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LEAD STORY

Life Sciences Regulatory Updates 2019 and Farther

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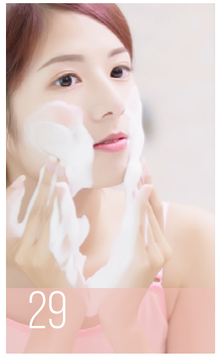

Freyr 360°

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FOREWORD

Howdy Patrons,

Welcome to the brand-new Issue of Freyr CONNECT!

We agree! It's been a little while since we had connected with you. We really hope you had a great holiday season. At Freyr, we had it too - in terms of achievements, the addition of new clients' logos to our hat, product upgrades, global expansions etc.

Having a month passed in the new year - 2019, we are sure that you are busy devising new strategies for reaching new business horizons, compliantly. To complement the same, here we start this Issue of Freyr CONNECT, with a lead story that discusses comprehensive information on global Health Authority regulations that will/may impact your strategies in 2019 and further.

Next to the upcoming regulations in 2019, we assume the next big thing in Life Sciences is Artificial Intelligence (AI) and we have furnished information on how it is going to be a game changer of MedTech. Moving ahead, we have also detailed the importance of CAPA, EMA's revised plan for risk management, TGA's electronic procedure, and various thought leadership articles.

That's not the end. As always, this Issue, too, is an amalgamation of Fun and Business. The fun aspect this time is our Festronix-2018, Freyr's Annual Day event. We have collaged few some memorable moments from the event. Make sure you get a glimpse of it.

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

Happy Reading!

Suren Dheenadayalan
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LIFE SCIENCES REGULATORY UPDATES 2019 AND FARTHER

With each year, Life Sciences industry is evolving and transforming in unpredictable ways, of course for the betterment of the end user's safety. The industry is progressing with technological advancements and Health Authorities (HAs) are equally striving to upgrade and simplify the existing Regulatory frameworks to streamline global product launches of Pharmaceutical, Medical Device, Cosmetic, Nutraceutical, and Biologic industries. We have seen many such regulations in 2018. But what is the path ahead for manufacturers in 2019? What are the mandates that are expected to be enforced in 2019 and farther?

From the implications of Brexit effect to new Medical Device Regulations to continuous upgrading electronic common technical document (eCTD) versions to introducing many global market-entry pathways, there are a plethora of guidance documents, regulations and rules concerning Medicinal Products, Medical Devices, Cosmetics, Nutraceuticals etc. that are expected to come into effect and change the face of Life Sciences in the year 2019 and farther.

To inform the manufacturers/sponsors/applicants about updated compliance practices, below we have briefly explained about some of the upcoming Regulatory changes that may influence the Regulatory strategies for 2019. Let's look at them industry wise.

Pharmaceuticals Regulatory Updates 2019

New Regulation for Clinical Trials of Pharmaceuticals in EU

Clinical Trial Regulation EU No 536/2014 was introduced in the European Union (EU) on June 16, 2014, to transform the rules for conducting clinical trials. The regulation was enforced to increase the standards of trials safety and transparency of trial information for the participants. It aims at fostering innovation and research while avoiding duplication of clinical trials or repetition of unsuccessful trials by creating an exclusive clinical trial portal and database. The agency will provide access to this information to public through the portal subject to rules of transparency.

The regulation is expected to replace the EU Clinical Trial Directive (EC) No. 2001/20/EC and national legislation that was put in place to implement the Directive. The portal was expected to go live in the later part of 2019. But due to technical issues and Brexit impact which triggered the need to relocate the European Medicines Agency (EMA) office, the system is expected to go live in 2020. However, it is in medicinal product manufacturers' benefit to align with the regulations while conducting clinical trials even before the portal goes live.

TGA Approves New PI Format

Therapeutic Goods Administration (TGA), the Australian Regulatory authority has approved a new product information (PI) form on November 8, 2017. The commencement date of the new PI form was January 1, 2018, with a transition period of three years ending December 31, 2020.

The key changes in the new PI form include reordering the content to bring critical clinical information together at the beginning of the document. The changes also include updating headings and sub-headings that align with international standards to facilitate the harmonization of formats with those used in New Zealand and Europe.

TGA to Adopt PIC/S Guide to GMP PE009-13

Therapeutic Goods Administration (TGA) of Australia, is a member of the Pharmaceutical Inspection Cooperation Scheme (PIC/S), which is a non-binding, informal, cooperative arrangement between the multiple Health Authorities that regulate Good Manufacturing Practice (GMP) for medicinal products. In response to the identified risks to end-user health and ambiguity leading to misinterpretation and compliance risks, TGA has sought to adopt the latest guide of PIC/S for GMP for the pharmaceutical manufacturers. The guide is relevant to the country's Mutual Recognition Agreements and assures equivalence to international markets.

The first notification of the guide was made in September 2017 and the adoption period began from January 1, 2018. A transition period of one year has been given for companies during which the agency addresses the questions concerning the GMP. Beginning January 1, 2019 adoption of PIC/S Guide to GMP PE009 - version 13 shall become mandatory for Regulatory compliance.

EU Module 1 Implementation Guidance for eCTD Version 4.0

On October 11, 2018, the final version of implementation guidance (IG) for module 1 of eCTD version 4.0 for EU was published. The guidance is expected to be used in conjunction with International Council for Harmonization (ICH) eCTD IG. Currently, eCTD is regarded as the principal electronic submission format and the only electronic format accepted by the EMA and the national competent authorities of EU.

Croatia's Health Authority - HALMED Sets Deadlines for eCTD Implementation

After Croatia was accepted as a member of EU, the country's health agency, HALMED (Agency for Medicines and Medical Products), was also included in EMA to become a full member of European Regulatory network and Heads of Medicines Agency (HMA). Following the ascension of HALMED to HMA, it has set deadlines for introducing electronic drug documentation in eCTD format for national procedures (NP) for new approvals until July 1, 2018 and for other requests such as amendments, updates, Active Substance Master File (ASMF), Periodic Safety Update Report (PSUR) etc. until January 1, 2019. But after further consultations with the domestic drug manufacturers and approval holders the deadline was postponed to January 1, 2020.

Post the implementation deadline, it will be mandatory in the Republic of Croatia to adapt electronic drug documentation in eCTD format. The Regulatory processes to be affected by the mandate are granting, modification, renewal, transfer and revocation of marketing authorization along with ASMF, work sharing, arbitration, and PSUR. If you are marketing a drug product or planning to do so in future, ensure you are prepared to document your submissions in eCTD format.

Falsified Medicines Directive (FMD) to be Enforced from February 9, 2019

In 2011, the EC and the EMA commenced an action to amend Directive 2001/83/EC to address concerns of falsified medicines and threat of counterfeits under the Falsified Medicines Directive (FMD) (Directive 2011/62/EU). The new directive and medicine verification system is expected to come into effect from February 9, 2019 and will be applicable on all medicinal products. The two main features listed below make

the label efficient to tackle counterfeit of medicines.

- Unique Identifier (UI): UI contains the serial number, product code, national reimbursement number, batch number and expiry date of the product.
- Anti-tampering Device (ATD): ATD is a device which verifies the details on packaging against the details encoded in the barcode. If there is any mismatch of product information, it is instantaneously identified.

With FMD enforcement, the Health Authorities across EU can ensure that only quality medicines are at the disposal of end-users. However, it may be noted that manufacturers in other member states, such as Greece, Belgium, and Italy have reportedly postponed this timeline till February 9, 2025.

Medical Devices Regulatory Updates 2019

Revised Standard ISO 13485: 2016 Becomes A Mandate

The global standard for quality management system of Medical Devices, ISO 13485 has been a guide for device manufacturers, especially for those marketing their products in Europe. With the need for increased Regulatory supervision, the standard has been revised and published on March 1, 2016, as ISO 13485: 2016 and the device sponsors were given a three-year transition period. The revision emphasizes on a risk-based approach. The notified bodies review and issue the ISO 13485 certificate as a first step towards compliance. With the deadline inching closer, ISO 13485: 2016 will be the new Medical Device Quality Management System standard from February 28, 2019, whose requirements must be met for continued marketing of the devices.

Health Canada Adopts MDSAP

Medical Device Single Audit Program (MDSAP) is an international initiative commenced by a group of Health Authorities. According to this program, an auditing organization can conduct single audit which is said to be accepted by multiple authorities in regards with Quality Management System (QMS) or Good Manufacturing Practice (GMP) requirements of a medical device. Australia, Brazil, USA, Canada and Japan ran a pilot of this program which ended in December 2016. Health Canada, has, however, stepped forward to accept the MDSAP certificate to declare a medical device's (of Class II, III & IV) safety and efficacy including the software accompanying the device. It has terminated the existing Canada Medical Device Conformity Assessment System (CMDCAS) and is accepting only MDSAP certificates from January 1, 2019.

Progression of MDR and IVDR Transition in EU

Although under transition from May 25, 2017, the EU Medical Device Regulation (MDR) and In Vitro Diagnostic Regulation (IVDR) are among the most prominent Regulatory updates concerning the medical devices in EU. Ever since their publication in 2017, organizations marketing their devices in EU member states have been striving to align with the renewed regulations in a phase-wise manner. The MDR fully replaces the old Medical Device Directive (MDD) from May 26, 2020, while IVDR will be fully effective from May 26, 2022. The transition time may seem long, but there are many Regulatory aspects that must be adhered to in individual phases. So, if you are a medical device manufacturer marketing your device in EU, ensure you are prepared for MDR compliance the earliest possible to avoid Regulatory hurdles.

Health Canada's Action Plan on Medical Devices to Improve Safety, Effectiveness and Quality

Health Canada (HC) has one of the most stringent regulations for medical devices. But there is still room for improvement in terms of safety and effectiveness and optimization of health outcomes for end-users. To strengthen the Regulatory framework further, HC has taken up a three-part action plan. The plan aims at promoting communication and engagement with users of devices and takes their perspective into consideration while developing policies and regulations in the future. The three parts of the plan and the activities with approximate timelines which are inclusive of each part are listed below.

1. Improve how devices get on the market
   - › Increase research by medical professionals and increase patient protection – starting early 2019
   - › Review evidence requirements and expand scientific expertize – starting January 2019
2. Strengthen monitoring and follow-up
   - › Implement mandatory reporting and expand the Canadian Medical Devices Sentinel Network – starting February 2019
   - › Establish ability to compel information on medical device safety and effectiveness and expand the use of real-world evidence – starting early 2019
   - › Enhance capacity in inspection and enforcement – starting 2019
3. Provide more information to Canadians
   - › Improve access to medical device clinical data – finalized by early 2019
   - › Increase the information on device approvals and publish medical device incident data – starting January 2019

The year ahead shall be dynamic due to the action plan of HC. Device manufacturers marketing their products in Canada must prepare to align with the possible changes in regulations.

