.5 months post-modifications.

2) Conditional Approval Policy

For drugs and medical devices specified for serious life-threatening conditions, significant unmet medical requirements, or rare diseases where early or mid-stage clinical data can be used to anticipate clinical benefits, the NMPA planned to grant conditional approval to allow the manufacturers/sponsors to market the products quickly in China. Thus, the NMPA introduced a Conditional Approval Policy (CAP). Companies/sponsors are required to share a risk management plan regarding the development of the product and provide documentation stating that they will complete the clinical trials after the NMPA's review. For example, the Ebola vaccine was reviewed and introduced in a short timeframe by the NMPA to combat the disease after the sponsor provided sufficient proof (B/R [benefi t/risk] ratio), along with a risk management plan and documents that clearly highlighted that clinical trials were to be completed in parallel to its use.

"China has become a business powerhouse for many pharmaceutical companies"

3) New Drug Registrations From Outside of China

The NMPA also created a new policy explicitly for new drug registrations from countries outside of China in 2016. This policy opened the first-in-human Phase I trials to new drugs developed outside of China and also simplified and reduced the clinical trial and drug registration process. Hence, international sponsors can submit an NDA in China without the condition of drug approval in the U.S. or any other country.

"Due to the higher competition level in the industry of generics, we've seen a dip in the number of homegrown companies investing in innovative novel drugs"

4) Trial Data Acceptance from Outside of China

Later in 2017, the NMPA introduced a new policy recommending the acceptance of clinical trial data from trials conducted outside of China, which further supports a significant improvement in the approval process. According to the proposed draft policy, a sponsor can use certain data generated in clinical trials conducted outside of China for the drug registration process in China after the NMPA's audit. However, due to its novel nature, the potential benefit of approval timelines is still to be evaluated in the coming years.

With all the reforms that have been introduced and implemented, and with the new policies supporting deficient drug development emerging, we can clearly state that sponsors may consider including China in their global Regulatory strategy. Moreover, the concept of conditional approval and priority review of drugs with clinical trial data generated outside of China has completely changed the imported drug registration process and enhanced the potentiality of drug acceptance. On that note, sponsors should consider the developmental conditions in China along with that of the U.S. and the EU – especially during the initial stage of product development rather than at the later stage as it gives the sponsors/manufacturers scope to enter new markets with similar timelines as those in the U.S. and the EU.

"Restricted" and "Promoted" Categories of Generics

The NMPA recently issued "Restricted" and "Promoted" categories for generic drugs, which signals a passage towards more rational control, course, and supervision of the generic industry. Due to the higher competition level in the industry of generics, we've seen a dip in the number of homegrown companies investing in innovative novel drugs despite having their manufacturing facilities aligned with the regional good manufacturing practices (GMPs). However, bioequivalence (BE) trials that use conventional routes for their drug registration are now encountering risk due to the NMPA's new requirements on maintaining generic drug quality and efficacy. For example, data considered inaccurate or incomplete will not be accepted and potentially, existing licenses could be revoked. Regulatory bodies will raise concerns about a Marketing Authorisation Holder (MAH), who does not hold a license for the manufacturing plant, to reduce the chances of inadequate drugs being introduced into the market. The announcement of these activities will create a more flexible, modernized arena in which research companies can be a MAH and can reach out to CMOs as long as required.

New Class	Definition	Local Clinical Trial Requirement	Application Process
1	The new drug not marketed anywhere globally	Phase I, II, and III	New drug process
2	Modified/improved new drug not marketed anywhere globally (E.g., new formulation, new combination, new indication, etc)	Phase I, II, and III	
3	A China-manufactured generic drug that is only approved outside China	Pharmacokinetics (PK) and Phase III	Generic drug process
4	A China-manufactured generic drug that is already approved in China	Bioequivalence (BE) study	
5.1	Imported innovative drug, approved outside of China	PK and Phase III	Import drug process
5.2	Imported generic drug, approved outside of China	BE study	

Reforms and their Impact Self-inspection of Clinical Data

Due to past instances of submission of forged or incomplete clinical data, the NMPA has launched a self-inspection programme for applicants, contract research organizations (CROs) and clinical sites to self-inspect 1,622 registration applications, which are pending at the approval stage. This initiative, which began in July 2015, has disclosed inauthentic and incomplete data accompanying disapproval or investigations

for appropriate results/trial cases. The authority has also mobilized its experts to inspect selected studies that required validation in terms of data authenticity. Additionally, for future NDAs, the NMPA requires applicants to include a clinical trial self-inspection report to enable further reviews. The NMPA reported that after 12 months (as of July 2016), approximately 90 percent of the 1,622 applications have been withdrawn by the applicants or rejected.

Priority Review

The NMPA needed to set up a system to encourage local and international new drug innovations to meet unmet medical needs and to encourage overseas sponsors to plan and perform clinical development in China in parallel with the U.S., the EU, and other countries. The new priority review, introduced in February 2016, can be requested based on the following criteria:

- Innovative drugs not approved anywhere worldwide
- Innovative drugs with a plan to transfer their manufacturing site to China
- Global Clinical Trial Application (CTA) applied in China in parallel with the U.S. or the EU
- Innovative drugs for HIV/AIDS, viral hepatitis, rare disease(s), malignant tumours and paediatric indications
- Newly-launched generic drugs

In this process, the applicants are allocated reviewers and additional resources to communicate and obtain quick feedback from the health authority. Approvals in this process generally take six months. This scheme has effectively worked for applications submitted in February 2016.

"China's regional Regulatory expertise is essential in order to closely monitor the changes and to ensure accurate and timely market entry"

Additional CDE Capacity

There was an urgent need to meet the CDE's target to reduce the backlogs in drug review procedures to zero by 2018. In 2015, there were only about 70 reviewers to handle the annual load of more than 7,000 drug applications in the CDE. Following the new recruitment exercise, 600 drug reviewers were in place by the end of 2016 and the number was increased during 2017-2018.

Rationalisation of the MAH System and New Classification/Definition of New Drugs

- The MAH system ensures that drug R&D institutions can obtain and hold the marketing authorisation while taking responsibility for drug quality. Now, any R&D institution can choose an existing established drug manufacturer that also allows regular site inspection to validate the process of manufacturing. This is a major incentive for local new drug innovators in China who can now hold marketing authorisation independently, which is going to be implemented in a phased manner starting with a trial in several selected provinces. With this change, the NMPA can now guide and encourage drug researchers/institutions to focus on R&D and alleviate the need to invest in their own manufacturing plants.
- The NMPA has created a new classification – 'new to the world' – to replace the 'new to China' category. This is based on the global marketing authorization approval status and the location of the manufacturing site(s), inside or outside of China. This removes the previous definitions that were based on the specific status in China and aligns the classification more closely to other Regulatory agencies.

Generic Drug Quality and Efficacy Consistency

To improve quality and efficacy, the NMPA requested that generic drug manufacturers start drug consistency research on quality and efficacy by the end of 2018. A product list was developed by the NMPA to inform which generic drugs need this consistency evaluation. For evaluation purposes, the reference product should be the "innovator drug," or a globally recognized one. An innovator drug is the first globally marketed drug with the full data package to support its safety and efficacy. This would be the situation where a generic company has previously performed the consistency evaluation, but the comparator was not the innovator drug. Hence, the generic company must re-evaluate against the innovator drug. Comparison studies include the formulation, quality standard, crystal form, particulate size, impurities and dissolution rate, and in vivo BE studies. Many generic drug manufacturers required clarity on the requirements so, consequently, the NMPA began relevant training in August 2016.

Simplified Process

This change accelerated the submission process for approval. It has been changed from "3-submission-3-approval" to "2-submission-2-approval". Previously, new drugs developed outside of China were required to undertake the following three submissions:

- Multinational Clinical Trial (MNCT) submission to request global Phase II/III trials in China
- After the drug has been approved and the Certificate of Pharmaceutical Product (CPP) is available from the U.S. or the EU (or any other countries), it has to be submitted to the NMPA to request a clinical trial waiver (requesting exemption from the need to conduct any additional local trial)
- NDA submission to the NMPA for market approval

This new change enabled the sponsor companies to apply for NDA/MAA submissions without the need for the second submission (to request NMPA for clinical trial waiver). This simplified the undertaking and shortened the whole approval process by at least one year.

In late 2017, the NMPA published a new Regulatory change stating that they accept clinical trial data from trials conducted outside of China. However, as per the draft Regulatory policy, a company can use certain data generated in international clinical trials for the drug registration process in China only after the NMPA's audit.

Conclusion

In a nutshell, China is already on its way to modernizing its compliance approach and improving the existing Regulatory processes of drug registrations. The Chinese government has set forth new rules and regulations to streamline the entire process by reducing the delays in drug approvals right from the product development to marketing stages. These major modifications are expected to bring about a positive change in China's healthcare system and have already made a positive impact with well-defined tracking and reporting systems.

