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Regulatory Crisis MANAGEMENT

Best Practices for Dealing with the Common Crisis Events for the FDA-Regulated Industry

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By

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Introduction:

Medical product companies face unique crises that go beyond typical business challenges, such as stagnant product pipelines, unexpected regulatory hurdles, and unforeseen safety issues with marketed products. Many companies are unprepared for these situations, making crisis management essential—especially in highly regulated industries like those overseen by the FDA.

When working with the US FDA, medical and healthcare companies frequently encounter crisis events that require strategic regulatory planning, precise execution, and diligent follow-up to resolve. Crisis management differs from risk management in that it addresses unknown threats that occur unexpectedly, rather than managing potential or known risks. If not handled promptly and effectively, a crisis can negatively impact FDA applications, public image, and financial stability.

This book takes readers through a simulated real-world crisis scenario that could endanger a company's reputation, profitability, and future. It focuses on regulatory management from an FDA perspective, offering insights on crisis communication, timely response, and reputation management. Readers will learn to develop and manage a crisis communications plan in real time, with a special emphasis on FDA guidelines and media engagement.

This practical guide, packed with tips from the author's regulatory experience, will benefit regulatory affairs professionals, project managers, executives, and crisis management personnel in FDA-regulated industries.

Chapter 1

Defining, Describing and Defending from Crisis Situations in the Medical Product Industry

A crisis is an event or series of related events expected to lead to a problematic, dangerous, unstable, and damaging situation affecting an individual or a company. If not managed adequately and timely, a crisis could have devastating impacts. It can negatively affect the affected party's economics, public image, and security.

Most crises arise from internal or external factors with little or no warning and require immediate decisions. The majority of these crises are multi-dimensional and require the involvement of diverse resources within a given organization. Additionally, most crises require a change in organizational practices as the existing system has failed. The crises described in this chapter are inherent to the medical product industry and do not include those caused by natural disasters and other universal human factors, such as rumours, workplace violence, terrorist attacks or artificial disasters.

Unlike risk management, which involves planning to deal with known threats of a narrow scope likely to occur in the foreseeable future, crisis management involves managing unknown threats during and after their occurrence. An organization can also build broad crisis management policies to address situations that could lead to a crisis. It is possible to prepare for potential situations by learning from similar organizations' experiences through rounds of risk analysis. Most common crisis management policies and plans include emergency and business-continuity management, which address past and current global existential issues.

However, medical product companies must address additional issues, such as stagnant product pipelines, unplanned regulatory hurdles, and unexpected safety issues with marketed products, which companies must address appropriately during planning. Since internal and external factors cause these situations, finding solutions requires managing the internal causes and controlling external reactions. These actions are considered part of risk management strategies, which help mitigate or prevent crisis occurrence.

Crises can happen regardless of an organization's size, location, available resources, and employee skill levels. In all cases, early identification and management of crises are vital for an organization's survival. Crisis management involves methods for responding to a crisis, establishing metrics for dealing with crises, and developing effective response mechanisms. A crisis management plan should include theoretical worst-case scenarios and solutions in the form of a contingency plan.

This chapter examines crisis situations in relation to variables and trends in the life sciences industry. It provides a list of resources available to assist in addressing risks and crises before, during, and after they happen.

Types of Crises Specific to the Medical Product Industry

The medical product industry is unique in its reliance on biological science and human response to its products. The resources invested and the risk of failure due to poorly definable and unpredictable events are unparalleled. Products developed by the industry have to go through some of the most extensive testing, review and approval processes compared to other industries. Products range from simple chemical drugs to complex biological products and sophisticated life-saving machines.

The industry's regulations are changing constantly, often as regulators react knee-jerk to isolated crisis events. The global market for medical products leads to additional issues related to international business and regulatory, legal, financial, logistical and social affairs. The industry is very diverse in terms of the profiles of the companies that compete side by side in the same market, from large multi-billion-dollar corporations with thousands of employees and worldwide operations to small businesses that pale in comparison to their competitors. Companies must constantly maintain their public perception and respond to adverse media reports.

With the above complex issues at play, there are three broad categories of crisis unique to the medical product industry:

- technological crisis
- regulatory crisis
- organizational crisis

Technological Crises

A technological crisis could involve urgent events requiring immediate attention or long-term events brewing for an extended period and requiring substantial operational and policy reviews. Examples of this type of crisis are unexpected issues with the safe use of a given product or failure of research and development activities to replenish dwindling product pipelines.