Cosmetics Regulatory Updates 2019

ANVISA's New Resolution RDC 250/2018 for Cosmetics Labeling

The National Health Regulatory Agency (ANVISA) of Brazil, on 22 November 2018, published a new standard - Resolution RDC 250/2018 related to the Official Gazette of the Union. The new resolution, related to Cosmetics labeling, was passed to enhance the agility of the cosmetics sector in Brazil and reduce the cost of labeling processes to the organizations.

With the new standard in effect, only changes that are related to safety and benefits of products will demand the submission of labeling or new art of labeling to the agency. It is also expected to eliminate the need for submission of labeling changes that do not pose a health risk, such as:

- data from customer service
- social name and
- addresses of the holder

FDA Permits the Use of Color Additives in Cosmetics

EU Plans to Establish New Glossary for Common Cosmetics Ingredients

Nutraceuticals Regulatory Updates 2019

Final Rule of USFDA Nutrition Facts Label – Extension of Deadline

On May 27, 2016, United States Food and Drug Administration (US FDA) published a new Nutrition Facts label rule for packaged goods redefining label in such a way that it reflects new scientific information, including the link between diet and chronic diseases. In the final rule, the FDA has extended the compliance date in two specific cases that are listed below.

- For food products with sales more than $10 million, compliance date has been moved from July 26, 2018, to January 1, 2020
- For food products with sales less than $10 million, compliance date has been moved from July 26, 2019, to January 1, 2021

Manufacturers of food products in the United States of America (USA) should evaluate their market and plan accordingly to ensure compliance before the deadline approaches.

The Brexit Impact

Ever since the United Kingdom (UK) voted in favor of exiting from the European Union (EU), the Brexit move has grabbed attention from all industries as is expected to trigger changes to a plethora of regulations. Among them, Life Sciences is one of the most affected industries, as the manufacturers marketing their products in the UK need to make multiple amendments to align with the evolving Regulatory framework. While a number of amendments are yet to be finalized, we have listed a few instances where Brexit impact is expected to be significant.

- Companies with a common 'Responsible Person' (RP) for the EU, should now appoint a new RP exclusively for the UK
- If the RP is from the UK, the company must appoint a European natural or legal person for the position in EU region
- The label changes, product information templates might be subject to change
- Product approvals in UK being used in EU based on mutual agreements and vice versa will become invalid
- Applicants are facing ambiguity concerning new product submissions as to how to proceed due to lack of new Regulatory guidance documents for the UK market
- The Pharmacovigilance data gets reduced leading to less efficient post-marketing surveillance in UK

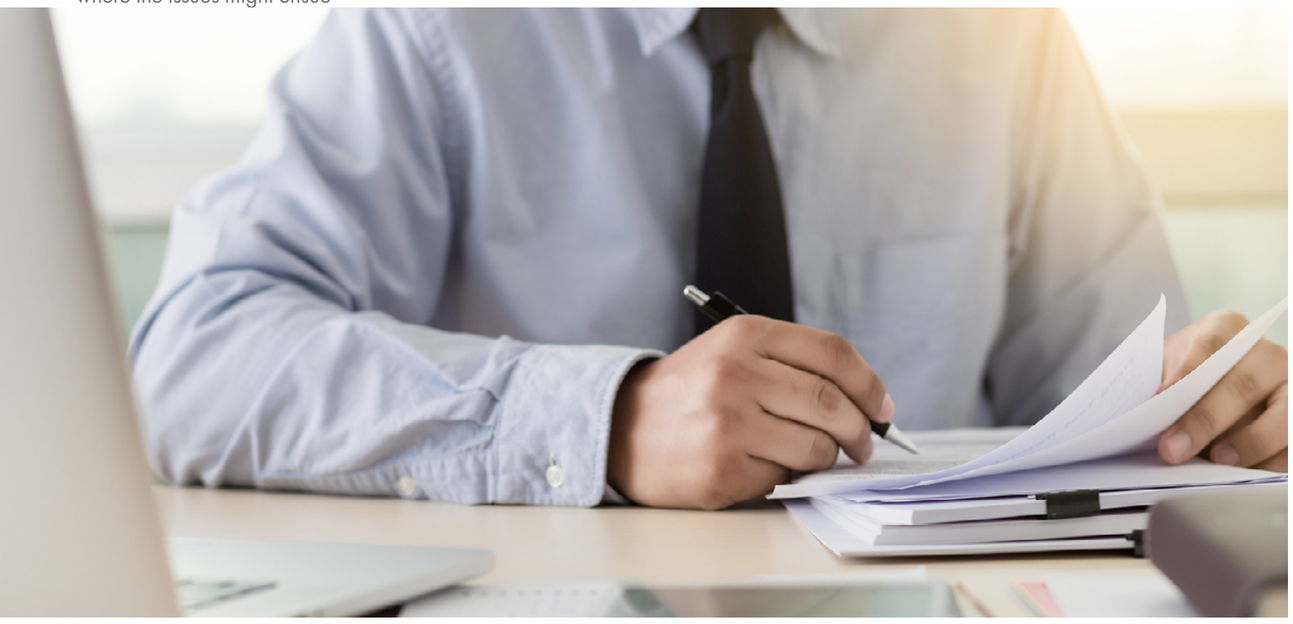
As part of the Brexit, recently the European Medicines Agency (EMA) has updated its relocation plans and the milestones. With the deadline for Brexit closer than ever (March 29, 2019), sponsors should evaluate their Regulatory preparedness by conducting a gap analysis. Basing on the analysis, they should also take steps to ensure compliance in an expedited manner.

All in all, be it Pharmaceuticals, Medical Devices or Cosmetics, a continuous track of global Regulatory frameworks will be helpful to assure compliant market entry going forward. How prepared are you to go compliant ready? Evaluate your existing processes, and try aligning them with new regulations, collate the accurate data, compile and publish it error-free for successful submissions to enable quick reviews for on-time approvals and global market-entry. Be informed. Be Compliant.

The covered regulations are a few of many major updates across the globe. If you wish to keep abreast of the above mentioned, reach out to sales@freyrsolutions.com.

CAPA PLAN: THE RIGHT APPROACH

Freyr recently released a white paper which demonstrates that CAPA should not only correct and prevent the quality issues, but also proactively apply the approaches practiced to prospective areas where the issues might ensue



INVESTIGATING QUALITY related issues and tracking them to closure is one of the most critical activities in quality management system (QMS). The increased importance of risk-based approaches is leading regulators to look for a well-defined process in investigating and identifying the root cause and method of implementation of the Corrective and Preventive Action (CAPA) plan. The crucial questions frequently asked by auditors during a CAPA review, include:

- Have the correct root causes been identified?
- Have the CAPAs been tracked and closed on time?
- Have the proposed CAPAs been reviewed for quality?
- Have all the proposed actions been implemented?
- Have the CAPAs been effective in preventing recurrence of the same problem?

Most pharma companies view CAPA as an activity intended to address identified quality issues but fail to take a holistic approach to address them. This is evident from the warning letters published by Regulatory Agencies. Such a partial approach to CAPA results not just in rework, but also loss of time and revenue.

Successful CAPA management requires addressing quality issues efficiently and effectively. CAPA should not only correct and prevent the quality issues, but also proactively apply the approaches practiced to prospective areas where the issues might ensue.By evaluating industry trends and pain points, this article will look into insights that help achieve Regulatory compliance.

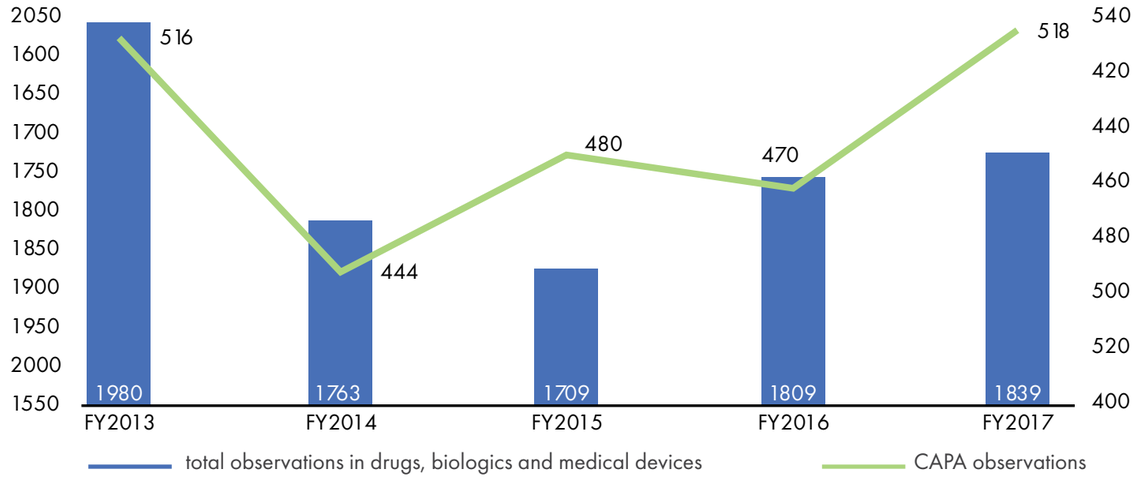
Overview

Most common method used for fixing any quality issue is the Corrective and Preventive Action (CAPA) plan. Following is a trend analysis of all non-conformities published by the Food and Drug Administration (FDA) in their 483s, which clearly outlines the impact of CAPA process on Regulatory agencies. The analysis clearly shows that almost 25-29 percent of non-conformities are CAPA related, which translates into more than ¼th of all the FDA's observations. Thus, establishing a robust CAPA system warrants that the number of non-conformances is reduced by a quarter. To understand if the existent CAPA system / process for companies is fool-proof and can withstand stringent audits, an analysis was conducted on the areas where issues related to CAPA were identified by the auditors. All CAPA related observations were broadly classified into the following categories:

- Inadequate procedures for CAPA
- Inadequate CAPA documentation
- Incorrect / inadequate / non-compliant CAPA

On detailed analysis of non-conformances, it was inferred that all the three categories: inadequate procedures, inadequate documentation and inadequate controls were interlinked. Inadequate measures were taken when there were inadequate processes. Inadequate documentation was observed when there were no adequate measures to record them, and hence no artefact to submit.