The new guidelines and their related projections are very important for manufacturers to understand before starting the clinical development and manufacturing processes. These are proven to benefit the Chinese market as compared to the setbacks experienced in previous years. Companies with headquarters outside of China are now required to become acquainted with these changes and their implications. The better these regulations are understood by global companies, the more streamlined their registration and market-entry processes will be. Finally, China's regional Regulatory expertise is essential in order to closely monitor the changes and to ensure accurate and timely market entry.

References

- www.sfda.gov.cn/WS01/CL0844/145260.html
- www.sfda.gov.cn/WS01/CL0087/134140.html
- www.sfda.gov.cn/WS01/CL0056/155020.html
- www.sfda.gov.cn/WS01/CL0056/146200.html
- www.sfda.gov.cn/WS01/CL0778/148660.html
- Taylor P. "China may Relax Trial Requirements for new Drugs, Allowing Foreign Data." 9 October 2017. https://www.fiercebiotech.com/biotech/

PHARMA 4.0
REDEFINING PRODUCT DEVELOPMENT & REGULATORY OPERATIONS

Aligning with the industry requirements has always been a priority for organizations. En route, they are heavily relying on revolutions that can help them stay ahead of the competition. One such revolution is Industry 4.0 – an amalgamation of pathbreaking technologies like Industrial Internet of Things (IIoT), Big Data, Artificial Intelligence (AI), etc. The industry 4.0 has automated and optimized companies' business processes and business models.

As industries across the world reaping the benefits of Industry 4.0 and its technologies, pharmaceutical industry, too, has taken a nimble step towards embracing and adopting the change which is commonly referred as Pharma 4.0. The move is aimed at digital transformation of two most important areas of pharmaceutical industry namely, product development and Regulatory operations.

Product Development: Using traditional approaches for manufacturing medicinal products is an arduous task. Every step must be reviewed from time-to-time and the process must always be closely monitored to ensure the safety and efficacy of medicinal products. In such cases, it is a viable idea to monitor such processes with the help of advanced tools. The entire facility can be functioned from a single interface with minimal human intervention, i.e. by virtually connecting all the equipment with Pharma 4.0 technologies such as, IoT and Cloud.

Regulatory Operations: The data collected during research, clinical trials, product development, and post-market surveillance often remains disparate. When put together, without a right means to analyze the entire data from various perspectives, the results can either be inconclusive or be ambiguous. There Pharma 4.0 comes into picture with its Big Data Analytics that implements algorithms to sum up clusters of data and to analyze it in relatively less time.

For sure, the Pharma manufacturers are willing to simplify their manufacturing processes and streamline Regulatory operations. But, do all the technologies of Industry 4.0 suit the needs of the Pharma industry? Apparently not. Only a few of them, as listed below, fit the required criteria.

- Big Data
- Smart Factory
- Internet of Things (IoT) and Cloud Computing
- Artificial Intelligence (AI)
- 3D Printing

Pharma 4.0 – Functionalities in Focus

Pharma 4.0 is here to help the medicinal product manufacturers to evolve and become more efficient and at the same time to reduce the costs. But in what way? Which part of the Regulatory operations can they be applied to? Let's look at some of their primary functions.

Drug Research and Development

Pharma companies rely heavily on innovation, and research for the drug development. Companies are slowly turning towards new revolutionary digital capabilities to reduce the time spent on R&D and boost their productivity. In such scenarios, AI-powered dashboards can help companies to keep track of the latest updates from the health authorities and comply accordingly.

As it is well-known, in the early stages of drug development, clinical data from public repositories is collected to analyze the history of proposed drugs' ingredients. With machine language and deep neural networks, and with the advanced extensions of AI, such data can be utilized to derive insights on possible effectiveness / risk / benefits of a new compound. They allow manufacturers to enhance the nature of the human study and their decision-making while optimizing their workflow. In a way, stakeholders can identify the patterns and nature of patients to develop more customer centric products and can bank upon less chances of failure and increase the cost efficiency.

Clinical Research

With a large number of resources involved in clinical research and trials, manufacturers should work upon developing statistical analyzes plans and protocols. Apart from this, there are several documents which demand ample amount of time for analysis.

With the help of AI-based tool integration, all these processes can be streamlined and expedited with minimal errors. AI-powered tools help researchers to go through research documents and extract necessary data with utmost accuracy within the time required. They can help in analyzing clinical information in real-time to ensure compliance while compiling, validating and submitting clinical trial data.

Manufacturing

Health authorities across the world are emphasizing on implementing continuous manufacturing process by applying concepts of smart factory which make the process more connected, flexible, smart, and precise. With the continuous process, manufacturers would not have a need to stop the manufacturing process in between for evaluation. This reduces the overall downtime of the process and also the human errors. This shift is helpful for manufacturers who are catering to the need of personalized medicines.

Pharma 4.0 assists manufacturers to minimize consumer risk and increase process optimization by statistically analyzing data with the help of big data. The insights drawn from the data can help manufacturers make necessary changes to the manufacturing process to achieve the desired level of product quality. It helps them to follow the manufacturing best practices.

Quality Management

The technologies of Pharma 4.0 have the capability of transforming each and every function of pharmaceutical value chain. It allows manufacturers to rely solely on results obtained from the real-time data. Digitization will help manufacturers to ensure better quality and compliance while reducing human errors.

For example, for publishing and submissions, companies have become paperless and are relying heavily on electronic records and electronic dossier submissions. With the Pharma 4.0 technologies, they are assured of data integrity maintained across the life cycle.

Pharma 4.0 – Challenges in Adoption

Though the revolution of Pharma 4.0 is set to create limitless opportunities, companies are still puzzled in its full-scale implementation because of the below challenges.

Unclear Regulations for New-age Technologies

Pharma 4.0 seems relevant and advantageous for both manufacturers and data reviewers, but there is still a vacuum in terms of regulating these technologies. While some health authorities are taking quick measures to establish the standards, others are waiting for regulated markets' reflections.

Lack of Skill Set

Pharma 4.0 requires an extensive technical skill set to carry out operations efficiently. The workforce to be deployed should possess knowledge with respect to Regulatory aspects and the technological improvements as well. As a radical improvement in the knowledge is necessary to sustain the revolution, organizations are required to build teams that are dynamic to adopt the technological transformations.

Data Integration

One of the main concerns for pharmaceutical companies is maintaining the data integrity. While many companies have started using technologies for electronic conversions and paperless submissions, some are lagging behind with the legacy technologies integrated. Without the electronic version of data sets, collating and migrating data on to virtual platforms will become a challenge for companies, which in turn will lead to difficulty in comprehensive data access and assessment.

To conclude, the pharmaceutical industry is on the verge of a radical change. Across clinical trials, manufacturing processes, technology integrations, and keeping track with ever-evolving regulations, the industry is in need of complete transformation. Having said that, the time is now to act in much more agile ways to be compliant all across.

By adopting the modern-age technologies, companies can streamline their processes, increase productivity, accelerate their Regulatory processes and reach the global markets in an expedited, cost-effective, and in a compliant way. But the question prevails. How regulated are these modern-age technologies? While some of the global health authorities are taking considerable measures to regulate the technologies of Pharma 4.0, a few of them are still considering their viability. But sooner or later, they are the future of the pharmaceutical industry. Keep abreast with regulations for the best of compliance practices.

References

- https://www.pharmout.net/pharma-4-0/
- https://www.veeva.com/eu/wp-content/uploads/2016/01/Manufacturing-Chemist-Pharma-4.0-1.pdf
- https://www.rdmag.com/article/2018/10/pharma-40-industry-40-applied-pharmaceutical-manufacturing
- https://www.pharmaceutical-technology.com/contractors/machines-labelling/dividella2/pressreleases/pharma-4-0-enabling-factory-future/
- https://www.ey.com/en_gl/life-sciences/how-medtechs-will-create-value-in-the-new-health-ecosystem
- https://www.contractpharma.com/issues/2018-03-01/view_features/automation-in-pharmaceutical-manufacturing
- https://www.tefen.com/insights/industries/Patient_Care/the_impact_of_industry_40_on_the_pharma_industry
- https://www.pharma-manufacturing.blog/shaping-pharma-4-0-concept/
- https://www.atkearney.com/documents/10192/5636407/Time+for+Pharma+to+Dive+into+Digital.pdf/e410a434-6b5c-4e20-9ed1-42359e784d92
- https://assets.kpmg/content/dam/kpmg/ch/pdf/digitalization-opportunity-compliance-matters-en.pdf
- https://www.dhc-vision.com/en/digital-transformation-in-quality-management-with-dhc-vision/
- https://www.accenture.com/us-en/insights/strategy/research-development-prescriptions
- https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/how-new-biomolecular-platforms-and-digital-technologies-are-changing-r-and-d
- https://www.saama.com/blog/3-key-big-data-challenges-that-pharma-companies-needs-to-solve-to-keep-their-competitive-edge/
- https://www.pharmamanufacturing.com/articles/2018/improving-digital-quality-in-the-pharmaceutical-industry/?start=1
- https://www.technologynetworks.com/informatics/articles/artificial-intelligence-real-solutions-how-ai-can-accelerate-drug-discovery-311063
- http://www.alliedacademies.org/articles/fourth-generation-technologies-in-pharmaceuticalsrevolutionizing-healthcare.pdf
- https://www.tcs.com/blogs/revolutionizing-pharma-clinical-research-integrated-solutions-business40-paradigm
- https://www.cbinsights.com/research/clinical-trials-ai-tech-disruption/

GOOD MANUFACTURING PRACTICE (GMP) AUDITS

Across the globe, several Medicinal Products and Medical Devices are being manufactured, every day. The manufacturers need to follow certain quality standards and guidlines without compromising on the safety and efficacy. These guidelines are recommended by global Health Authorities and commonly referred to as Good Manufacturing Practices (GMP).