New Safety Concerns for Product

Despite extensive testing of medical products in experimental systems (in vitro and in vivo) and human subjects, it is almost impossible to predict all the possible adverse events that a drug, biological product or medical device could cause. The best-case scenario is when early studies with an investigational product indicate a safety issue, and further development stops. However, discovering unexpected product safety issues during late-stage clinical trials, or worse still, after marketing approval, could lead to a significant crisis that requires making decisions about educating consumers or withdrawing the product from the market.

There are several guidance documents from regulators in the US and EU regarding the management of safety events during the investigational phase and after marketing approval.[2] [3] During the investigational phase, the safety profile of a drug, biologic or medical device is closely monitored, and adjustments are made as new information arises during this phase. Hence, finding new, unanticipated adverse events late in a product's development phase is generally considered an accepted risk. Rejection of a product late in development may be an existential event for a small company with one or few products in development; however, this can be prevented by diversification of the pipeline and judicious planning.

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) provide numerous opportunities to interact with regulators to discuss how to address safety issues identified during development. Hence, premarket safety events generally do not meet the definition of a crisis.

On the other hand, safety events identified after obtaining marketing approval can lead to a crisis. Regulatory authorities expect companies to establish robust pharmacovigilance programs to promptly identify and report safety events. Failure to comply could lead to a crisis. Not all adverse events associated with a medical product lead to a crisis. A crisis is an event that requires product withdrawal, consumer warnings, and management of exposure to the product.

Managing Post marketing Safety Events

FDA and EMA guidance documents[4,5] require the following elements for pharmacovigilance:

- planning of pharmacovigilance activities throughout the product lifecycle
- science-based approach to risk documentation

- effective collaboration between regulators and industry
- applicability of the pharmacovigilance plan across the three ICH regions

Planning of Pharmacovigilance Activities

A pharmacovigilance program starts with the safety profile established during a product's investigational phase. A pharmacovigilance program includes the anticipated adverse events based on preclinical and clinical testing to support the marketing approval application. Specific populations typically are not included in the investigational phase, such as;

- children
- pregnant women
- patients with relevant co-morbidity (such as hepatic or renal disorders)
- patients with disease severity different from that studied in clinical trials,
- relevant genetic polymorphism and,
- patients of different racial and ethnic origins.

Such populations will likely be exposed to the product once it is available in the marketplace, hence defining the potential or unknown risk. The pharmacovigilance program should document a given product's anticipated, potential and unknown risks, followed by expedited or periodic safety reporting to regulatory agencies.

Pharmacovigilance should involve a combination of passive and active reporting, observational studies and even targeted clinical trials, depending on a product's safety profile. Safety events are to be resolved promptly, thoroughly and transparently. Event management should include a public relations exercise whereby the company makes the public aware of its risk management practices and actions to safeguard consumers.

Two case studies highlight event management practices: the 1982 Johnson & Johnson Tylenol episode is an example of good safety event management, and the 2005 Merck Vioxx episode is an example of bad safety management. These examples can help create safety crisis management programs.

Declining R&D Productivity

Despite considerable advances in scientific, technological and managerial practices in the last 20 years, the number of new products developed by the industry per billions of dollars spent on R&D activities has steadily declined. By some estimates, 95% of drugs under development fail to meet the safety and effectiveness criteria and could cost anywhere from $350 million for a small company developing a single product to up to $5 billion per product for a large company working simultaneously on multiple candidates. [6]

The severe decline in R&D productivity has created a crisis regarding diminishing product pipelines and frustrated development programs. This R&D decline is due to improper development programs that lack focus, adequate planning and resource mismanagement. [7] Another hypothesis for this decline is an over-conservative, risk-averse culture stifling innovation. [8]

The management of R&D-related crises requires long-term planning and a change in a company's core policies and competencies. A development program should have realistic goals, with a view toward the current regulatory expectations. Adding additional financial resources to failing projects without initially analyzing and troubleshooting the core reasons for failure is not helpful.

Regulatory Crises

The worst kind of crisis for a company in the medical product industry involves a major dispute with regulators regarding a decision to grant marketing approval or a product recall post approval. However, disputes can happen at any stage in a product's lifecycle, starting with the investigational phase.