Type of CAPA observations	Frequency of observations				
	Fiscal Year 2017	Fiscal Year 2016	Fiscal Year 2015	Fiscal Year 2014	Fiscal Year 2013
Inadequate Procedures	400	344	378	362	380
Inadequate Documentation	115	99	97	101	133
Inadequate Controls / Actions	3	1	5	7	3
Total CAPA Related Observations	518	444	480	470	516
Total Observations in FY	1839	1709	1809	1763	1980
Percentage of Observations on CAPA	28.17	25.98	26.53	26.66	26.06

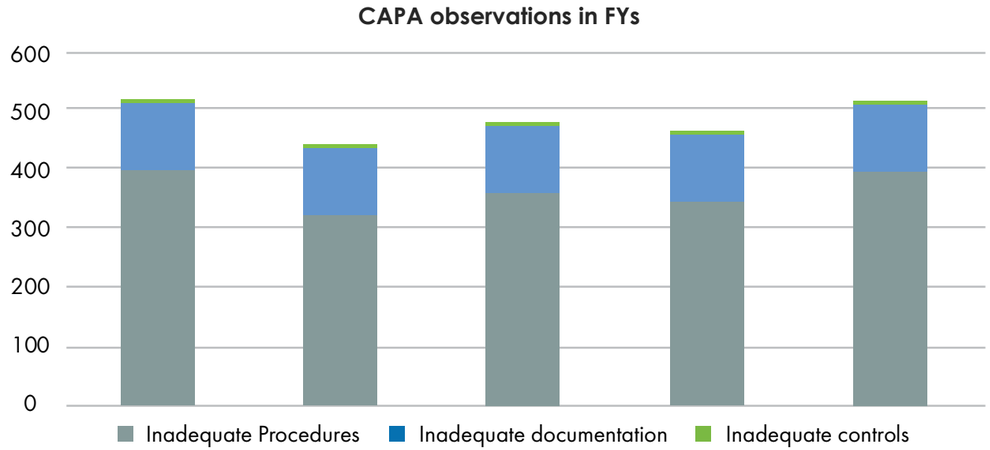


Inadequate procedures

Understanding and implementation of current Good Manufacturing Practice (cGMP) includes updating the procedures in line with current Regulatory requirements. Legacy procedures do not include mitigations for known risks in the process and risks due to CFT interactions. Additionally, lack of proper training and procedure implementation is a widespread problem in the industry.

Effectiveness checks

The cases discussed above reiterate the untapped stepwise verifying effectiveness of CAPA. If the measures taken on the CAPA are not effective, the process requires re-opening of CAPA, re-investigation, identification of root cause, and if required, a new CAPA plan. Freyr's 40+ years of combined compliance resources experience has been providing effective and efficient solutions to its customers on a wide range of CAPAs. Implementing simple changes in a procedure and re-training of personnel is the key, as a CAPA action requires a straightforward approach to measure effectiveness. Some CAPAs propose more extensive changes, such as changes in testing process, change in vendors, changes in infrastructure layout, implementing a new system, to name a few. Effectiveness checks for such CAPAs require niche experience since this involves analysis and monitoring of adequate sample data. Quantitative approaches are recommended over qualitative ones to measure effectiveness checks as the former not only provides proof of effectiveness, but also offers opportunities for improvement. Effectiveness checks not only help us to determine if the CAPA is constructive, but also helps us to determine if it is feasible to implement. In the process of establishing a concrete process which leaves no scope for errors, organizations fail to consider the challenges that the ground level staff encounter. This makes the process difficult to adhere to, which in turn leads to other non-conformities and errors despite proper training. Assessing risks to the process with appropriate stakeholders will identify various hurdles in implementation and thus prevent such issues.



THE FOLLOWING INFOGRAPHIC ILLUSTRATES THE KEY STEPS FOR EFFECTIVENESS CHECKS

Conclusion:

To resolve institutional complications, every organization must conduct an effective investigation, identify root cause(s), and implement timely and practicable corrective and preventive action(s) (CAPAs). An effective CAPA process should aim to promote critical thinking within the organization at all the levels. The process must provide a common model and risk-based framework within organization, which allows investigators to master the process quickly and easily. This would anchor common logic behind investigations and bring unity to problem solving. The goal is to implement a reusable, standardized, and complete process that can avoid similar CAPAs.

CASE STUDY - I

Incorrect / Inadequate / Non-compliant CAPA

A warning letter issued to a drug manufacturer in the year 2017, stated, during inspection of your analytical lab, the firm invalidated 101 out of 139 (about 72 percent) initial, out-of-specification (OOS) assay results for six-month stability assay, without conducting proper investigation. The initial failing result was invalidated without sufficient investigation, following which re-testing was performed and then reported as being within the limits.

The firm failed to determine the assignable cause and did not take appropriate CAPA to ensure that the significant "analytical bias," to which the initial analysis failure was attributed to, did not impact other analyses performed in the laboratory. The firm's investigation assumed that there was analytical bias in the laboratory but failed to determine how this error in analysis could be eliminated or mitigated in the future. The firm's response was termed inadequate by the FDA since they failed to implement CAPAs to mitigate the issue that was attributed to their process. However, the firm initiated an investigation into the OOS identified and a CAPA was assigned for the same. Despite the firm's efforts, this was considered inadequate by the authorities. Authorities expect the CAPA plan for a given issue to be effective in preventing its recurrence. This, unfortunately, did not happen in the above-mentioned case, resulting in its relapse. To address this non-conformity, it is crucial to identify exactly where the process was ineffective. The non-conformity may be due to any one of the following reasons:

1. The root cause identified after investigation was inappropriate: The OOS identified could have been the result of some other issue such as complications in manufacturing, faulty storage conditions for the sample etc., which led to its 138-times recurrence.
2. The CAPA plan was not suitable: The root cause identified, i.e., analytical bias, may have been due to a variety of reasons such as material, machine, calibrations, persons, methods and so on. The cause identified is far from the bull's eye and identifying a CAPA for an unknown factor with vague causes is difficult to achieve. Additionally, it was not evident if the CAPA plan covered all the areas of analytical bias and efficiently rectified them.
3. The proposed CAPA plan was not validated for its effectiveness: Effectiveness checks need to be periodically conducted during the CAPA process. Not performing these effectiveness checks to determine if the identified plan has resolved the issue, results in repetition.

In the above case in point, the issue has occurred over a span of six-months. Some issues may even occur over a longer duration. Monitoring every issue that occurs in a facility and trending them on periodic basis is beneficial to the process. Additionally, validating the CAPA for its effectiveness closes the loop between issue identification and remediation, while also providing proof for the same. Thus, leading to a closed loop CAPA process.

CASE STUDY - II

In a warning letter issued to a Medical Device company, the FDA stated, "Failure to establish and maintain procedures for implementing corrective and preventive action, as required by 21 CFR 820.100(a).

For instance,

Your firm's CAPA control procedure, does not include requirements for:

- Analyzing all sources of quality data to identify existing and potential causes of non-conforming product, or other quality problems
- Verifying or validating the CAPA to ensure that such action is effective and does not adversely affect the finished device
- Implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems

Your firm's procedures indicate that three different CAPA forms can be used:

- The CAPA and Improvement Record
- Customer Complaint Record
- CAPA and Non-conformance Record

During the investigator's review of the CAPA files, four CAPAs were found to be documented on forms called "Quality Problem Records", that was not mentioned in your firm's procedure. None of the four CAPA files included documentation of all corrective actions, implementation dates, or effectiveness check information as per your CAPA procedures. Your firm stated that a retrospective analysis of all historical and open CAPAs would be performed. However, your firm did not include documentation or evidence of the correction and the corrective action."

When such non-conformities are identified, the integrity and oversight of the Quality Assurance (QA) department are questioned. In the iterated instance, the procedure does not define various triggers for a CAPA, such as internal and external audit observations, out of specifications, deviations from procedure and so on. All these are quality issues which ideally should have been included in the procedure. Adopting a risk-based approach will help in identifying more failure scenarios for CAPA initiation. When an issue or discrepancy is identified, it is difficult to identify all possible causes without usage of rational methods. Detailed investigation involving use of methods such as 5-why analysis or Ishikawa diagrams in conjunction with critical thinking methodologies such as K-T problem solving techniques help in the identification of the accurate root cause.

Once the root cause has been identified, it is imperative for the organization to correct the issue immediately to avoid having repeated issues. The correction may be technical or procedural or both, which did not occur in the above case. Designing a standard operating procedure (SOP) that encompasses every possible error, that is easy to comprehend and practical, as well, is the first step to address the above observation. This, in turn is critical for efficient operation and seamless closure of retrospective investigation of CAPA.

Inadequate documentation

Regulatory authorities emphasize on the availability of documented proof or objective evidence for any activity performed. Failure to provide the same consequently leads to non-conformities. For an inspection, manufacturers are required to present CAPA documentation that can demonstrate to the auditors that the manufacturer's QMS is efficient and effective in identifying issues quickly and can implement effective CAPAs. Any discrepancy in the documentation provided attracts unwarranted questions and mistrust from the agency.

CASE STUDY - III

In a warning letter issued, FDA states, "IM-CAPA-007 was opened for bladder ruptures and remained open for (b)(4) days. The root causes identify (b)(4); (b)(4); and (b)(4) of the (b)(4). The corrective actions include implementing an (b)(4) and adding preventive maintenance on the (b)(4). Your effectiveness verification after three months was performed with a review of complaints which determined that the corrective actions were effective. The effective summary opened for the Intermate and Infusor bladder ruptures states that the validation document number V07-055 demonstrated that the (b)(4) of the bladders improved by (b)(4) %. Protocol document number V07-055 validated the new compounding rubber process using (b)(4) equipment with water-cooling system. A review of the documentation (protocol and records) revealed:

- The protocol specifies that the (b)(4) test is for information only and it does not specify an (b)(4) acceptance criterion for bladders
- There is no record showing 50 samples were pulled from three production lots
- There are inconsistencies within the production lot numbers as specified in the protocol and final report

In the illustration, the organisation did have an efficient procedure for addressing issues through CAPA. However, the organization failed to implement and enforce the same at an operational and process level. Gaps and discrepancies in processes and documentation gave rise to irregularities in data, thus presenting difficulties in validating effectiveness.