Process Requirements and Compliance Best Practices

How significant are they for product manufacturing and health authority inspections? Why it is necessary to adhere to GMP best practices after the product has been approved for marketing? Let's decode.

The Audit Precursor

Despite comprehensive Regulatory processes in place for compliant manufacturing, decoding every individual practice and implementing them as per the mandate is an arduous task. It is an internal quality control team's responsibility to ensure every system in the process is duly checked for its functionality. If any corrections are noted they should be addressed at the earliest possible to keep the facility up and running. Only then can a facility be audit-ready in case of sudden Health Authority inspections. But as a manufacturer, how do you prepare for an audit? It is indeed a good practice to be ready.

Need for Audit Readiness

From a product's pre-approval to post-authorization stage, the facilities where the product is being manufactured are periodically monitored and audited to ensure that the end product's quality is not compromised and is safe for use. Without periodical audits, companies are prone to Health Authority findings, which might lead to penalties and recalls in worst cases. Thus, manufacturers must always be audit-ready.

The audit could be internal or external, depending on the intended purpose. An organization outsourcing the manufacturing of Active Pharmaceutical Ingredients (APIs) or Medical Device components or partnering with suppliers must ensure that the affiliates should also adhere to the GMP guidelines. In this case, the affiliates' GMPs must be applicable and they must be aligned with the parent company, for which an external audit is necessary. Besides product quality, periodic evaluations are also critical to keep a check on internal shortcomings. These often point out the internal deficiencies that might be hindering the productivity at a facility which in turn strongly proposes an internal audit.

Either the way, the onus lies on the parent company to correct deficiencies and choose a suitable supplier and thereby to maintain end-to-end manufacturing quality and compliance. Right from preparing SOPs to training the personnel at the facility to internal quality maintenance to compliant documentation; every aspect of the manufacturing process must be thoroughly audited and validated for compliance.

Audit Preparation

Freyr determines the audit scope and agenda based on response to self-appraisal checklist provided by the auditee. The self-appraisal checklist is a list of customized questions with respect to (but not limited to) plant size, number of employees, route of manufacture, and status of previous Regulatory inspections that is circulated 6-8 weeks before the scheduled audit date (audit schedule).

In this case, the lead auditor determines SME auditors, requirement of translators, and regional experience of the auditor, audit scope, and number of audit man days based on the information provided in the self-appraisal checklist by the auditee. Thus, response to self-appraisal checklist becomes an auditable document.

Pre-audit meetings are conducted to explain the audit scope and audit agenda where requested auditor profiles are shared. Audit agenda is a joint exercise between Freyr lead auditor and auditee as it would need information related to the auditee and venue of the audit. This approach ensures that auditee is taking complete responsibility for the availability of resources, and dates of manufacture for manufacturing lines.

- **Self-Appraisal:** In the initial stage of an audit, the auditor requests the organization to fill up a self-appraisal checklist to understand a facility's current status. The organization is expected to respond fairly as the checklist might be a trigger point for the auditor to decide the size of the team and inclusion of experts for the audit.

- **Agenda of Meeting:** Simultaneously, pre-audit meetings are held to discuss and explain the audit agenda and scope. Depending on the requirement of the parent company, the agenda may vary. Once the agenda has been finalized, the date and time of an audit are determined.

- **Scope of an Audit:** The scope of an audit includes six main areas which are cumulatively divided into 28 functional areas. A total of 700 preliminary checks are conducted in all these areas with horizontal and vertical audit approaches. This will make the auditee to be inspection-ready and provides assurance on supplier quality and GMP adherence, if the audit is performed on behalf of parent company. Some of the common areas in an audit's scope include:

AREA/ ACTIVITY / FUNCTION
I - Facilities and Equipment system
Building, Location, and Surroundings
Water System
Ancillary Areas
Utilities
Equipment
Computerized Systems
II - Quality System
Quality Manual
PQR/ APQR
Site Master File
Documentation and Records
Quality Management
Personnel
Personnel Hygiene and Gowning
Complaints and Recalls
Trend Analysis (OOT, OOS, OOC)
III - Material System
Warehouse Area
Raw Material, In-process and Finished Goods
Disposal of Waste
Vendor Management
IV- Production System
Production Area
Manufacturing Operations and Controls
Sanitation in the Manufacturing Areas
Process Validation
Reprocessing and Recoveries (For APIs)
Batch Process Records and Batch Manufacturing Records
V - Laboratory Control System
Quality Control Area
Analytical Method Validation
VI - Packaging and Labeling System
Labels and Packaging material – PMQC
Labeling Operations and Controls

Additional checkpoints such as - history and experience, previous audit reports, warning letters, if any; resource capability (Infrastructure as well as HR), capacity management, active pipeline, etc., are audited when performing the supplier evaluation on behalf of the parent company.

The process flow depicted in this paper is commonly applicable for different types of audits. However, depending on various product types, formulations, compounds, medical devices, or drug-device combinations, there might be changes in the way audits are conducted. In such cases, manufacturers must be prepared to cater to the dynamic requirements that may arise during an audit. Below mentioned are some important issues that an organization must note either during or after an audit.

- Auditor(s) can request information regarding various aspects of equipment, product, and the process for which the company shall be prepared to provide

- All processes must be duly documented and provided when and if requested

- In case of findings, the auditor(s) shall request additional information or a clarification. In such cases, information or clarification should be provided within the prescribed time failing to do so may lead to an official observation (e.g., 483 from the U.S. FDA)

- The resources who accompanies the auditor(s) shall respond only to what is asked and not extend any further communication unless necessarily required

- The company should remain completely transparent as any conceived information only leads to criticalities

- All corrections should be done within the time prescribed by the auditing committee, and any delays must be duly communicated as per the Regulatory policies

- The company must ensure that all confidential data is concealed to safeguard intellectual property

- The company should take up corrective and preventive action (CAPA) seriously in immediate response to the audits

While these are commonly observed areas to be acted upon, there could be many other requirements and preparations that make a company to be audit ready. Below are some of the testimonies that show how Freyr perceives an audit, and how it plans and stretches through its comprehensive implementation.

SAMPLE AUDIT PLAN AND IMPLEMENTATION FOR MULTI-SITE AUDIT OF MULTIPLE MANUFACTURING LINES

Sample 1 **Implementation Plan for GMP Audit of the First Manufacturing Plant**

Dosage Forms	Number of Lines
SACHET	2
TABLET	13
CAPSULE	2
STERILE	2
SUSPENSION	5
SYRUP	3
ANTI-CANCER TABLET	1

Audit Line	Description	Audit Line	Description
Audit Line 1	P***l Sachet Line	Audit Line 15	P***l Suspension Line
Audit Line 2	M***n Sachet Line	Audit Line 16	R***x Suspension Line
Audit Line 3	P***l Tablet Line	Audit Line 17	Tu***ol Syrup Line
Audit Line 4	At***in Tablet Line	Audit Line 18	Pe***n Syrup Line
Audit Line 5	Ce***u Tablet Line	Audit Line 19	Di***x Syrup Line
Audit Line 6	De***n Tablet Line	Audit Line 20	En***ir Capsule Line
Audit Line 7	Su***en Tablet Line	Audit Line 21	En***ir Suspension Line
Audit Line 8	Ta***ol Tablet Line	Audit Line 22	He***vir Tablet Line
Audit Line 9	Ga***am Tablet Line	Audit Line 23	F***a Tablet Line
Audit Line 10	R***x Capsule Line	Audit Line 24	Ci***tin Tablet Line
Audit Line 11	Kl***er Tablet Line	Audit Line 25	Le***t Tablet Line
Audit Line 12	Kl***er Suspension Line	Audit Line 26	Ata***s Tablet Line
Audit Line 13	E***x PFS Line - Sterile	Audit Line 27	Tri***s Tablet Line
Audit Line 14	P***lLine - Sterile	Audit Line 28	Tri***s Suspension Line