The FDA and EMA have well-defined processes for resolving disputes between regulators and sponsors. In most other parts of the world, disputes among regulators and sponsors are addressed in less publicly described processes on a case-by-case

Regulatory Crises During the Investigational Phase of Development

Most issues that arise during clinical trials and when marketing approval applications are submitted are discussion topics in meetings with regulators. There are well-defined processes for meeting with FDA reviewers, and nine similar processes are in place for meetings with EMA reviewers.

FDA meetings allow a sponsor to discuss with the reviewers any anticipated, potential or unknown risks of a development plan and to troubleshoot issues before they happen. Meetings with regulators should incorporate the following rules:

1. Provide specific questions supported by sufficient background information.
2. Provide potential answers to questions and ask for concurrence; address any objections.
3. Ask questions relevant to the given product under discussion's stage of development.
4. Encourage scientific discussion and counter-arguments and defend the proposed rationale.
5. Involve individuals with a direct role in discussion with regulators.

Dispute Resolution Process

Postmarketing disputes with regulators usually lead to legal proceedings, resulting in extensive loss of resources and public relations situations. However, several regulatory processes are available for a sponsor to address disputes with the FDA. [10] [12]

Ideally, a sponsor should attempt to address disputes using the FDA's internal processes before taking legal action. Following the FDA's ombudsman processes does not close the legal resources; however, the reverse is untrue. When resolving disputes with the FDA, a company should remember the following rules for discussion:[13]

1. **Regulatory history of a given product is cumulative**: FDA considers all information and documents submitted to it throughout the life of a project. FDA does not like to ignore information previously submitted unless the sponsor presents a justification deemed acceptable by agency reviewers.
2. **All data available for a given product is relevant to FDA's scientific review**: All data submitted to FDA for a given product by a manufacturer plays a role in the agency's final decision about that product.
3. **All human experience data for a given product should be used in FDA applications:** Human experience with a given product from non-US regions or published literature could provide an important rationale to support the product's safety and efficacy claims and should be used by the sponsor. Such data can be collected in a retrospective analysis of patient experience in ex-US or non-IND and non-IDE clinical trials.

4. **All commitments made to the FDA during previous discussions should be kept:** The FDA expects sponsors to keep all promises made. Regulatory is often called a "moving target," where policies, review guidelines, criteria for review, and more change over time as the FDA reviews new products.

5. **Periodic discussions with the FDA are necessary for all programs:** The dispute discussion should not be the only time a sponsor talks to the FDA. FDA meetings are, perhaps, among the most valuable tools available to a manufacturer to increase the likelihood of securing a product's approval. These meetings can address issues such as trial design, procedures, study parameters, statistical methods for data analysis and pharmacovigilance plans to avoid a dispute. Regulatory strategy should always be confirmed directly with the agency before or early in implementation.

6. **Conflict resolution should be systematic:** Try to work with the reviewers to address their concerns about data validity by providing additional information before taking more aggressive action. Suppose the data from a given application are challenged based on scientific rationale. In that case, there are only two ways to resolve it: 1) initiating a scientific peer-to-peer discussion between subject matter experts and FDA reviewers to understand their concerns and provide an explanation, and 2) identifying the key missing data and filling those gaps with newly-generated data in further clinical trials or using other methods discussed above.

7. **FDA is neutral about products:** The FDA is mandated to protect US patients and consumers and ensure that all products available to patients have adequate justification for safe and effective use. FDA reviews are neutral with regard to a product's commercial success or failure. So, when FDA reviewers have comments about a product, manufacturers are better served by listening and trying to resolve scientific issues.

Organizational Crises

Unlike the previous two categories of crisis management, where companies have to deal with issues partially under their control, organizational crises are almost entirely due to deficiencies in the company's management, quality processes, and resources. These crises can erode a company's credibility with regulators and investors and damage its public image. Most of these events become crises due to the failure of a company's internal processes and are avoidable.

Negative Findings from FDA Audits

FDA audits are detailed reviews of an organization's quality systems and are unavoidable events for all medical product companies. A successful FDA audit greatly benefits an organization's credibility and public image.14 Most FDA audits are announced in advance to give the organization adequate time to prepare; the audits are based on the FDA's inspection manual on the agency's website. FDA auditors make frequent public presentations and speeches highlighting the critical elements of an audit. With all the available resources and guidance, it is inexcusable for an organization to be ill-prepared for an FDA audit or, even worse, to be noncompliant.

An example of what negative FDA findings and noncompliance can do to an organization is Ranbaxy Pharmaceuticals' experience. Ranbaxy was found to have committed fraud, misrepresentation, and illegal activities.[15] Most of these findings were based on deliberate acts of misconduct, leading to a fine of more than $500 million from the FDA; in addition, several similar legal proceedings occurred in other countries, and the company lost revenue due to public backlash to its products overall.