In the above case, the firm failed to establish a sampling methodology, hence leading to inconsistencies in sampling and documenting them. Also, it failed to define the acceptance criteria based on which the process could be deemed effective. In addition to this, there was an increased risk of receiving observations on data integrity and Attributable, Legible, Contemporaneous, Original and Accurate + (ALCOA+) practices in the organization.

The outcomes of adequate documentation are bountiful. It not only helped us in achieving the famed '0 Observations', but also provided the management with opportunities for improvement.

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EXPRESS PHARMA
www.expressbpd.com

References are available at
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BIOSIMILARS IN EUROPE AND THE USA: DECODE MARKET & REGULATORY SCENARIOS

Biosimilars, which are viewed as supplements for their equivalent biologicals in terms of safety, quality and efficacy (if & when proved), are opined as value gainers in the days to come. An external survey predicts an exceptional surge in demand for these products whose value is expected to rise significantly by 2020. With many high-value petitions of biological products nearing their expiry, biosimilars can prove productive for manufacturers in the current scenario.

To understand the global outlook of biosimilars in terms of market and Regulatory perspectives, let us look at the market and Regulatory scenarios of biosimilars in two of the world's biggest markets, the United States of America (USA) and Europe.

Biosimilars: Europe

With an increase in number of approvals of Biosimilar market authorization applications, Europe demonstrates a favorable environment for biosimilars and it is expected that more products

are to join the list by the end of the year. As per the reports, in the last two years, the market has seen a two-fold rise in Biosimilar approvals. The year 2017 was called a record-setting year for Biosimilar approvals. With the growing demand, the market is also expected to venture into new therapeutic areas and new classes of biologics.

Regulatory Scenario: Amid the market growth, one major change that requires additional focus for Biosimilars in Europe is the Brexit, which is expected to come into effect on March 29, 2019. As the European Union (EU) first introduced the Regulatory pathway for the Biosimilars, making their central authorization valid through all the member states, their validity might be questioned post-Brexit. To evade noncompliance in this ambiguous market conditions, manufacturers may have to look out for possible transitions to align with the Brexit which can be mitigated with an expert opinion.

Biosimilars: USA

In 2017, the United States of America (USA) has relatively doubled its Biosimilar approvals. There were five biosimilar approvals recorded last year and all of them were of complex blockbuster therapeutic antibodies including first time cancer treatment biosimilars. This is evident from the Food and Drug Administration (FDA) reports.

Regulatory Scenario: The FDA is eyeing at making the Regulatory process less complicated by lowering the size of studies needed for bio-similarity demonstration. To ensure the same is practiced, FDA has released the final guidance for labeling biosimilar products in July 2018 which showcases how Biosimilars can be labeled in line with that of the Generic models.

Influential Factors of Biosimilar's Market-Entry

Apart from Regulatory updates, there are other factors that affect a biosimilar's market-entry in any given region. Understanding them and acting accordingly is the need of the hour for organizations aiming to make a difference at a global level. Some predominant factors are listed below.

- **Competition:** With the anticipation of biosimilars' growing value, established players and new entrants are competing vehemently. So, manufacturers must proceed with increased market vigilance and keep abreast of market trends and Regulatory environment.
- **Go-to-market strategies:** Biosimilar markets are evolving and changing. With the increased clinical restrictions, manufacturers must incorporate expert capabilities which should reinforce their competence as an organization.
  - › Be agile and bold on decisions to establish a commercial foothold
  - › Cleverly place resources and make changes in response to short-term outcomes of market
  - › Partner with capable market players to mitigate the risk involved
  - › Partner with Regulatory experts in the domain for complaint submissions
- **Cost-effective measures:** As revenues are deciding the future of biosimilars, saving on procedural expenses proves optimal for manufacturers. Especially, streamlining the approach towards therapeutic equivalence trials (clinical and non-clinical) that account for major share of product development costs will be greatly beneficial for the stakeholders.
- **Market-preparedness:** Understanding the markets has become increasingly tough. But with technological support such as analytics, the applicants can walk in with reliable data and predict possibilities effectively, and thus stay prepared and relevant while innovating new products.

With more patented biologics set to expire in near future, releasing biosimilars with better compliance efforts may result in expedited reviews and quick approvals. It is suggested that organizations adopt better Regulatory practices and invest in intelligent Regulatory partnership while they continue to investigate the new therapeutic areas. Be informed and compliant.

ARTIFICIAL INTELLIGENCE: THE GAME CHANGER OF MEDTECH

What's the Regulatory landscape for AI-enabled devices?

The year 2018 has seen a good influx of innovative medical devices. Artificial Intelligence (AI) serves as a critical component in most of these novel devices.

FDA has defined Artificial Intelligence as:

"A device or a product that can imitate intelligent behavior or mimics human learning and reasoning. Artificial Intelligence includes machine learning, neural networks, and natural language processing. Some terms used to describe artificial intelligence include: computer-aided detection/diagnosis, statistical learning, deep learning, or smart algorithms."

While AI has long been relegated to perform tasks like managing medical records and medication management, it has now become an intelligent contributor wherein it can interpret the results on its own, without the need of a physician or a caregiver. This has drastically reduced the consultation time for physicians. However, with no existing predicates in the market, it has been a tough task for Food and Drug Administration (FDA) to update the existing regulations to suit these AI-integrated devices. Also, the devices themselves are quite diverse in terms of function and still need strong proof in order to interact with the human body.

AI in Medical Devices – Regional Regulatory Landscape

Here is what is unfolding in the United States (US) and in Europe.

United States

Medical devices were brought under the governance of the US FDA quite recently (1976) when compared with drugs and other products. Most devices were hardware driven, and digital components such as software were not featured back in the day. Hence regulations pertaining to them were not drafted. However, there has been a phenomenal shift in the role of digital technology in the healthcare sector in the past decade. Considering the timely need, FDA has started a digital health program under which it has brought all unregulated novel devices under Digital Health Technology.

Several enforcement discretion

guidance documents like the Mobile Medical Applications Guidance have been released periodically in the past five years. However, these guidance documents were insufficient and failed to clarify FDA's viewpoint towards regulating such products.

To remedy this situation, the 21st Century Cures Act was enacted in December 2016. One key takeaway from this act is the exclusion of certain types of "medical software" from the definition of "device," therefore amending section 520 of the FD&C Act. One category of excluded "medical software" is the "clinical decision support" (CDS) software. A subsequent draft guidance was issued by FDA on December 2017 clarifying the exclusion criteria of CDS from the definition of "device." This narrows down the list and drives swift decision. Also, the recent Digital Health Innovation Action Plan substantiates FDA's claims toward laying the groundwork for stronger regulation for governing the digital health products.

Europe

In contrast to the United States, Europe currently lacks a proper directive to guide AI-enabled medical devices entering the market. New regulations adopted on April 5, 2017, have broadened the guidelines for novel device companies, but the deadline for enforcement is quite far: May 26, 2020. Even a technology organization that has pioneered the deep learning domain had trouble in getting approvals for its AI-integrated medical devices for the U.K. market.

Recent Approvals

FDA, under the De Novo Premarket Review Pathway, has recently cleared two novel medical devices with no legally marketed predicate devices:

- Device I: The device is an AI-based software program that can detect retinopathy, interpret results, make decisions based on the results, and further evaluate them, all without the need of a healthcare professional.
- Device II: This is a contact application that analyzes images of blood vessels in the brain and alerts a first-line healthcare professional for complications. Additionally, it can intuitively notify a specialized professional for diagnosis if the detected complications can lead to higher risks.

The possibilities for AI are far reaching, and the cases cited above are primary level. The approvals shine light on the great possibilities for AI when combined with medical devices in the rapidly advancing healthcare sector. Also, FDA's current thinking of approving the devices in the De Novo pathway helps similar-product innovators with a predicate for quick master access through 510(k) clearances.

Regulatory Bottlenecks

As digital technology progresses, regulators are bound to enter unknown realms resulting in several bottlenecks. One such bottleneck is the lack of a clear demonstration of the technology's intended health benefit(s). The manufacturers either go overboard or underplay without knowing the full spectrum of capabilities, losing ground in both cases. Even if in rare cases the device gets approved, post-marketing complications might threaten the very existence of the manufacturing organization. Another bottleneck is that of user privacy. With a popular social media platform facing serious allegations over leakage of personal information without user consent, it points to the potential dark side of technologically advanced devices, in which the user needs to share his personal data that could in turn fall prey to data theft.

There are several other roadblocks concerning device classification, compliance with QMS requirements, and document compilation. But most important to consider on a global scale is that harmonization is the key driver. Digital healthcare products are at a clear disadvantage given the fact that local authorities themselves haven't clearly addressed primary challenges so far. Any mutual understanding between region-wise authorities will be a long-pending task in the years to come.

Possible Solutions

If an organization is unclear about the wide variety of health benefits of its digitally advanced technology, it could define a single indication that can be a prerequisite in the initial stages of approval. At later stages, it could identify other indications and seek approval simultaneously. Any post-approval deviations can also be managed through robust post-marketing surveillance.

To secure user privacy, the onus lies on companies to assure healthcare agencies that no untoward situation will arise. In this regard, the United States has put in place the Health Insurance Portability and Accountability Act of 1996 (HIPAA) to deal with the sharing of personal data. With support from industries and legislative amendments, when needed, agencies can instill faith among users. Other regulatory issues can be resolved with proper technical assistance from experts and third-party consultants with strong presence in the market. The harmonization of novel device regulations involving global health authorities will be achieved over time.

Devices empowered by AI are sure to explore new areas and create new possibilities within the healthcare industry. The technological advancements may not be clearly predictable right away, with AI exploring newer realms, but they will catapult markets to better prospects and newer heights.

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References are available at
https://www.mddionline.com/artificial-intelligence-gamechanger-medtech

TGA MANDATES ELECTRONIC PROCEDURE FOR CERTIFICATE OF FREE SALE OR EXPORT CERTIFICATE

According to a recent announcement by the Therapeutic Goods Administration (TGA), sponsors of medical devices have a new procedure to follow for certificate of free sale or export certificate. The new application format allows the sponsors to submit their applications and receive the certificates electronically without any hassle and delays. The change in process is in response to the issues faced by the sponsors while notarizing and endorsing certificate of free sale or exports.

The purpose of the electronic procedure is to help device sponsors meet the needs of the importing country as quickly as possible. In this scenario, however, the sponsors are required to contact the importing country to know the specific requirements.

What is a certificate of Free Sale or Export Certificate and Why Is It Needed?