Audit Scope	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
QMS	LA (xxx)									
APQR										
Audit Line 1	SA 1 (F)									
Audit Line 2		SA 1 (F)								
Audit Line 3			SA 1 (F)							
Audit Line 4				SA 1 (F)						
Audit Line 5					SA 1 (F)					
Audit Line 6						SA 1 (F)				
Audit Line 7							SA 1 (F)			
Audit Line 8								SA 1 (F)		
Audit Line 9									SA 1 (F)	
Audit Line 10										SA 1 (F)
Audit Line 11			LA							
Audit Line 12				LA						
Audit Line 13					LA					
Audit Line 14						LA				
Audit Line 15							LA			
Audit Line 16								LA		
Audit Line 17									LA	
Audit Line 18										LA
Audit Line 19	SA 2 (A)									
Audit Line 20		SA 2 (A)								
Audit Line 21			SA 2 (A)							
Audit Line 22				SA 2 (A)						
Audit Line 23					SA 2 (A)					
Audit Line 24						SA 2 (A)				
Audit Line 25							SA 2 (A)			
Audit Line 26								SA 2 (A)		
Audit Line 27									SA 2 (A)	
Audit Line 28										SA 2 (A)

Sample 2 Implementation Plan for GMP Audit of the Second Manufacturing Plant

Products	Number of Lines
STERILE	1
TABLET	2
SUSPENSION	2
API	7

Audit Line	Description
Audit Line 1	P***l Infusion Line
Audit Line 2	Kl***at Tablet Line
Audit Line 3	Su***at Tablet Line
Audit Line 4	A***in Suspension Line
Audit Line 5	Su***at Suspension Line
Audit Line 6	Os***vir Line
Audit Line 7	A***ine Line
Audit Line 8	En***vir Line
Audit Line 9	En***rin Sodium Line
Audit Line 10	Te******xil Fumarate Line
Audit Line 11	Zol***c Acid Line
Audit Line 12	Pa***ol Line

Audit Scope	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
QMS	LA (YYY)					
APQR						
Audit Line 1	SA 3 (F)					
Audit Line 2		SA 3 (F)				
Audit Line 3			SA 3 (F)			
Audit Line 4				SA 3 (F)		
Audit Line 5					SA 3 (F)	
Audit Line 6						SA 3 (F)
Audit Line 7	SA 4 (A)					
Audit Line 8		SA 4 (A)				
Audit Line 9			SA 4 (A)			
Audit Line 10				SA 4 (A)		
Audit Line 11					SA 4 (A)	
Audit Line 12						SA 4 (A)

Sample 3 Logistics and Tour Plan for Multi-centric GMP Audit

Post-audit, an Executive Summary and Elaborate Report is provided within one-day to appraise the parent company on audit progression as per audit agenda and any finding that is classified as critical. An elaborate report is provided within 30 days from the date of the audit.

Freyr does not believe in giving an audit report limited to just findings without representing the right practices and findings at each process area. The findings classified as critical, major, and minor by considering potential impact and risk if not addressed by the auditee.

Critical

A deficiency which has produced or leads to a significant risk of producing either a product which is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal.

Major

A non-critical deficiency, which has produced or may produce a product, which does not comply with its marketing authorization; or which indicates a major deviation from Good Manufacturing Practice; or which indicates a major deviation from the terms of the manufacturing authorization; or which indicates a failure to carry out satisfactory procedures for release of batches or a failure of the Qualified Person to fulfil his legal duties; or a combination of several "other" deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such.

Minor

A deficiency, which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice or because there is insufficient information to classify it as a major or critical.

Appropriate, auditee approved, and blinded artifacts are collected during the audit to support the audit report and these are cross-referenced in the report at the appropriate description of facts and findings. However, the report is blinded by masking the confidential information about molecules and formulations. Thus, it creates a fine balance between confidentiality of business sensitive information but availability of information and traceability up to a batch level so that the report is taken into confidence both by the auditee as well as health authority inspectors.

Freyr would conduct a meeting with the parent company to explain the complete audit report along with relevant artifacts, address, and queries that the parent company might have. If the audit is performed on behalf of parent company, the report is submitted to parent company or their designee as decided by the parent company.

Further closure of the audit findings including CAPA plan, follow-up audits, and closure of audit is performed as per contractual scope between Freyr and the parent company.

Proven Case

First Scenario: A global, Switzerland-based leading pharmaceutical, generic, and CMO organization approached Freyr to conduct a cGMP audit at its API supplier's manufacturing facility.

The company was scheduled for a health authority inspection and audit. There were two different API suppliers and within very short timelines they had to be audited for global cGMP guidelines in addition to Swiss medic regulations. Freyr successfully audited the facilities with right-first-time approach that included:

- Pre-audit checklists that were customized and sent to API suppliers to understand facility and organization structure and determine the scope of the audit
- The audit of QMS documentation and facility were separated to prevent any delay
- Draft of the audit report was generated within one week and discussed with the company
- Complete audit report was submitted in 10 working days.

While solving the client's business challenges, Freyr proved beneficial in terms of:

- Planning, execution, and report preparation in quick turnaround timeframes; within two weeks
- High quality audit with recommendations as per the latest agency standards
- Avoiding a potential non-conformance from Regulatory authority (regarding auditing API suppliers)

Second Scenario: Another proven case is where Freyr was approached by a US-based pharmaceutical company committed to the development and distribution of high-quality, branded, and Generic Pharmaceutical products.

The parent company gave Freyr the responsibility of auditing its potential vendors for APIs and corresponding formulation. Thus, providing Freyr with an opportunity to audit mass production of end-to-end drug manufacturing

cycle. Post-audit, based on the report submitted by Freyr, the parent company could decide on to shortlist the potential vendors. In this case, Freyr had to work collaboratively with six different stakeholders – the parent company, the Japanese partner of the parent company, the Indian joint venture company, the API manufacturer, and the sterile formulations manufacturer. Freyr's audit report was reviewed by a former FDA inspector as well.

Third Scenario: In the other case of Medical device GMP Audit, the challenge was to upgrade company's existing systems. Freyr performed audit of SOPs as well as facilities and provided recommendations along with migration plan for changes. The Medical Device company successfully achieved the USFDA compliance.

Conclusion

Audits are an essential part of compliance best-practices. Aligning with the GMPs is in the interest of the company. With that said, waiting to prepare only for health authority audits when it is about to be conducted may prove counter-productive. With so many quality areas in focus, an ever-ready approach is must to ensure continued compliance. Be fully equipped to conduct internal or external audits to appraise your current condition and take up corrections in time. Be compliant. Be audit-ready.

With regards to GMP audits, Freyr can provide support for internal mock audits and external evaluations of suppliers/ vendors. Freyr can also assist in the creation of quality and information security agreements between parent company, and its respective potential vendors; and further maintenance of annual supplier audit calendar of the parent company.

Are you confident that your facility or your supplier's facility follows GMP and is audit-ready? Freyr will evaluate and give you an entire audit report. To know more, reach us at **sales@freyrsolutions.com**.

References

- United States Food and Drug Administration (US FDA) 21 CFR 211: Current Good Manufacturing Practice for Finished Pharmaceuticals
- United States Food and Drug Administration (US FDA) 21 CFR 820: Quality System Regulation
- European Commission EudraLex – Volume 4 – Guidelines for Good Manufacturing Practices for Medical Products for Human and Veterinary Use
- EU (2003/94/EC Part I, II, III)
- PIC/S Guide to Good Manufacturing Practice for Medicinal Products. Health Canada - Health Products and Food Branch Inspectorate – Good Manufacturing Practices Guidelines
- WHO Good Manufacturing Practices (GMP) for active pharmaceutical ingredients
- Applicable ICH guidelines (ICH Q7, Q9)
- ISO 13485:2016: Medical Devices Quality Management System
- CE Marking

MANUFACTURING SITE CHANGE SUPPLEMENT DECODE THE USFDA'S FINAL GUIDANCE

In December 2018, the United States Food and Drug Administration (US FDA) published the final guidance on Manufacturing Site Change Supplements: Content and Submission. Replacing the 2015 draft guidance, the final guidance clarifies the responsibilities of medical device manufacturers who are willing to change their manufacturing site for an approved device.

What is a Manufacturing Site Change Supplement?

A manufacturing site change supplement is a form of submission to the FDA informing about the manufacturing site change which may affect the already approved medical device's safety and efficacy. It is a part of a premarket approval application (PMA) supplement also known as '180-day supplement' submitted by the medical device manufacturers. A PMA supplement is applicable to:

- All Class III device manufacturers (in the US) who already have an approved PMA or a product development protocol
- Companies manufacturing devices covered under the humanitarian device exemption (HDE) (HDE holders are required to submit a 75 day supplement)

The final guidance outlines specific circumstances under which a site change requires PMA supplement filing with the FDA. The guidance's prime focus rests on the following details:

- Situations under which a manufacturer should submit a PMA supplement
- Documentation that should be submitted to the FDA with a site change supplement
- Factors the FDA will consider when determining whether to conduct an establishment inspection prior to approval of a site change supplement

Manufacturing Site Change Supplement and The Information to be Submitted

A site change supplement should contain:

- An updated description of the device
- Details stating the nature and purpose of the site change
- A list of manufacturing functions that will be performed at the proposed new site
- A flow diagram identifying the individual steps involved in the manufacture, processing, packaging, or distribution of the device at the new site
- Details on equipment and processes that will be affected by the site change
- A list of standards (if any) that will be used in the manufacturing process (this applies to both national and international standards)
- The process validation and revalidation master plan for the site, including validation procedures and protocols, and a list of processes at the new site that are not in the plans to validate, but will be verified by inspection and test
- Procedures for environmental control and contamination control
- A detailed explanation of how the inspection, measuring, and test equipment are routinely calibrated, inspected, checked and maintained

With the increasing number of warning letters being issued to manufacturing sites because of not following Good Manufacturing Practices (GMPs), there seems a dire need for extensive Regulatory scrutiny before declaring any change. Though the guidance elucidates manufacturers with instances that might be considered for submitting a manufacturing site change supplement, decoding and implementing all of them comprehensively might be challenging. To be absolutely clear about the Regulatory proceedings while submitting the change in the prescribed format, it is advisable for manufacturers to clearly discuss the requirements with a medical device expert like Freyr. Go for accurate consultation for compliance. You can reach us at sales@freyrsolutions.com.