Clinical Trial Risks

As with audits, numerous resources are available to help understand, plan, avoid and troubleshoot clinical trial risk management. Clinical trials can run over budget rapidly and exceed timelines through mismanagement. Common issues with clinical trials' management include;

- failure to recruit subjects
- compliance issues with clinical sites
- mishandling of investigational products and
- loss of biological samples due to improper shipping and storage.

All these issues can be planned and addressed by implementing a clinical trial risk management plan, including crisis identification, timely review and appropriate corrective and preventive actions.

Off-label Use and Whistle-Blowers

Illegal marketing of off-label uses of medical products is a punishable offence. The FDA has recently fined several companies for such marketing practices. [16–18] Most were fined because they intentionally promoted off-label uses of their products. Many of these cases were brought to FDA's attention by whistle-blowers within the companies. Formal legal processes exist for a sponsor to promote additional uses of its products, such as implementing a process to train sales staff. Such processes can help avoid this crisis while allowing free speech and scientific discussion.

The Medical Product Industry Needs Specific Crisis Management

Crisis management is a relatively new field compared to other management areas. Crisis management incorporates elements of risk management, including such proactive activities as forecasting potential crises and planning how to deal with them. Since many crises cannot be anticipated, any crisis management plan should be generic. Companies should develop policies for addressing common themes across all kinds of crises. In general, crisis management should be based on the following core principles:

1. **Create a crisis management policy**: A company should create broad principles or practices to be used in all events that meet the definition of a crisis. The policy should define the role of senior management, designate responsibilities and establish timelines for addressing issues. A crisis profile that includes expected, potential and less-likely crisis events is helpful in training personnel;

2. **Define the crisis management team**: This core team should consist of personnel from different departments in a company based on the identification of all possible and probable crises. The plan should include the roles and responsibilities of the individuals involved in crisis preparation and mitigation.

3. **Communication**: Effective communication is vital in any crisis. Any crisis plan should have an efficient and detailed communication strategy. Companies should ensure an adequate infrastructure to support rapid communication with internal and external stakeholders in times of crisis.

4. **Training**: Training is an important part of crisis management. It ensures organizational preparedness for facing the crisis and usually takes the form of mock drills. Many companies have regular fire alarm drills, which, while usually a bother, form part of a wider crisis management plan.

5. **Surveillance**: Establish processes and practices for constant surveillance of internal and external activities and monitoring the regulatory environment, news and industry trends to forecast potential events and plan contingencies.

Chapter 2:
Changing Trends in Drug Discovery Research

More than 95% of all basic research is carried out in academic, non-profit and government research centres. Unsurprisingly, the technology behind at least 85% of all medical products originate from these organizations, which typically license it to private industry. Most of this technology, especially from universities, is in the early stages and, therefore, reasonably risky.

These statistics perfectly illustrate the different research priorities pursued by academia and industry. In academic circles, the premier goals are publications, grants, intellectual property (IP), long-term interest and perhaps fame. In contrast, the industry primarily concerns IP, return on investments (ROI), focused goals, and short-term interest.

Lately, however, there have been increased collaborations between private industry and universities to pursue mutual goals such as healthier product pipelines and broader funding opportunities. These often take the form of research grants in exchange for preferential licensing opportunities. Major funding agencies such as the National Institute of Health (NIH) are also encouraging investigators to conduct more translational science research, which is more readily amenable to commercialization.

Such pursuits seem to have substantial support in the private sector, with Pfizer, AstraZeneca, Eli Lilly, and others all providing NIH's new National Center for Advancing Translational Sciences (NCATS) with access to dozens of promising but abandoned compounds for drug repurposing research on novel uses. From the industry perspective, the main drivers for this rapprochement include:

- Declining product pipelines within private industry.
- Actual and anticipated loss of profits due to IP expiry and loss of market exclusivity.
- Myriad challenges in innovation.
- Pursuit of more creative development models.
- Pursuit of more creative regulatory pathways

In other words, the fabled tension between academic and industrial research is primarily grounded on misplaced belief.

It is, for instance, assumed that research carried out in one academic lab is always easily transferrable to a new lab or that an academic research team can readily transform itself into a commercial development entity. There is also a common belief that conducting

academic research costs less than in the industry. On the other hand, private industry can transform just about any idea into a product. However, its supposedly characteristic impatience makes it partial to late-stage products. Fortunately, future trends point towards greater collaboration between these two sectors.