A certificate of sale or export certificate is a document issued by the TGA which indicates that the particular medical device is included in the Australian Register of Therapeutic Goods (ARTG) and can be sold in Australia and exported as well.

Whenever the sponsor tries to export the device, the certificate is required by importing country to validate whether the medical device being imported is eligible for import and contains all the important information such as ARTG number, Global Medical Device Nomenclature (GMDN) code, etc.

Eligibility

To be eligible for the certificate, the applicant must meet the following criteria:

1. Must be a sponsor of medical device
2. Should have an inclusion in ARTG for the kind of medical device in question
3. Should be exempted under item 1.2, part 1, schedule 4 of the Therapeutic Goods (Medical Device) Regulations 2002

Limitations

The application may be rejected if any incongruity exists, like:

1. If the application is submitted for “export-only” devices
2. If there is a mismatch of GMDN codes in your application and that on ARTG certificates
3. If you are not a sponsor but an agent in sponsor’s eBusiness Services (eBS) account

The TGA aims to review the applications for Certificate of Free Sale or Export Certificate in approximately 10 business days. However, it may take longer if there are any discrepancies related to the application.

As more health authorities (USFDA, Health Canada) are taking their device application processes through electronic filing systems, manufacturers and sponsors need to have comprehensive understanding of the new procedures and their consequences. In such scenario, an expert in medical device Regulatory affairs and procedures can help to steer through the necessary procedure. Stay up-to-date. Be Informed. Be complaint.

EMA'S REVISED FORMAT FOR RISK MANAGEMENT PLANS WHAT YOU NEED TO KNOW

Pharmacovigilance (PV) has been undergoing continuous transformation over the years with respect to evolving processes, technology, legislation, and guidelines to ensure enhanced patient safety and improved monitoring of the safety profile of medicinal products. Since the execution of the International Conference on Harmonization (ICH) E2E Guidelines in 2004, proactive risk management strategies have significantly progressed at a global level in the PV domain. Over the years, the global perspective diverged into a U.S. FDA concept and a European concept governed by the European Medical Agency (EMA). The U.S. risk management strategy started in 2005 with the Risk Minimization Action Plans (RiskMAPs). The current format of the Risk Evaluation and Mitigation Strategies (REMS), which replaced the RiskMAPs, has been enforced since 2007 through the Food and Drug Administration Amendments Act (FDAAA).

The European risk management strategy was first implemented in a guideline on risk management systems for medicinal products for human use in 2005. It was then developed as a template for the EU Risk Management Plan (RMP) in Volume 9A of The Rules Governing Medicinal Products in the European Union in 2006. Later, it was described and updated in the Good Pharmacovigilance Practices (GVP) modules as 'Guidance on the format of the risk-management plan in the European Union – in integrated format. Revision 1 of the guidance was released in April 2014, and the latest update, Revision 2 of the guideline and guidance on the format of RMP, was released in March 2017. Revision 2 is effective from March 31, 2017, and the Revision 1 format was accepted only until March 31, 2018. It has been observed that most of the rest of the world's health authorities maintain their own format for RMPs, which is quite like the earlier version of the EMA RMP format.

Generally, the strategy of both concepts for risk management (REMS and RMP) is to manage and prevent the known or potential serious risks associated with a medicinal product to ensure that the benefits outweigh risks. Each REMS is designed to address a specific and serious safety concern, including information communicated to and/or required activities to be undertaken by healthcare providers, pharmacists, and patients (elements to assure safe use). REMS is generally required by the FDA, depending on the size of population likely to use the medicine, the seriousness of the disease, expected duration of treatment, expected benefits of the drug, and seriousness of known or potential risks. RMP consists of a medicine's complete safety profile; how its risks will be prevented or minimized; plans for further studies and other PV activities to gain more knowledge about the safety and efficacy of the medicine; and effectiveness of risk-minimization measures. The EMA requires submission of the RMP at the time of application for a marketing authorization of a medicine in the EU and additionally as required by a national competent authority whenever information affecting the benefit-risk balance of a medicine is available. RMPs are continually modified and updated throughout the product's life cycle as and when new or significant information is available.

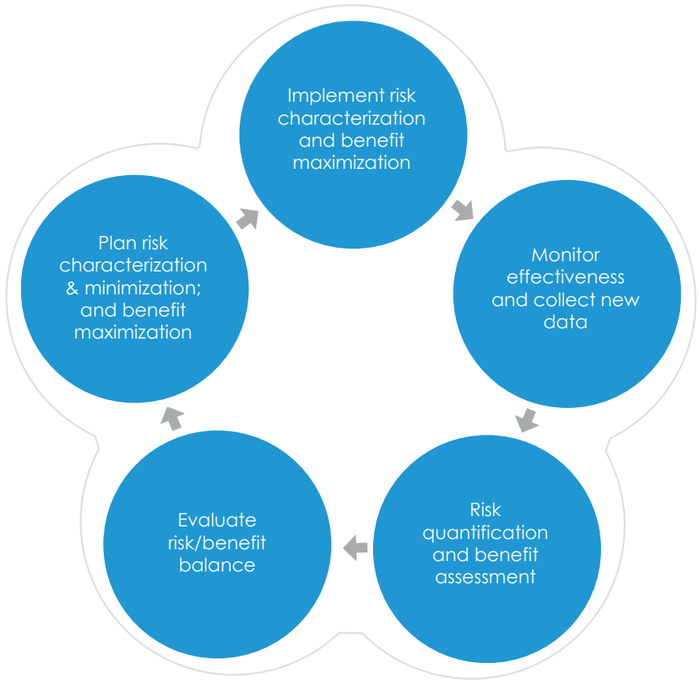


Figure 1: Typical presentation of a risk management cycle

What Has Changed In Revision 2?

The revised format for RMP sets a new milestone in a progressive approach to risk management. The new RMP template is a straightforward and well-structured document that can be used by RMP experts, and the concepts behind risk management have been justified to better reflect the stages of the life span of a medicinal product. Revision 2 of GVP module V addresses most of the areas identified for improvement based on experience and feedback to EMA and other stakeholders.

Major revisions include:

- Further clarification on what the RMP should focus on with respect to an important identified risk, important potential risk, and missing information
- Guidance on the expected changes in the RMP during a product's life cycle
- Removal of duplication within RMPs and other submission documents
- Updated minimum requirements for various initial marketing authorization applications (MAAs)
- An amended RMP template

Redefined Safety Concerns

The major change in the revised guidance on RMP has been with respect to safety concerns, which ensures RMP will be more risk-proportionate in terms of consideration criteria and characterization of important identified risks, important potential risks, and the missing information. The safety concerns are now more precisely defined, helpful in understanding what is relevant for inclusion in safety specification (Part II) of the RMP, how the important risks are characterized, and how the safety concerns evolve through the life span of the medicinal product.

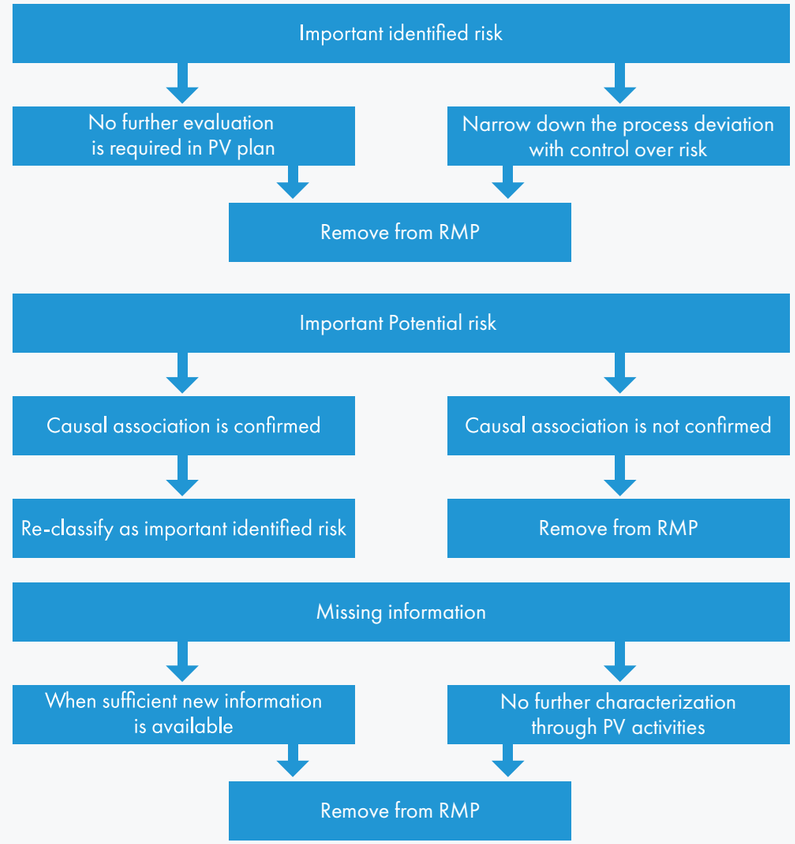
Table 1: Differences in Definitions of Safety Concerns in GVP Module V Revision 1 and Revision 2

Safety Concern	GVP module V Revision 17	GVP module V Revision 28
Identified risk	An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest.	Undesirable clinical outcomes for which there is sufficient scientific evidence that they are caused by the medicinal product.
Potential risk	An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed.	Undesirable clinical outcomes for which there is scientific evidence to suspect the possibility of a causal relationship with the medicinal product, but where there is currently insufficient evidence to conclude that this association is causal.
Important identified risk and important potential risk	An identified risk or potential risk that can impact the benefit-risk balance of the product or have implications for public health.	Important identified risks are likely to impact the risk-benefit balance of the product which would usually warrant: -Further evaluation as part of the PV plan (e.g., to investigate frequency, severity, seriousness, and outcome of this risk under normal conditions of use, which populations are particularly at risk); - Risk minimization activities: product information advising on specific clinical actions to be taken to minimize the risk, or additional risk minimization activities. The important potential risks to be included are those when further characterized and if confirmed, would have an impact on the risk-benefit balance of the medicinal product and would usually require further evaluation as part of the PV plan.
Missing Information	Gaps in knowledge about a medicinal product, related to safety or use in a particular patient population, which could be clinically significant.	Gaps in knowledge about the safety of a medicinal product for certain anticipated utilization (e.g., long-term use) or for use in a particular patient population, for which there is insufficient knowledge to determine whether the safety profile differs from that characterized so far.