FOOD SAFETY MODERNIZATION ACT (FSMA) – DECODE THE ESSENTIALS

Prevention of food safety issues has been a primary focus for the United States Food and Drug Administration (US FDA) over the past decade. To monitor and enhance food safety, FDA has introduced Food Safety Modernization Act (FSMA) in 2011, which emphasizes on all the aspects of food production, and supply chain; from farm to fork. The FSMA is aimed not only at preventing foodborne adversities but also at defining how the food is grown, harvested, packed, processed, shipped/imported into the U.S. To prevent food contamination at each stage of supply chain, the US FDA has finalized seven major rules as part of the FSMA.

The FSMA and Final Rules

- **Preventive Controls for Human Food** – The final rule for preventive controls for human food sets new requirements to develop and implement hazard analysis and risk-based preventive controls (HARPC) at foreign and domestic facilities. Once preventive control is identified for a potential hazard, manufacturers must ensure that these controls are implemented in the facility and monitored diligently.
- **Produce Safety Rule** – The Produce Safety rule establishes minimum standards for safe growing, harvesting, and packing of fruits and vegetables for human consumption. The rule sets requirement for the quality of agricultural water used for the production as well as for the assessment of soil and manure to minimize the risk of contamination. It outlines new rules specifically for sprouts as they have been associated with food borne diseases.
- **Foreign Supplier Verification Program (FSVP)** – This rule has been finalized in 2017. The rule of FSVP requires importers to carry out necessary risk assessments to ensure that the food being imported into the U.S. has been produced as per applicable U.S. safety standards. The rule helps the FDA to verify that the manufacturers provide the required level of health protection to the public, and to make sure the food products are not adulterated.
- **Accredited Third-Party Certification** – This rule establishes a voluntary program for the third-party auditors to conduct audits for food safety and it issues certification for foreign entities. It outlines the

requirements and framework for the third parties seeking accreditation as auditors from the FDA. Further information related to the Accredited Third-Party Certification can be decoded here.

- **Sanitary Transport of Food and Feed** – As the name suggests, the purpose of the final rule of Sanitary Transport of Human and Animal Food is to prevent any occurrence of food contamination during the transportation; from farm to table. It proposes requirements for all shippers, loaders, carriers, and others involved in the transportation of human as well as animal food.

- **Mitigation Strategies to Protect Food Against Intentional Adulteration** – This rule aims at preventing any intentional harm caused to human food, which may indeed harm the public on a large scale. The rule proposes risk-mitigation strategies for certain registered food facilities. It applies to all the major companies which target a large number of consumers.

- **Voluntary Qualified Importer Program (VQIP)** – The VQIP, a voluntary fee-based program, benefits participating importers and consumers. It allows accelerated review and import entry of animal and human products. However, to participate in this program, participating importers should first check their eligibility criteria.

Having discussed the above finalized rules, it is clear that the FSMA is completely redeveloped and the FDA is all set to make sure that human and animal food products available to the consumers are safe. Are you a food product manufacturer aiming to market your products in the U.S.? Then it's time to get a hold of the FDA's FSMA and its Regulatory requirements. Stay up-to-date. Stay compliant.

COSMETICS AND THE BAN ON ANIMAL TESTING WHERE DOES THE WORLD STAND?

Animal testing has always attracted a lot of attention from the industry because of its controversial nature. From the last decade, Cruelty Free International (CFI) has been encouraging companies across the world to stop the testing of cosmetics on animals to create a harmonized, cruelty free global market. Even though a lot of companies claim to be cruelty free, many still rely on animal testing for accurate results.

In accordance with this, recently, China declared a complete ban on animal testing. According to the government, animal tests will not be a part of post-market testing for imported/domestic cosmetic products. However, the ban is only on post-market testing. The regulations for pre-market testing are yet to be agreed upon. The CFI is organizing a pilot program in China to help companies comply with the animal testing regulations.

Apart from China, quite a few countries have taken a step towards creating a cruelty-free cosmetics market, in the last few years. Some of them are:

Australia

In February 2019, the Australian government passed a bill to completely ban animal testing for cosmetics. The Industrial Chemical Bill 2017 of the Australian government includes a ban on the animal tests performed on the cosmetic ingredients for the collection of relevant data. The ban is also applicable on the cosmetic ingredients used in another product sector. However, it is not applicable to medical testing and ingredients which have been tested in the past. The government has given a deadline until July 2020 for the companies to align their operations as per the new regulations. In association with the Humane Society International (HSI), they have also come up with a number of measures to ensure that all cosmetics are covered under the ban.

European Union (EU)

On May 3, 2018, the EU announced a complete ban on animal testing for the cosmetics industry. Companies

are given time till the year 2023 to ban animal testing on cosmetics completely. The EU has also banned the sale of all cosmetic products which have been tested on animals since 2013.

Canada

Canada has also taken a step towards creating a cruelty-free market. In order to do so, the Senate of Canada has passed Bill S-214, Cruelty-Free Cosmetics Act. The bill is forwarded to the house of commons for review. According to the bill, sale of cosmetics which are developed following animal testing is strictly prohibited in the country. The bill also includes a phase-in period for the companies to allow them to comply with the new regulations.

California

In September 2018, California became the first state in the US to ban animal testing. The California State Legislature passed a bill to ban the sale of animal-tested cosmetics in the state. The law will come into force from the year 2020.

Likewise, countries across the world are gradually accepting that the cosmetics can be manufactured without harming animals. Hence, they are finding alternatives for animal testing methods to comply with the regulations of their respective health authorities and to stop animal cruelty. Are you aiming at entering the global cosmetics market? It is advised to consult a cosmetic Regulatory expert to understand the local cosmetic regulations. Stay up-to-date. Stay compliant.

Infographic

Center of Excellence
Regulatory Intelligence

ACCELERATE TIME-TO-MARKET
WITH ACTIONABLE INFORMATION

Is your business compliant with all the region-specific Regulatory requirements? How informative are you on evolving global/regional Regulatory guidelines with respect to formulations, dossier compilation, registration procedures, submissions, and post-approval requirements? Accelerate time-to-market with actionable Regulatory information. Gain access to Freyr Reports.

Win over the regional Regulatory complexities.
Speak to us on your information requirements.