Good Laboratory Practices and Good Documentation Processes

For laboratory research to be readily applicable in medical product development, academic institutions and other organizations must follow reasonable standard procedures. These consist of Good Laboratory Practices (GLP) and Good Documentation Practices. These practices allow researchers who are not involved in the original work to reconstruct or reproduce experimental findings more straightforwardly.

The quality requirements can be easily implemented by training researchers in GLP methods. This practice entails compiling a clear and complete methodology regarding protocol development, data collection, results analysis and communication of the principal findings. Furthermore, the personnel conducting the research must be qualified to perform their duties and do so under a defined chain of decision-making.

Similarly, documentation practices must be attributable to someone in addition to being legible, contemporaneous, original, and accurate, i.e., they must satisfy the ALCOA criteria. In other words, for any scientific data to be entirely usable, it must be derived from a logical plan of work with systematic and unbiased data collection and analysis.

The reportage of results must be fair, and the conclusions drawn must be justifiable. The entire work should withstand independent review. Finally, it may be helpful to remember that while peer-reviewed publications carry great respect in the industry besides being virtually sacrosanct in academia, their utility with the FDA is somewhat limited by the agency's emphasis on good laboratory practices above much else. FDA does, however, seek counsel from subject matter experts, primarily from academia, to help its reviewers make informed decisions regarding complex subjects.

Problems Arising from Poor Implementation of GLP and Good Documentation Practices

Crisis events in discovery research frequently originate from improper record-keeping, keeping concerns about the quality of research-grade material used in the laboratory and non-clinical testing. There are also issues arising from using GLP and non-GLP data to support IND applications and GMP-related issues.

Other problems that sometimes appear are related to the management and use of IP for R&D and IND/IDE support, assessment of IND readiness vis-à-vis FDA requirements, and assessment of the need for clinical trials for specialized products such as non-prescription human cells and tissues (HCTs).

A Process reconstruction from laboratory notebooks is notoriously problematic owing to incomplete records from unreported troubleshooting and improvements expected in academic research. The unavailability of personnel who conducted the original research is also a regular occurrence due to the temporal nature of most research positions in academia.

Academic INDs and other investigator-initiated INDs have unique challenges, including completeness regarding data capture for regulatory filing and their expandability. In itself, the assessment of IND readiness is an involving exercise regardless of the nature of the sponsoring organization. The assessment can be broken into the following three significant steps:

1. Creation of a development plan, which has three main components:
2. Gap analysis to ascertain what data is available or outstanding, and laying out strategies for advancing the development of a proposed product for FDA approval
3. Calculation of the expected costs of carrying out a plan in terms of time, financing and other resources.
4. Analysis of anticipated technical hurdles
5. Experimental design of the proposed clinical trial.
6. Conduct the pre-IND studies, including animal toxicity studies, proof of concept or mode of action studies, and an analysis of all relevant chemistry, manufacturing and controls (CMC) information.

Of all the concerns the FDA has concerning fundamental research, the most complex is the quality standardization of research-grade material. This is because the process of generating it defines a product. The primary purpose of good manufacturing processes is to produce material of consistent specifications for product processing.

However, the material used in specialized basic research must, by default, be small-scale and often derived from processes still under development. Such material is unlikely to be of manufacturing grade and tends to be of varying quality.

Specifications such as acceptable batch-to-batch variability, stability and trace composition also tend to be undefined or incompletely documented. Still, this material is

beneficial and necessary for early proof of concept experiments and exploratory mechanisms or mode of action studies. The material may also be used in early animal studies to establish the efficacy and pharmacokinetics of the active compound(s).

It is generally acceptable to conduct most veterinary drug studies using research-grade material. Non-GLP safety studies consisting of small-scale pilot experiments to explore the safety profile of candidate compounds can also utilize such material. Research-grade material can be standardized by defining the composition and source of the raw material, describing and validating its production process, and scientifically establishing its specifications and associated range of deviation. Some form of stability testing also needs to be completed. The material is considered standardized once all this has been done and at least three independent batches of defined specifications have been produced.

The criterion for GMP-grade processing is more stringent than traditional processes because it requires standardized material in a properly designed facility operated by qualified personnel. There also ought to be a complete documentation of all batch records. For a process to be GMP-certified, the manufacturing must be GMP-grade. Beyond that, there needs to be an independent quality assurance (QA) process and a history of audit compliance with the FDA.