Evolution Of Safety Concerns Through The Product's Life Cycle

The information required to be provided in the safety specification of the RMP varies depending on the stage of the product's life cycle and the need for post-authorization data. It is well known that a full RMP should be submitted for initial MAAs, whereas for products with an established safety profile and post-marketing knowledge (e.g., generic drugs, fixeddrug combinations), most modules of the safety specification are not required. Similarly, risk-proportionate RMP in a true sense implies that knowledge regarding a medicinal product's safety profile is expected to increase and safety concerns are expected to evolve through the product's life cycle. The GVP module V Revision 2 provides guidance on the removal of safety concerns from the existing RMP post-authorization. This encourages marketing authorization

holders (MAHs) to critically revise the list of safety concerns, PV activities, and risk minimization measures in the post-marketing phase. The product's safety profile will thus change, confirming or refuting a causal association with the medicinal product. In addition, PV activities and risk minimization measures may also change over time. Duplication of the information on identified and potential risks already covered in the safety sections of the dossier, including signal evaluation, periodic benefit-risk evaluation, or safety variations procedures, is avoided. The module SVII is now confined to "New safety concerns and reclassification with a submission of an updated RMP."



Other Changes In Safety Specification

The revised guideline states that the RMP should provide summary information of the patients studied in clinical trials in an appropriate format (e.g., tables/graphs) in the clinical trial exposure section (module SIII) of the initial RMP or when there is a major update due to new exposure data from clinical studies (e.g., in a new indication). In the case of absence of new significant exposure data, this section is not required to be updated. The excluded populations from the clinical trial development program should be included as missing information in module SIV, "Populations not studied in clinical trials," only for approved and proposed indications and if the use in such populations might be associated with any risks of clinical significance. It has now been made clear that the information on post-authorization experience of the product in other regions outside the EU or from other authorized products with the same active substance from the same MAH should also be discussed in module SV, "Post-authorization experience."

Plans For Post-Authorization Efficacy Studies (PAES)

The scope of the modules for PV plan and post-authorization efficacy studies is now more restricted with clear understanding. The revised format of RMP is confined to a list of post-authorization efficacy studies imposed as conditions to the marketing authorization or when included as specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances.

Summary Of Changes To The Risk Management Plan Over Time

A new annex 8 has been added to the revised format, which lists all the significant changes to the RMP in chronological order, with the date and version number of the RMPs prepared. This should mention if any safety concerns were added, removed, or reclassified; whether any studies were added or removed from the PV plan; and whether any risk minimization activities were modified in the risk minimization plan.

Changes In The Template

The name and signature of the qualified person for pharmacovigilance (QPPV) should be presented on the title page to ensure that the RMP has been reviewed and approved by the MAH/applicant's QPPV and that the electronic signature is documented.

The revised guidance text is streamlined by removing duplications within the RMP modules or in other safety reports, including the periodic safety update report (PSUR) or elsewhere in dossier submission. The update focuses on conciseness in sections that often contain duplicate information, including the summary table of safety concerns, epidemiology, populations not studied in clinical trials, summary of treatment results, etc. The summary of minimum RMP requirements for different initial MAAs (full MA application, generic product, fixed combination product, biosimilars, etc.) allows the stakeholders to clearly understand the information to be included in various sections of the RMP.

Other changes in Revision 2 are small and simple. For example, the Part I Product Overview of the RMP does not require the date and country of first worldwide authorization and launch to be recorded.

Most of the sections are largely unchanged from the original document, but there are some significant differences. The mapping between RMP modules and information in the electronic common technical document (eCTD) remains the same in the revision.

Challenges With The Revision

The organizations working on RMPs should update their standard operating procedures and work instructions with new definitions of terminology of safety concerns. With the revision of the RMP format, there also exists a major challenge in terms of time, data integrity, and Regulatory compliance with the transfer of content from the existing template to the new template when an RMP update is required. Converting an RMP from the Revision 1 format to Revision 2 is not a simple job of condensing or transcribing the content. There have been issues observed while making the changes in a "track change" version due to the addition and removal of sections in the new format. However, with the streamlined process and the expertize of the authors involved, it is not an impossible task. The scope of the revised RMP format is substantial. The question always remains as to whether MAHs will be able to justify the available evidence enough for a critical review, and whether the assessors from the agency will agree to the proposed changes.

Moving Forward

Since April 1, 2018, EMA requires that MAHs submit RMPs in the Revision 2 format for all initial MAAs, D91, and D121 responses and for RMP updates. Health Authorities in the rest-of- the-world (ROW) countries requiring the EMA RMP Revision 1 format have also adapted to the revised format. The authorities of other countries requiring their own specific templates, like Mexico, Chile, etc., have been continuing with the same for RMP submissions.

In the near future, we can hope and expect the health authorities of all the ROW countries to adapt to the EMA Revision 2 format of the RMP to ensure a consistent global risk management system for medicinal products, with a prospect of better patient safety.

Conclusion

Revision 2 of GVP module V results in simpler RMPs. The safety concerns are redefined to clarify relevant information to be incorporated in the RMP of a medicinal product, leading to RMPs that are not loaded with information on risks already covered in other documents. Indeed, the focus is on identifying or characterizing the safety profile of the medicinal product, proposing measures to prevent or minimize the risks, and including an assessment of the effectiveness of the proposed measures. The revised RMP format provides a clear, focused, and scientifically justified vision for risk management, as well as saving companies time through a more concise, less repetitive approach.

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www.pharmaceuticalonline.com

References are available at

https://www.pharmaceuticalonline.com/doc/ema-s-revised-format-for-risk-management-plans-what-you-need-to-know-0001

Infographic

Center of Excellence
Global Cosmetics Regulatory Services

EU COSMETICS REGULATIONS THE BASICS

Why?

EU Market Value – **Euros 80 Billion**

- Increasing preference for vegan, organic, and natural cosmetic products
- Skin care and toiletries segment has the major share in the EU Cosmetics market

What?

EU Cosmetics Directive (76/768/EEC)

EU Cosmetics Regulation (Regulation (EC) No. 1223/2009)

EU Regulation 655/2013

CosIng is the European Commission database for information on cosmetic substances and ingredients

Where?

CPNP Portal

Cosmetic Product Notification Portal (CPNP) was created for the implementation of Regulation (EC) No 1223/2009 on cosmetic products and aimed at harmonizing the 28 EU Member States + 4 European Free Trade Association (EFTA) countries covered under this legislation

Who?

Person importing cosmetics into European Union can act as a local agent or responsible person

How?

To know more about various country specific cosmetics' Regulations please Scan Here

4 KEY ASPECTS TO REGISTER/NOTIFY COSMETICS IN BRAZIL

Brazil's cosmetic market is flourishing, showing no signs of slowdown even in the economic fluctuations. In Brazil, cosmetics in various segments such as organic, skincare, haircare, etc. are gaining popularity among users, and their market extent is increasing day by day. It is the responsibility of National Agency of Health Surveillance (ANVISA), functioning under the Ministry of Health, to regulate and approve the manufacture, import and trade of cosmetics in Brazil.

Be it low-risk products such as simple shampoos or high-risk products like baby products with special claims, it is mandatory to inform the Health Authority before being marketed in the country. To do so, manufactures and importers must obtain approval from ANVISA either through registration or notification. The success of registration or notification, however, highly depends on how compliant the manufacturer is when implementing the following 4 key aspects.

Product Classification

Before heading for approval with the health authority (HA), categorizing the product is important as it decides the mode of approach i.e., registration or notification. As with any other major market, even Brazil has its own classification for cosmetics. Based on the degree of risk, a cosmetic product is categorized as risk degree 1 or risk degree 2.

- Risk degree 1 is for low-risk cosmetics which comprise of simple shampoos, conditioners, shaving foams and lotions, make up products, and other products which do not claim anti-aging, anti-dandruff benefits and comprise of UV filters in chemical formula. These products are notified through dossier with basic product data and labeling text and can be imported and distributed immediately after notification.
- Risk degree 2 is for high-risk products. Generally, these products have anti-aging, anti-dandruff and other similar claims. They comprise of sunscreen filters, creams used close to eyes' area, hair colouring products, baby products, etc. These products must be registered with ANVISA with extensive product information and other details as requested by the HA.

Ingredients Listing

In accordance with Brazilian regulations for cosmetics, the ingredients that are allowed, controlled and prohibited are listed after due study. Before formulating a cosmetic product, listed ingredients must be thoroughly referred to, and ingredients banned must be avoided for successful compliance with ANVISA. The lists can be accessed through the official website of ANVISA.

- Positive and restrictive ingredients - Chemicals that are restricted for use in product formulation, except in conditions and exceptions laid down as per current regulations. They may be used in special conditions and controlled quantities.
- Listing of UV filters – UV filters which are allowed in formulation of cosmetic product without causing any side effects to skin during the usage.
- Negative Listings – Chemicals which are deemed hazardous and are prohibited from using in cosmetics by ANVISA.

Product Dossier

The final dossier submitted for notification / registration must comprise of a set of documents to support and declare the safety, quality and efficacy. As mandated by the ANVISA, they can be listed as:

- For Notification
  - › Product composition sheet (PCS)
  - › Function of ingredients in the PCS
  - › Ingredients' bibliography / technical references
  - › Physical, chemical and organoleptic specifications of the final product
  - › Microbiological specifications of final product
  - › Packaging specifications of final product
  - › Test results of product stability
  - › Label artwork (in both original language and Portuguese language)
  - › Description of product finality
  - › Free sale certification (from country of origin, if imported)
- For Registration: All documents needed for notification are also required for registration too. Additionally, two more documents are mandated to be attached in the dossier
  - › Test results proving the products' claims
  - › Safety test data of product in use

Notification / Registration Validity

A notification/registration is compliant only if it is valid with ANVISA. Its validity expires after 5 years from the date of approval following which it must be renewed. The renewal must be initiated 6 months ahead of the actual expiration date. Mandatory annual inspections are also conducted to ensure the adherence to regulations.

Apart from complying with the aforementioned requirements, there is additional Regulatory information that must be investigated for compliance. Make a compliant market-entry. Be informed.

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RIGHT FROM THE FIRST STEP

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WHAT ARE QUASI-DRUGS?