CONSULT

Case Study

Center of Excellence
Compliance, Audit and Validation

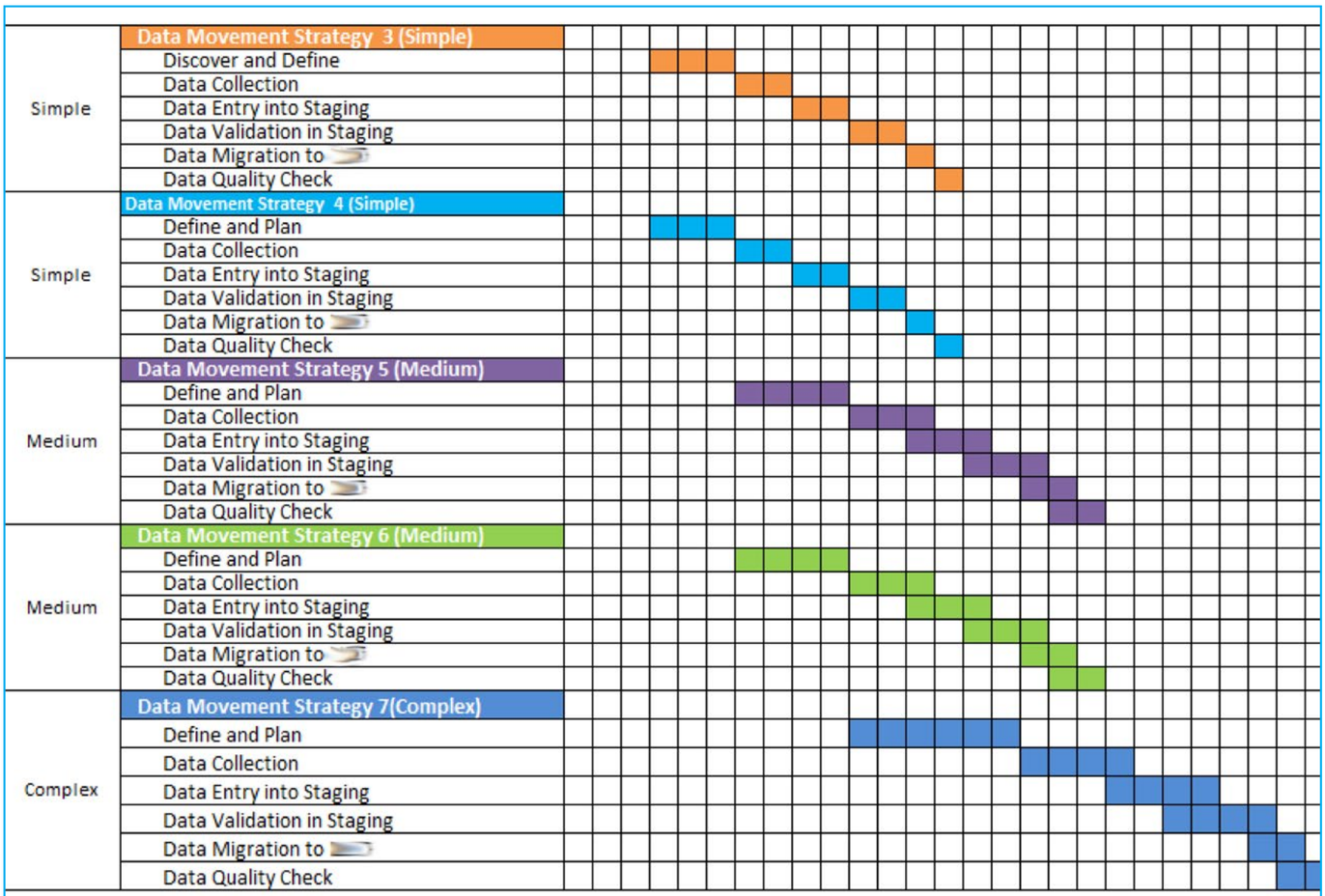
SUCCESSFUL LABEL TRACKING & DATA MIGRATION

Project in Scope & Business Imperatives

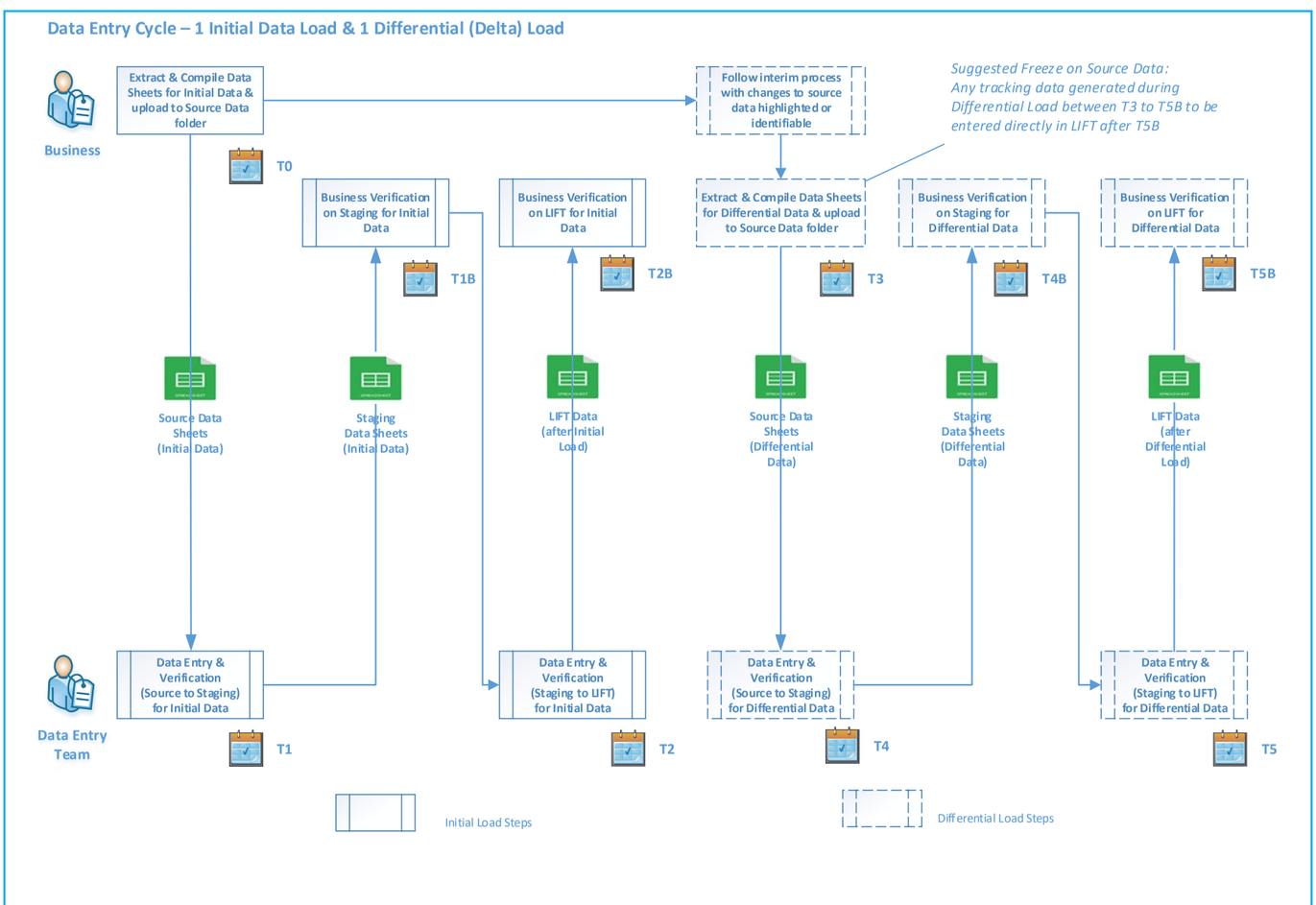
- Large Global Pharmaceutical Company
- Label Tracking and Data Management for Multiple Product Categories/Portfolios and 50,000+ Tracking Records and Additional Downstream System Datasets
- Transformation and Migration of Change Control, Labeling, Artwork and Supply Chain Systems from Multiple Sources to a Single Tracking System
- Ensuring Smooth Cutover and Process Transition as per Compliance Standards

Freyr's Solutions and Services

- Multiple Data Movement Strategies (Portfolio/ Source/ Scope/ Complexity)
- Migration Requirements & Plans
- Mapping & Rule Books
- Work Instructions, Templates
- Protocols, Scripts, Checklists
- Summary Reports



Mutli-complexity Data Workstreams



Movement Strategies and Processes

LifeCycle Classification Code	LifeCycle Classification	In Scope	Target Field ID	Module.Sector	Field Name	Data Staging Sheet Name	Staging Column Name	Source File	Source File Sheet Name	Source Field Name	Business/ Conversion rule required?	If data is available, Business Rule for any transformation	If data is not available, Business rule
L1-CCD	CCDS Change	Yes	-	NA	This will not be entered in [redacted] (this is only applicable to identify unique CCDS updates from CCDS Tracker because unique key [redacted] does not exist in CCDS Tracker to identify unique CCDS updates)	Request	CCDS ID	CCDS Tracker	Consolidated Sheet	CCDS ID (this field does not exist in CCDS Tracker, it will be created in copy of CCDS Tracker before data entry starts)	Yes	-	Create a new unique ID to identify each global CCDS update by concatenating data from columns J number, Version, Special Category for PSMF report, CLCN date, CLCN category and active ingredients.
L1-CCD	CCDS Change	Yes	TF1	RMT.Request Details	Origin	Request	Origin	CCDS Tracker	Consolidated Sheet	-	Yes	-	Select "Migrated Data"
L1-CCD	CCDS Change	Yes	TF2	RMT.Request Details	Product	Request	Product	CCDS Tracker	Consolidated Sheet	CCDS/RSI for active ingredients	Yes	Generic names are available in this column but there are mismatches with product names in [redacted] because in CCDS tracked these names are entered manually and in different formats/combinations. Add all generic names from ARIS Register report based on UID. Suffix "CON-MED" will be added to all consumer product names as in [redacted]	-
L1-CCD	CCDS Change	No	TF3	RMT.Request Details	Other Impacted Products	-	-	-	-	-	-	-	-
L1-CCD	CCDS Change	Yes	TF4	RMT.Request Details	Request Topic	Request	Request Topic	[redacted] User Manual	-	-	Yes	Due to restricted capacity of field, CCDS J Number, version and abbreviated generic names will be entered in this field Format: CCDS v. xxx (eg. J0076522 v. 011 xxxxx)	If RSI version not available, use NA (Not Available) in place of version xxx

Mapping and Rule Books

Take the reason from column "Reason for non-submission" of SP-Impact Assessment sheet

Enter in column "Reason(s): If "No Submission/Notification Required"" of Tracking sheet

Sheet/Column in COMPLIANCE TRAC-KERACTELION	Sheet/Column in Staging Data Sheet
SP-Impact Assessment / Reason for nonsubmission	Tracking / Reason(s): If "No Submission/Notification Required"

1.1.1.1. Entering data regarding dependency under Country Administration

a) **Entering Brief Change/Save Reason Description Text**
Please refer Data Entry Rule Book for the associated business rule.

b) **Entering Tracking Path**
Please refer Data Entry Rule Book for the associated business rule.

c) **Entering Start Tracking Date**
Please refer Data Entry Rule Book for the associated business rule.

d) **Entering Final Tracking Dat**e
Please refer Data Entry Rule Book for the associated business rule.

e) **Entering Dependent On Milestone/Tracking Date**
Take the dependent milestone from column "**Dependent On Milestone/Tracking Date**" of **SP-Reference Countries** Sheet.