The scenario is unique for non-conventional products such as cell-based therapies and herbal products (e.g., cosmetics, dietary products and botanical drugs), which must follow GLP rather than GMP regulations. Cell-based therapies are regulated under 21 CFR 1271 and need to be minimally manipulated, with their manufacture entailing only the addition of water, crystalloids, preservatives and stabilizers before sterilization. Cell-based therapies can have homologous or autologous use. Under homologous use, a human cellular or tissue product (HCT/P) is used clinically in a manner that is essentially the same as the natural endogenous function that it performed but is derived from other persons. This differs from autologous use only because, under this designation, the donor and recipient are the same person.

Chapter 3:
Managing Safety Issues

Overview of Adverse Effects (AEs)

All substances have associated adverse effects (AEs) drug product would, therefore, be expected to have negative effects of varying degrees linked to its usage. In the real world, not all issues are fully tested or sorted out during product development, clinical trials, or even upon approval. The effects themselves could result from any number of individual factors or combinations thereof, including the dose, drug interactions, route of administration, formulation, and off-label use. The term 'drug' is used loosely, referring to chemical drugs, biologics, and medical devices alike. The AEs could arise from the product's mode of action, interaction with the patient's physiological and psychological profile, and interaction with other drugs, food, or other products that the patients might be taking.

Tracking of all AEs (both concerning individual and cumulative reviews) is necessary to help mitigate serious harm to clinical study participants. Beyond compliance with statutory requirements and development of accurate toxicity profiles, this practice enables everyone concerned to benefit from experiences with other similar approved or investigational products. It also allows a more informed risk/benefit analysis that precedes market approval of all products. Safety does however remain an important matter in post-marketing as well.

Definition of Adverse Effects According to FDA and Key Terms

Due to the FDA being a safety-centric organization, most of its urgent inquiries are concerned with AEs. These are defined as "any untoward medical occurrence, or unexpected negative effect associated with the use of a drug, whether or not it being considered drug-related." Additionally, this definition does not imply any judgment about causality. An event is considered "unexpected" if it is not listed in the investigator brochure or at least not at the specificity/severity observed or if it is not consistent with the risk information described in the general investigational plan [FDA Ref].

For a reaction to be defined as a suspected adverse reaction, there must be evidence suggesting a causal but still uncertain relationship between the drug and the adverse event. Following the confirmation that it is drug-related, it is termed an Adverse Drug Reaction (ADR). The FDA's safety reporting regulations have historically been somewhat vague

about the usage of such terms as "associated" and "reasonable possibility," leading to frequent misinterpretation. To address this concern, the precise definitions, as currently used by the FDA, are spelled out under regulation 21 CFR 312.32(a). The designations themselves have to be made by the sponsor and the investigator. Some of the common terms that were more clearly defined included the following:

- **Associated with the drug**: happens after drug intake, but the cause of the AE is unconfirmed
- **Related to drug**: caused by drug intake
- **Suspected adverse drug reaction (SADR)**: consumer has known drug effect based on history that is most likely due to drug intake or other evidence that suggests a causal relationship.
- **Expected adverse drug reaction**: this should happen upon drug intake at a known frequency and grade of seriousness
- **Unexpected ADR**: a new event that is unknown for a particular drug that is most likely caused by the drug. A reaction is unexpected if it is not listed in the Investigator's Brochure, inconsistent with available risk information or not previously known to occur with the drug being tested

Grading the seriousness or severity of the AEs is also more clearly defined, although this issue remains largely subjective since it is dependent on the investigator's and/or subject's assessment. Seriousness is a label appended to an adverse effect when it meets certain criteria; severity, on the other hand, describes an event in measurable terms, although it is still a subjective evaluation. A serious adverse effect (SAE) designation is applied when an event:

- is life threatening
- requires or prolongs hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly or birth defect
- meets other conditions specified in the protocol

The severity designation grades the intensity of the AEs in the following linear scale:

- Grade 1: mild effects
- Grade 2: moderate effects
- Grade 3: severe effects
- Grade 4: effects judged to be life threatening or requiring hospitalization
- Grade 5: death related effects

Grades 3-5 are considered serious adverse effects (SAE). Grades 1-2 could lead to SAEs if the frequency is higher than expected.