Quasi Drugs are one of the two primary categories of beauty products in South Korea. The other category of beauty products is cosmetics. There is a thin line between drugs and cosmetics, which can be considered as quasi-drugs. Since their benefits are not as suitable as drugs; South Korea's health authority (HA), the Ministry of Food and Drug Safety (MFDA) has categorized them under pinpoint skincare products like acne for skin dullness. Quasi-drugs are generally classified into two coordinates:

Group 1

- Items used for sanitary purposes such as sanitary pads, tampons, and menstrual pads
- The textile used for manufacturing masks such as dust and surgical masks
- Wet wipes for oral hygiene
- Sanitary products used for protection, preservation, and treatment of affected areas that includes different kinds of bandages such as eye bandage, plastic bandage, cylindrical elastic

bandages, and elastic bandages. Absorbent cotton, gauze, and plaster are also a part of it

Group 2

- Odor inhibitors like toothpaste, antiperspirants, and bath products
- Hair care products that are only meant for external usage
- Products that don't contain nicotine for those who smoke
- Contact lenses
- Ointments and anti-inflammatory products for external use
- Products for oral hygiene such as teeth whiteners, vitamin tablets, and energy drinks
- Disinfectants which are not directly applied to human beings

If a person files an application for the approval of Quasi Drug for the first time, he/she must be registered as a quasi-drug manufacturer or an importer. The registration process for quasi drugs is systematic, and it has few protocols to qualify. Listed below is the step-by-step description.

- Submission- The data must be submitted to the HA for product approval. Then for the safety and efficacy evaluation of the product will be submitted to the Cosmetics Evaluation Division (CED) and National Institute of Food and Drug Safety Evaluation (NIFDS). Lastly, for the product to be waived from safety and efficacy evaluation it will be handed over to Medical Products Safety Division, Regional Food, and Drug Safety.
- Review- After HA receives the safety and efficacy evaluations, they will review the specifications. Meanwhile, they will also inspect the manufacturing sites to assess the condition and quality of the production.
- Approval/Notification- HA will issue approval, and notification both if it qualifies in the Korean Pharmacopoeia, and other pharmaceutical compendia recognized by the MFDS.

Data Required for Approval & Notification

- Origin and development history of the drug, structure identification, physical, and chemical characteristics with specifications, and test methods
- Stability, toxicity, efficacy, and effectiveness data for the current use in foreign countries
- Comparative review with other similar products domestically manufactured, and data on the characteristics of the product
- The data demonstrating the product is subject to notification with specifications, and test methods

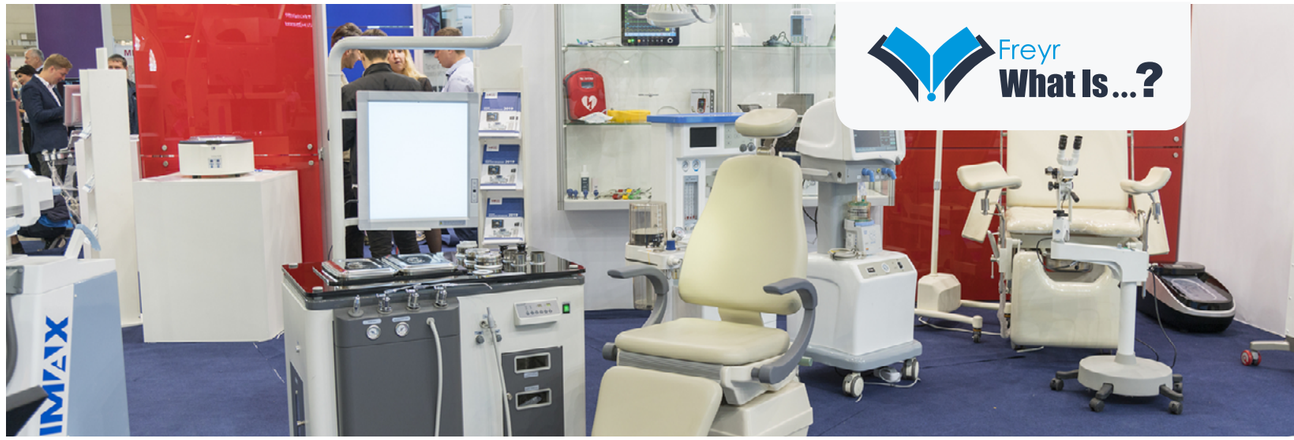
Processing Period and Fee

- Approval- Quasi-Drugs' Specifications, and Test Methods (Safety and Efficacy) takes 70 working days for first approval. If done online, the charge is 695,400 KRW and 768,600 KRW through mail. For second approval, it takes 55 working days with 308,750 KRW if done online and 341,250 KRW through mail.
- Notification- In the same way, it takes 10 business days for the 1st notification with 76,950 KRW through online, and 85,0560 KRW by mail. Likewise, for the second notification, it takes 40 days with 308,750 KRW online, and 341,250 KRW through mail.

Basic Requirements

- For imported products, a certificate must be issued/attached proving the product is manufactured, and marketed according to the law of the corresponding country
- Ointments, and cataplasma which are used externally should follow Manufacturing Standards of Quasi-drugs notified by MFDS; which is necessary for inspection of good manufacturing practices (GMP)
- The above mentioned are general requirements for Quasi Drug registration in South Korea. It may vary from case-to-case. What's your requirement? Let us know. We can answer your queries and address any concerns you may have. Contact our experts at sales@freyrsolutions.com

WHAT ARE TODOKEDE, NINSHO AND SHONIN?



The complex registration process of medical devices in Japan makes the market one of challenging markets for foreign manufacturers. Upon understanding the process, the complication eases, and the results are compliant and worth the efforts. Medical device companies interested in offering their products in Japan, must abide by Japan's Pharmaceuticals and Medical Devices Act (PMD Act). Medical devices in Japan are classified based on their risk; which are divided into 4 classes such as:

- CLASS I- General (low-risk)
- CLASS II- Specified Controlled (low/medium risk)
- CLASS II- Controlled (medium-risk)
- CLASS III- Highly Controlled (medium/high risk)
- CLASS IV- Highly Controlled (high-risk)

Based on the class of the device, Regulatory pathway is defined. Following are the Regulatory pathways for registering medical devices in Japan.

Pre-market submission (Todokede)

General Medical Devices (Class I) can file a pre-market submission to the PMDA. This is a notification, and no review/assessment by the PMDA will be conducted. Class I devices only require registration via the Todokede process.

Pre-market certification (Ninsho)

Class II (and a limited number of Class III) devices which have an associated certification standard (Japan Industrial Standard - JIS), are subject to pre-market certification. Many, but not all, JIS are based on existing ISO/IEC standards. Your MAH will file your application with a Registered Certification Body (RCB). The process is like the European CE Marking process where reviews are outsourced to a third party like a Notified Body. Class IV, and the majority of Class III devices, require the Shonin process. Most Class II devices, and a few Class III devices, follow the Ninsho pathway.

Pre-market approval (Shonin)

Class II and III devices without a specific certification standard, are subject to the pre-market approval process. This also applies to all Class IV devices. In this case a MAH will have to file a pre-market approval application with the PMDA to obtain approval from the MHLW. Class II products that do not hold, or comply, with the Ninsho Certification Standard can be approved via the Shonin pathway.

For Todokede and Shonin Regulatory pathways, the permission is granted by the PMDA, whereas for Ninsho it is done by the third-party agency i.e. Registered Certified Body.

With the growing demand for medical devices in Japan, manufacturers must be aware of region-specific terms and their definitions in detail. To know more about Todokede, Ninsho, Shonin Regulatory pathways for Medical Devices, reach us at sales@freyrsolutions.com.

Case Study

Medical Device Labeling Gap Analysis

Center of Excellence
Global Medical Device Regulatory Services

CLIENT
Leading manufacturer of Laryngoscopes

GEOGRAPHY / LOCATION(S)
USA

SERVICE(S) / SOLUTION(S)
Labeling Gap Analysis

THERAPEUTIC AREA(S) / INDICATION(S)
Emergency Medicine

PRODUCT(S)
Laryngoscope

Business Imperatives

- It is a class I device and the client was re-listing the device in FDA FURLS
- The label has not been checked as per the latest 21CFR 801 requirements
- The client wanted to obtain CE mark for the device and wanted the label to comply for EUMDD requirements

Challenges

- The turn-around-time required for the analysis was very short
- The amount of label to be analyzed were about 10 pages

Freyr Solutions & Services

- Freyr provided a comprehensive gap analysis of the labeling based on 21CFR801 in the stipulated time
- Freyr identified key components missing from the label for e.g. the labeling indicated the device cannot be used in an MRI environment, but the corresponding symbol was missing; the product is provided a single use device which was missing in the labeling

Client Benefits

- Timely completion of the requirements thereby saving time to listing and continuation of the product availability
- Compliance to the latest and key 21CFR 801 requirements thereby avoiding any non-compliance issues

Case Study

Regulatory Strategy and Submission Services

Center of Excellence
Publishing & Submissions

CLIENT
A contract research organization and genome-scale diagnostics services company specializing in genome guided medicine

GEOGRAPHY / LOCATION(S)
USA

FUNCTION(S)
Determination of EU classification

SERVICE(S) / SOLUTION(S)
Product Classification

THERAPEUTIC AREA(S) / INDICATION(S)
Oncology

PRODUCT(S)
Next Generation Genomic Sequencing (NGS) based medical device

Business Imperatives

- To support researcher engaging in case-control, family-based, or proband-only genomic studies of disease, pharmacogenomics, and cancer. Since the product in scope is based on latest NGS (Next Generation Sequencing) based technology, the classification is complicated

Challenges

- There were no regulations in use pertaining to the NGS technology-based devices

Freyr Solutions & Services

- Freyr collated all product specific information from Personalis
- Freyr classified the product as per EU specific regulatory guidelines as detailed in the below section
- Freyr also interacted with the competent authority and confirm on the classification of the product with the respective Health Authorities
- Based on the classification, Freyr provided the high-level Regulatory approach for product registration as per the classification for development of overall Global Product Registration Strategy

Client Benefits

- The EU Classification of the NGS based product is identified

NURTURE THE CULTURE OF COMPLIANCE WITH SRIDHAR SARVA

General Manager-Compliance & Audit

Getting things done is good. But getting them in a way that they are intended to be is what makes all the difference. To make us, Freyr, a key differentiator across the globe in any Regulatory activity we take up, standardizing the procedures right from the first step for the best outcomes during audit and validation is our own Sridhar Sarva. Known for his diligent work attitude, Sridhar Sarva is heading the Center of Excellence for global compliance and validation services.

Do you know? Many of a times we see you as a teacher, invigilator, warden, and a field coach, in the presence of whom we seldom cross our limits to keep things and processes out of order. Thank you so much for making us stick to the roots.

Here, I would like to take a pause and thank everyone. It is not possible without your understanding of my job-binding nature. Your understanding and cooperation makes it possible.