Enter it in column "**Dependent On Milestone/Tracking Date**" of Tracking sheet.

Work Instructions

Data Collection

- Milestones completion, compliance
- Quantitative Summaries
- Data Quality Dashboards

Quantitative Summaries

Sector	Project	Data	Records remaining to be analyze	Not Applicable	Awaiting data	Good	Need Clarifications	Quality Issues	Total	To be excluded from scope	In Scope	Data provided to Freyr for Analysis	Data complexity as provided and creating links with other systems	Data Quality
												Data availability (Sample)	Data complexity	
Pharma	Rx-Track-CCDS-Global	Global CCDS Changes				80	58	132	270		212	100%	M	30%
Pharma	Rx-Track-CCDS-Global	Country level data				4712	3030	6773	14858	343	11485	100%	C	32%
Pharma	Rx-SPS-CCDS-All	SPS CCDS Global plans (non migrated)					184		184			100%	S	
Pharma	Rx-SPS-CCDS-All	SPS country level (non migrated)					10374		10374			100%	S	
Pharma	Rx-Track-Local	Locally initiated changes					60		13944	8491	5393	100%	M	
Pharma	Rx-Track-Local	Locally initiated changes (RLCP only)							4704			100%	M	
Pharma	Rx-Day0-CCDS-Global	Day 0 to TSD Tracker				212		224	436			100%		
Pharma	Rx-EDG-SUP-All	EDG data			All							0%		
Consumer	Cx-CCDS-Global	Global CCDS Changes				63	113	282	560	216	344	100%	M	11%
Consumer	Cx-CCDS-Local	Country level data				1897	1862	6860	11260	2503	8757	100%	M	17%
Consumer	Cx-Cocoon-Art	Artwork Mgmt data			All							0%		
Consumer	Cx-EDG-SUP-All	EDG data			All							0%		
[redacted]	Ax-CCDS-Global	Global CCDS Changes (only CCDS updates)				20	5		32	7	25	100%	S	63%
[redacted]	Ax-CCDS-Local	Country/License level data (only CCDS updates)			421	572			1158	165	993	100%	S	49%

Qualitative Dashboards

Staging and Validation

- Staging Data Sheets (manual)
- Validation Checklists
- Data Import Logs (automated)

S. No.	Item Description	Yes	No	Issues found/ Comments
A	Staging Data Sheet: Request			
1.	Origin verified as per business rule ?	☐	☐	
2.	Request Topic verified as per business rule?	☐	☐	
3.	Request Description verified as per business rule?	☐	☐	
4.	Priority verified as per business rule?	☐	☐	
5.	Day 0/Decision to start note verified as per business rule?	☐	☐	
6.	CCDS LC Sign Off note verified as per business rule?	☐	☐	
7.	Target Submission Date note verified as per business rule?	☐	☐	
8.	Target Submission Date Timeline Extension note verified as per business rule?	☐	☐	
9.	Target Submission Date Timeline Extension reason verified as per business rule?	☐	☐	
10.	Legacy Tracking Number verified as per business rule?	☐	☐	
Request Sheet verified with no issues ?		☐	☐	
B	**Staging Data Sheet: Request Text**			
1.	Request Text ID verified as per business rule?	☐	☐	
2.	Request Text verified as per business rule?	☐	☐	
Request Text Sheet verified with no issues ?		☐	☐	

Validation/Quality Checklists

Migration and QC

- Migration Logs & Summary Reports
- QC Reports & Analysis

Phase	Migration Input File #	Round	Start Date/End Date/ executed by/ verified by	Migration Results	Re-run	1% Sample Verification post run
1	Pharma_Global_Changes _2015-16.xlsx	1	Start Date:29-Sep-2017 End Date:29-Sep-2017. Executed By: Kishore Kumar.H Verified By : Kamalteja Konidena Verification Start Date:29-Sep-2017 Verification End date-29-Sep-2017	Completed; with 0 errors(s)	NA	Sample Size:32 Passed: 32 Failed:0

Migration Summary Reports

Client Benefits

- 50,000+ Tracking Records
- Qualitative Summaries
- Periodical Validation and Quality Checklists
- A Single-stop Comprehensive Tracking System
- Smooth Transition and Compliance

Case Study

Center of Excellence
Technology
Regulatory Services

LABELING DOCUMENT MANAGEMENT WITH OPENTEXT ™ CONTENT SUITE

Client
India-based, Global, $1+ Bn Pharma Company

Geography
India-based, Global

Solution
End-to-end implementation of a validated Document Management System (DMS) for Labeling on OpenText™

Therapeutic Area / Indication
Multiple; Including Dermatology, Respiratory, Cardiology, Diabetes, Oncology and Anti-infective

Function
Global & Local Labeling

Products
300+ Generic APIs and FDCs

Benefit Highlights

- System to manage labeling in 100+ countries
- Global visibility and tracking of Reference Safety Information
- Meeting commitments to Regulatory authority
- 21 CFR Part 11 & Annex 11 Compliance

BUSINESS IMPERATIVES

- The client was looking for a compliant system to manage labeling worldwide and meet its commitments with respect to control and maintenance of Reference Safety Information

CHALLENGES

- Multiple region/country specific labeling, formats, repositories and processes
- Manual co-ordination and lack of consistency within regions
- Lack of co-ordination between global labeling, local labeling, pharmacovigilance etc. and challenges with end-to-end tracking of safety variations
- To meet commitments with aggressive timelines
- Global project co-ordination, diverse stakeholders and inputs, low exposure of users to workflow based tools etc.

FREYR SOLUTIONS & SERVICES

- Comprehensive requirement analysis and process mapping
- User-friendly document storage, lifecycle workflows, powerful search, notifications, tracking and reporting for all regions and document types
- Fully developed on the OpenText™ Content Suite and integrated with ArisGlobal Register™ for master data
- End-to-end computer system validation as per GAMP 5
- Comprehensive SOPs, WIs, Training & Roll-out
- Complete migration of existing labeling with consistent metadata and naming

CLIENT BENEFITS

- Meeting commitments to Regulatory authority
- Centralized repository - single source of truth for Labeling
- Global dissemination & tracking of signals/ safety assessments impacting regional Labeling
- User-friendly, tailored to internal processes and as per Regulatory information management best practices
- Significant cost savings and leveraging existing investments
- Designed to support Artwork Management, Submissions Management processes and/ or tools
- CFR Part 11 and Annex 11 compliant system

GLOBAL HEALTH AUTHORITY MANDATES

With respect to Global Life Sciences and Med Tech Industries

Jordan Food and Drug Administration	Jordan Food and Drug Administration (JFDA) has started accepting JO eCTD format (Version 1.0.2) for marketing authorization submissions.	EFFECTIVE SINCE Mar 1, 2019
EDQM	EDQM has announced that eCTD is mandatory for all CEP applications including notifications, revision, renewal and new applications.	DEADLINE Jan 1, 2020
HALMED	Croatia's Health Authority, HALMED, has announced the adaptation of eCTD documentation.	DEADLINE Jan 1, 2020
FDA	USFDA has extended the compliance dates for nutritional facts and supplement facts label.	DEADLINE Jan 1, 2020 & Jan 1, 2021
CDSCO	CDSCO, India has included 8 new device types to the list of regulated medical devices.	DEADLINE Apr 1, 2020
Australian Government Department of Health and Ageing Therapeutic Goods Administration	TGA has asked all the affected sponsors to update their medicine labels and relevant documentation in accordance with the new ingredient names.	DEADLINE Apr 30, 2020
FDA	The USFDA has extended the Type III DMF's eCTD submission deadline.	DEADLINE May 5, 2020
European Medicines Agency	EMA's new EU MDR will be effective from May 26, 2020.	DEADLINE May 26, 2020
Australian Government Department of Health and Ageing Therapeutic Goods Administration	The TGA has introduced new labeling requirements for medicines supplied in Australia.	DEADLINE Aug 31, 2020
Australian Government Department of Health and Ageing Therapeutic Goods Administration	Australia's TGA has announced new Product Information (PI) Form, which is going to be mandatory.	DEADLINE Dec 31, 2020

As deadlines are just around the corner, isn't it time for compliant transition?
Get Ready. Consult an Expert.