FDA Regulations Relating To Adverse Effects (AEs)

The FDA has a well-established practice of creating and updating regulations and guidance documents to fulfill its regulatory mandate better. Updating of the current IND safety reporting regulations goes back more than two decades to the early 1990s. A federal register notice was published on March 14, 2003, seeking to amend draft rule 21 CFR 312.32. It sought to improve the quality of safety reporting, help the FDA with critical safety monitoring, and harmonize the regulation with other international agencies, particularly EMA and ICH. The draft guidance document was released on September 29, 2010, and became effective on September 28, 2011.

The following are some of the major outcomes of the regulation:

- Clear definition of AEs in regard to expectedness, relatedness and seriousness
- Use of internationally acceptable definitions and standards
- Revision of the requirements for expedited reporting
- Clarification of circumstances allowing un-blinding of an ongoing study
- Clarification of format and frequency of reporting
- Clarification of FDA- and IRB-reportable AEs to minimize noise
- Render bioavailability (BA) and bioequivalence (BE) studies (which apply to generics, alteration of non-API formulation, and addition of a new indication for an approved product) are subject to IND safety reporting requirements.

According to FDA regulations, all AEs must be recorded in detail and managed promptly to address the subject's comfort or health concerns. They must also be assessed by the investigator to establish whether there is any relationship to the study product or procedure and to grade their severity and seriousness. This evaluation will inform the investigator whether an expedited report is required, which would necessitate informing the study sponsor. AEs records must contain the following information:

- name of the observed event
- the start/stop date and time
- any treatment performed
- an indication of the intensity i.e. whether mild, moderate or severe
- relationship of event to the study drug, and the action subsequently taken regarding the drug's prescription
- the outcome or resolution arising from the event
- an indication of whether the event was expected

The investigator is also responsible for recording the AEs on protocol-specific case report forms (CRFs), collecting and storing all supporting source documents, reporting all SAEs to the sponsor, and consulting with the sponsor regarding IRB reporting. On the other hand, the sponsor is responsible for reviewing and assessing all SAEs for expedited reportability, reporting the safety data to the FDA and IRBs, and maintaining a safety database to conduct cumulative assessment of all AEs.

Safety databases are a requirement for clinical trials, and even following product approval, it is essential to have a pharmacovigilance program that maintains one. The database contains all observed AEs, whether considered severe or not. New SAEs must be evaluated in the context of all previously reported AEs in the database, including aggregate analysis, to see if similar events have been previously reported. IND safety reports must only be submitted if the SAEs are 1) suspected to be adverse drug reactions, 2) are severe, and 3) are unexpected.

Safety Management in Clinical Trials

Before initiating any clinical trial sites, a safety management plan developed by an independent medical monitor must be in place. It must set out a manual or SOP for a trial's

safety monitoring practices. Additionally, all investigators must be trained on proper protocols for reporting adverse effects and IRB processes. In all submissions, the FDA must be provided with the original physician evaluation and reporting and the internal company medical monitoring documentation.

An independent medical assessment is preferred and almost always carries greater weight. The other important facet of safety monitoring consists of periodic newsletters, typically monthly updates from all sites, regarding common issues and solutions, progress made, and other developments.

FDA meetings arising from safety issues are categorized as Type-A meetings. They only discuss AEs. The sessions are arranged (with very short preparation time) by FDA medical monitors and are usually over the phone. The meetings review adverse event reports and interrogate the sponsor's decision to continue or discontinue a given study. The interaction between the investigator(s) and the medical monitor is often assessed. The review's outcome can include continuance, recruitment, and IRB review.

Protocol Amendments and Reporting Challenges

Several decisions can be made upon review of a safety report, including stoppage of a trial or continuation under an amended protocol. There can be additional reasons for amending protocols, and these can be broadly classified into 3 groups based on the following:

- Logistics of a trial: this is dependent upon the eligibility of participants, feasibility of study processes and the need for additional sites.
- Clinical trial experience: these involve sample size adjustments and changes in the study design. There must be a standardized approach for amending protocols, with the result sometimes referred to as an adaptive clinical trial
- Process for amending protocols: his follows a particular SOP or related documents, which can be derived from diaries, manuals or ICF methodologies. The execution and implementation need to be well defined.