The global scenario of life sciences industry is evolving and adopting digital platforms aggressively. Do you foresee any new GxP will be defined for digital or Artificial Intelligence? Or Would they be covered in existing GxPs?

This is a good question. Adopting digital platforms is good to minimize manual efforts but man should not become slave or victim of stringent GxP workflow. Digital platform should be able to provide flexible, yet compliant and seamless solutions equivalent to manual processes.

Artificial intelligence is good if adopted for harmonization without diluting human creativity.

Guidelines in GxP evolve over time and as digital platforms, AI and IOT are more adopted by GxP companies, the evolution continues. I am sure the GxP fraternity would consider above points on seamlessness and retaining human creativity as the guidelines get amended.

Once you said, compliance is a journey not a destination. Could you please let us know, how far we have come in that journey? And how best we are doing. Enroute, which is the most difficult and discussed compliance issue we had to deal with?

Many questions in one question. Let me take them one by one.

There can be milestones but no destination in Compliance journey. Continual improvement (journey), an essential element of Compliance is the only Mantra to sustain and progress. Some of the yesteryear giants lost the race because of lack of continual improvement while others sustained their market position with vertical and horizontal improvement initiatives.

Most difficult part is to cultivate a culture of compliance.

Most discussed have been "Why" and "Why not"

If Sridhar Sarva was a fictional character/superhero, who would he be?

Gulliver

Given a chance, what is the one thing that you would like to change about the global audit and Regulatory compliance framework?

I wish to change the "Stereotyping" approach / thinking regarding audit and compliance.

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

Three of them:

1. "When you innovate, you've got to be prepared for people telling you that you are nuts"
2. "Second Place is the First Loser"
3. "Your freedom is till my nose"

Lastly, beyond the realms of Freyr, what is your definition of a perfect day? What is Sridhar beyond Audit, Compliance and Validation?

Perfect day is boring as it would be like a vacuum post-victory. However, the day I don't complain and no one around me has any complaints about anything is a perfect day.

Beyond my profession, I like nature (Nature Lover) and discovering life.

PERFECT DAY IS BORING AS IT WOULD BE LIKE A VACUUM POST-VICTORY. HOWEVER, THE DAY I DON'T COMPLAIN AND NO ONE AROUND ME HAS ANY COMPLAINTS ABOUT ANYTHING IS A PERFECT DAY.

SWITZERLAND

CHERISH THE ALPINE TRANQUILITY

What is the first thing that pops into your head when you hear "Switzerland"? Snow covered mountains, cheese, chocolates? What if I tell you that Switzerland is much more than that?

I have always believed that traveling is like meditation. It helps you find your lost soul, cleanses it and gives you a clearer perspective of life. And after visiting Switzerland, this belief of mine has grown even stronger, because the country is nothing less than an enchantment. One of the places where we were staying had a picture of mountains on the wall with a quote that said, "Going to mountains, is like going home." And I couldn't agree more. So with the Pixar motto, adventure is out there, we began our week-long holiday in Switzerland, the home of Alps.

Torgon

Our first destination in Switzerland was Torgon. We decided to make it our base as it offered picturesque landscapes and the best skiing resorts. What we didn't realize was that reaching Torgon is quite a task. We took a flight from Mumbai to Geneva via Munich and from Geneva, we took a train to a station called Aigle. One thing which a traveler must know while travelling in Switzerland is to buy a Swiss rail pass. It's cheaper compared to other transportations and the train journeys are just WOW! So, from Aigle we finally took a 45-minutes bus ride to Torgon.

Torgon is an extremely small village amidst Swiss Alps. It is located in the canton of Valais overlooking the Rhone valley and Lake Geneva. The moment you step down in Torgon, all you can see is snow covered mountains and tall, lush-orange/yellow trees (as it was autumn). Even the best of the camera cannot capture the beauty that beholds Torgon. The place is famous for two things: skiing and archery. Torgon has best the archery range in Valais and of course best landscapes for skiing. Oh, and beautiful hiking trails too. After a lovely afternoon of hiking through the woods, we decided to call it a day as there is nothing much to do after sunset.

Aigle

The next day we left Torgon to explore Aigle, the base of Torgon. I assumed that it would be similar to Torgon, but what I didn't know was that Aigle has a lot of Vineyards. Wherever you look, there is a vineyard; at your eye-level, on the mountains, on the slopes, everywhere! And the view was even better as it was autumn. So as you move your eyes across the vineyards and trees, the shade of leaves also changes. From green to yellow, to red, to brown, it was like mother-nature was painting those leaves herself. We walked through the streets of Aigle which looked like straight out from a stunning painting.

Aigle is famous for protecting its heritage, culture, and art of winemaking. You can find many tours here that takes you through the Vineyards, introducing you to the art of fine winemaking. The heart of the town is Château d'Aigle (Aigle Castle). Located between Lake Geneva and Swiss Alps, the castle of Aigle dates back to 12th century and holds wine production in its heart. Guarded by vineyards from all the sides, the castle also holds interactive visits for The Vine and Wine Museum which is a part of the castle tour. The museum takes visitors through the journey of wine from grapes to table. It showcases the tools and equipment from the 12th century and exhibits their evolution. They play particularly with your senses to make you understand the process of winemaking.

It takes almost an entire day to roam around the castle and the museum and when you come out of the castle, all you crave for is some really good and fulfilling food. And what is better to eat in Switzerland on a chilled night than a Swiss fondue?! If you didn't eat traditional Swiss fondue in Switzerland, then your trip to Switzerland is a waste!

Interlaken

If you don't like staying in a crowded area, yet, you want to explore the best of the country, then Interlaken is the place for you. Interlaken is the gateway to Swiss Alps and is situated between emerald colored stunning lakes of Thun and Brienz. It is a beautiful traditional resort town with old timber houses and parklands. It actually leaves you spellbound. The town is surrounded by dense forests and alpine meadows which makes it look like a fairy tale town. It is also the adventure capital of Switzerland. You can paraglide, hike, or ski. It is astonishing to see a bunch of people paragliding (read: flying) over your head, literally.

We shifted our base to Interlaken for a few days because it gave us better accessibility to tourist spots. And the first place that we went to see was Glacier 3000. I was way beyond excited! Glacier 3000 had been on my list of places to be, ever since I know anything about Switzerland and the place didn't disappoint me at all. As the name suggests, the place is 3000 meters above sea level. To reach there, we took a big aerial tram and the view was heavenly. Imagine mountains covered in yellow trees on one side and snow on the other, that's what it was! Well, we reached to the top and it was freezing at -2 degrees (along with high wind alert). But the view compensated for the cold weather and wild wind. Once you reach the top, there is an alpine coaster, the peak walk, dog slides, and glacier walk too but because of heavy wind, all of them were closed except the peak walk. The peak walk is a 170-meter-long suspension bridge between two mountain summits. It is a thrilling experience to walk on a suspension bridge which is 3000 meters above sea level. Though it is extremely safe, a chill runs down your spine when you look down and see just snow.

Our next stop was Harder Kulm, the top-most location in Interlaken. They have a saying in Interlaken, "If Interlaken had a king, he would reside in the Harder Kulm." Why? Because it is 1322 meters above sea level and gives a breathtaking view

of the little town and the two rivers. And it takes only 10 minutes on a funicular cable car to reach Harder Kulm from Interlaken. You can practically spend your entire day just staring at the view. The emerald lakes, blue sky, clouds, and the small town, it is absolutely surreal and a must-visit. Did I mention there are hike trails too? After witnessing the magic of Harder Kulm we decided to head to St. Beatlus caves. To be honest, the caves are way prettier from the outside than inside

Bern

I am horrible at geography, so I assumed that the biggest city, Zurich, would be the capital of Switzerland. But to my surprise, Bern is the capital of the country. This extraordinary city is an epitome of old classic architecture. Getting around Bern is pretty easy as transportation is quite tourist friendly but it is advised that if you really want to explore Bern, then just walk around. Even if you get lost in the city, it is highly possible that you'll end up finding something splendid.

The old city of Bern is a UNESCO world heritage since 1983 and it has preserved the tradition and culture of Bern ever since. The city is perfectly preserved and is apt for a random stroll. You come across cute little houses, walls covered in red maple leaves, people jogging in the afternoon, small streets, random huge chess boards (open to play), flowers hanging out from balconies; all of it is so heartwarming! There are many classic places where you can hang out such as Zytglogge Clock Tower, parliament house, bear park etc., or you can just walk by river Aare. Also, Bern has many museums out of which my favorite is Musée d'Histoire de Berne (Bern Historical and Einstein Museum). The museum is home to many artifacts related to prehistoric times of Bern and others from Asia, Oceania, America, and Egypt. The other part of the museum is entirely dedicated to the work and life of Albert Einstein who spent a significant time of his life in Bern. In 2005, what started as a temporary exhibit, Einstein

museum is now a permanent part of Musée d'Histoire de Berne. After a nice fondue break, we continued to stroll around the city and decided to head to the famous Rose Garden. Initially, we were a little hesitant as it was autumn and we weren't sure as to what awaits us but the locals said that we must visit the garden because it's a dream. And they were absolutely correct. I never knew autumn could be so beautiful. The Rose Garden was way beyond my expectations. Apart from the trees and plants, there is a path which leads you to a balcony of the garden from where you can enjoy a panoramic view of the old city and the Aare river. This was the main highlight of Bern! Also, there is a small restaurant by the balcony where you can sit and enjoy the sunset with a cup of chocolat chaud.

In the past two years, I have traveled quite a few places, but none of them has stolen my heart the way Switzerland did. It was, indeed, a trip to remember. And it wasn't special because we decided to explore each and every inch of Switzerland, but because we followed the path that our hearts guided us onto. Robert Frost once said that the lesser travelled road makes all the difference in the world. Well, it is absolutely true. We decided to visit off the beat places of Switzerland and guess what, it was tranquil, it left me wanting more.

I'm going to visit this beautiful country again and very soon, to pick up from where I left off. But until then, Switzerland, Au revoir!

FREYR FESTRONIX 2018

SPORTS SHOWS SAGAS

Center of Excellence
Regulatory Strategy

#10YearsChallenge

How Compliant Is Your Benefit-risk Evaluation, Then and Now?

During Clinical Trials

Post the Product Launch

PERFORM PERIODIC BENEFIT-RISK EVALUATION FOR A MEDICINAL PRODUCT/MEDICAL DEVICE FOR CONTINUED COMPLIANCE

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