CONSULT FOR COMPLIANCE

ARTICULATING SCIENCE IN THE RIGHT AND THE RAGHU ALUR WAY

Hi Raghu, firstly, a big thanks to you and the entire team for being proactive in all the platforms. And of course, for your thought leadership on Orphan Drug Designation both in US and Europe perspective. We must say, that was quite insightful.

Thank You. When we started working on ODD, the concept was new for the entire team. We had enough discussions, interpretations, late evening readings, building confidence in client's mind and ourselves that we can deliver to the requirements. Although challenging, we had lot of learning and fun.

Medical writing and Medical communication. Is there any difference in between? What exactly are we dealing with?

Good one to ponder upon! Although both Medical Writing and Medical Communication have broad horizons, I would emphasize on the main differences between these activities.

Medical Writing:

- It is a core scientific activity mainly focused on describing and reporting the output from the trials (Non-clinical and Clinical) including PK, PD, Efficacy, and Safety as major parameters. Medical writing specifically, Regulatory writing works with highly evolved setting called CTD, containing modules wherein all the relevant documents would be grouped by the applicant seeking marketing authorization. As this activity runs around the pre-defined frame of CTD, it is less creative. The information, results, and the data are highly confidential.
- It requires exhaustive efforts to author clinical developmental documents (Protocols, CSRs, IBs etc.) and comprehensive literature-based documents (clinical and non-clinical overviews).

Medical communication:

- It is a sector ranging from publication writing to promotional medical education. Medical communication depends upon clinical development documents such as clinical study reports for creating the information in the form of manuscripts for publications in journals, abstracts and posters for presentations.
- Medical communications represent lots of varieties of documents. This activity requires special presentation skills and relatively higher creativity considering the varied audience. Most of this information might be received by the end user, hence not so confidential.

At Freyr, we are dealing with the core medical writing. However, we are interested in doing medical communication as well. In fact, we have started contributing to small projects under the umbrella of Medical communications.

People don't just choose a job; they also choose a boss. Do you agree with this? If yes, as a boss how would you like to credit your team?

In my view no one is a boss. All are equal and doing their job. It is as similar as people don't choose marriage and they choose partner. There should be a balance between what we do (work) and with whom we collaborate. A mentor is equally important as that of a job to push our boundaries and achieve greater results both on organizational and on individual fronts.

We have always seen you open for discussions and debatable. What drives it in real-time? The knowledge one possesses or the curiosity to know the other side of the self-perspectives?

I believe that active listening is one of my strengths. I keep myself open for discussions to understand the other side of the discussion and wait to put forth my perspective. When there are two different opinions, there is always a debate between two parties. However, the conclusion should be based on evidence/justification.

Like a usual style guide for academia, is there any standard style for medical writing?

I should say yes but "one does not fit all". The style of medical writing (presentation of data) always depends at least one of the following parameters.

- What is the Objective of the document?
- Who is the Audience for the document?
- Are there any Guidelines/Templates that restricts/drives the documentation?
- Is the document scheduled for any specific country submission?

There is a different perception that the field of scientific communications is always being layered. Most of the times, it is clubbed with other departments/CoEs/functions as an offering. Do you really think that there exists this perception? If yes, what do you think the main reason for this?

The perception exists to some extent. Medical Writing is a broad sector. However, it works hand in hand with many other functions namely, clinical development, statistics, Pharmacokinetics, Regulatory affairs, and so on. It doesn't mean that it is clubbed with other departments. It depends upon the set up within an organization.

If not Medical Writing and Life Sciences, what would Raghu choose as his career? What is he passionate about?

If not a Medical Writer and Life Sciences, I would have been an Entrepreneur (Specifically Owner for chain of Hotels and would have been involved in manufacturing of essentials for Hotel Industry)

How competitive is it to become a medical writer? Any advice would you like to give to aspiring medical writers?

Medical Writing is a vast sector and highly competitive in my perspective. It is always better to understand our strengths and take a decision. Please be focused on what you want to do and what fits with your strengths. "Every Expert may not be a good writer and every writer may not be an Expert." The balance between both communication skills and domain knowledge will make any one a good writer. Although, we use the same 26 letters and symbols to communicate the information to the audience, the skill sets of the individual should match the Job requirements.

> "Every Expert may not be a good writer and every writer may not be an Expert.

On a lighter note, would there be a pen name for medical writers?

I can define it as follows:

P- Patience (Every MW should have it and strive for better and best way of presentation of data)

E- English (Language, most of the communication we do with this language as a MW)

N-Narration (Need to know storytelling to impress the reader even if it is technical, the flow of thoughts matter)

Quick to Answer

Your Motivation

Smile on the face of my Kids

Your Inspiration

Do better, better, better!

We know perfection is not attainable, but we chase perfection. On the way of chasing perfection, we achieve excellence. Are we not near to perfection?

These words inspire me a lot.

Best Holiday

Enjoying life with Nature, have fun with family members and eat a lot.

Freyr CLIENT WINS

The Customer: A UK based, top multinational consumer goods company

Project Details: Staff Augmentation

The Customer: A UK based, global speciality pharmaceutical company

Project Details: Staff Augmentation

The Customer: A Korea based, leading life sciences company

Project Details: Publishing support, product registration in Nigeria and Egypt

The Customer: A UK based, leading multinational consumer healthcare products company

Project Details: Regulatory compliance of home care products across 4 CEE countries

The Customer: A Sweden based, leading medical devices company

Project Details: Provide support for Mexican Registration Holder Services (MRH) in Mexico for 02 Medical Devices

The Customer: An India based, fast growing pharmaceutical company

Project Details: Provide variations submission to Europe markets

The Customer: A US based, leading multinational health care company

Project Details: Provide eCTD publishing support to Bahrain

The Customer: A US based, multinational food and beverage company

Project Details: Staff Augmentation

The Customer: A US based, pharmaceutical OTC and Prescription (Rx) products company

Project Details: Publishing and Submission

FREYR EYES STRATEGICAL MARKET GROWTH WITH NEW CORPORATE APPOINTMENTS

Robert MacDougall
Vice President, Business Development

Rob joined Freyr on Sep 9, 2019 and is currently based at the company's headquarters, New Jersey.

Before joining Freyr, Rob has over 30+ years of experience contributing largely to enterprise sales, marketing, and consulting. Rob has earlier associated with industry renowned Dassault Systèmes, Sparta Systems, AT&T, etc.

Claudia Ribaudo Fields
Vice President, Global Sales

Claudia brings years of industry experience in business development and the management of professional service teams. Prior to joining Freyr, she was the Vice President of a life sciences practice for a publicly owned firm.

Claudia embraces the art of understanding clients' challenges by leveraging talented subject matter experts and technology through various stages of the sales process.

We are pleased to welcome industry experts like you – Robert and Claudia.
Together, let's redefine the Regulatory solutions and services landscape.

CLIENT TESTIMONIALS

That's amazing! Freyr LABEL 360 is true to its brand preposition. The tool enabled us not only to track the global label changes in real-time, but also to implement them across the impacted geographies simultaneously. We are overwhelmed to have this tool easily integrated with our existing systems.

Thank you Freyr for this one-stop labeling solution.

Vice-president, Regulatory Operations,
A Fortune Top 20 Pharmaceutical Company

Thank you very much Freyr for all your support in creating the strategies. There have been a lot of documents and discussions based on very little information from us. I am happy to see that you have provided all the deliverables as agreed within tight deadlines.

VP Established Portfolio, Global Development
A Multinational Danish Pharmaceutical Company

We appreciate Freyr for handling complex submission with grace. The Russian Health Authority made a lot of requests which required multiple preparation meetings, as well as LEAD meetings. Freyr team handled it very well, especially given the limited turn-around time

Senior Specialist
One of the World's Largest Pharmaceutical Companies

Thank you very much for working with us on the India Cosmetic project. We appreciate your resource's diligence and focus and attention to detail. Very lucky of you to have them in your team

Senior Specialist
One of the World's Largest Pharmaceutical Companies

I have to compliment Freyr for their knowledge and investigation that brought to light an obsolete label that had not been inactivated in the LAB database. They went and found the inactivation form! Made me wish I had thought of that. I really appreciate the time they always put in to answer my questions.

Labeling Cluster Head
Director, Global Labeling Management
WRO, Worldwide Safety & Regulatory

A leading Research-based Biopharmaceutical Company

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

About Freyr

Freyr is a leading, niche, end-to-end global Regulatory solutions and services company supporting large, mid, and small global organizations across different life sciences verticals - Pharmaceuticals | Generics | Medical Devices | Biotechnology | Biosimilars | Consumer Healthcare | Cosmetics | Nutraceuticals. Freyr supports life sciences organizations in their entire Regulatory value chain - Intelligence Driven Submissions/ Product Registrations | Labeling | Artwork | Post- Approval Change Management | Regulatory Software and other related services.

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