One of the more frequently encountered problems is reporting errors; these often result from the over-cautious approach taken by sponsors. This leads to frequent submission of unnecessary expedited AE reports to the FDA. Some reports categorized as SAEs could have arisen from expected events. These include events due to underlying disease, e.g., death in late-stage cancer; common population characteristics, e.g., acute myocardial infarction or strokes among the elderly; or they could be the actual endpoints for a study,

e.g., whether a drug reduces the rate of an occurring event. Regardless of the cause, over-reporting does not offer any meaningful safety monitoring help to regulators, nor does it help define a drug's safety profile. Instead, it drains the FDA, investigators, and IRBs' resources without fulfilling the intent of the regulations.

Crisis events related to safety reporting that are often encountered include:

- Lack of clarity about the protocol for clinical trial safety reporting to FDA and the general public
- FDA meetings for safety issues, and the decisions arising
- Amending clinical protocols and investigator brochures
- Amending informed consent and re-consenting of trial participants without prejudice.
- Educating investigators and teams about safety issues

In summary, managing AEs is multidimensional and complicated. The effects must be described fully and their seriousness graded. Their relationship to the studied product must then be defined, along with their history regarding the individual clinical trial participant(s) evaluated and assessments made on treatment strategies, when applicable.

Next, decisions must be made on whether changes in patient selection, route of administration, dosing, or any other procedure must be made. The protocol to be followed when documenting the occurrence must also be defined, and conclusions must be made about how and to whom the report needs to be submitted. To avoid over-reporting, the protocol must better describe the safety reporting procedures, including assessing anticipated AEs based on the study population, natural disease progression, background events, known co-morbidities, and past experiences.

Each unexpected adverse effect must be evaluated for evidence of causality by the investigator and the sponsor. There also needs to be a periodic aggregate analysis of all AEs in the IND/ IDE annual or semi-annual reports and during special events such as the interim analysis and the DSMB (data and safety monitoring board) review. The Investigator's Brochure (IB) should detail the clinical and non-clinical safety information, possible risks and side effects associated with a drug, and any special monitoring or preventive measures that might be required. It is essential to update the IB with new information from pre-clinical and clinical studies and other publications or research reports.

Lastly, current good practices require the sponsor to designate an independent medical monitor to review all adverse effect reports, discuss the observations with the investigators, provide the sponsor with an assessment, and create the IND safety reports.

Chapter 4:

Post-Market Safety Issues, Product Shortages and Recalls

Marketing approval is not carte blanche. The FDA and other regulatory agencies require sponsoring companies to continue monitoring the safety and efficacy of approved drug products or medical devices. A crucial part of this responsibility is to maintain a stable and reliable supply of all approved products, ensuring that patients can always access the medications they need. Companies are also expected to respond promptly to any emergency issues that may arise, including product recalls, resolution of manufacturing crises, and effective handling of product shortages.

Maintaining a perspective when confronted with crisis events is crucial because they can run the whole gamut from a batch recall to a total product recall. The latter, potentially catastrophic for a company, underscores the need for comprehensive crisis management strategies. All aspects of a response need to be adept, as illustrated by the Vioxx®, where clumsy communication by Merck, rather than deliberate misconduct, appears to have initiated the crisis. To handle these obligations properly, companies must adopt the best practices in pharmacovigilance, including collection, analyses, management and reportage of accurate post-market safety information. This requires the conduct of registry clinical trials and patient surveys, in addition to interaction with physician focus groups.

Some regulatory agencies, most notably the European Medicines Agency, allow conditional market approval, which, by definition, obligates a drug company to monitor safety and effectiveness for up to five years with a mandatory annual renewal of licensure. Pharmacovigilance is a risk mitigation strategy that should inform the response to a crisis. This is because adverse effects of some kind are expected following drug administration, and the task then is to make sure that their occurrence is met with an appropriate response.

Risk mitigation strategies include dispensing drug products in child-safe containers and barcoding to identify counterfeits. In order for companies to respond appropriately, they need to be fully aware of the risks involved. Risk analysis is, therefore, an essential component of any post-approval strategy. The analysis can be classified as prospective or retrospective. Planning and training are considered prospective practices, while problem identification, corrective, and preventive actions are retrospective.

Manufacturing Crisis and Product Strategies

Manufacturing crises are some of the more frequently encountered post-approval issues. They can take the form of recalls, product shortages and partial or complete production shutdowns due to process failure, such as a change in biologics yield or activity level. Product shortages can arise from unanticipated manufacturing delays following supply chain interruptions, artificial or natural disasters and upstream quality problems. It is illegal to knowingly create a shortage whether or not it is associated with price gouging because of its intrinsic potential for developing severe health crises amongst patients. Manufacturers must file reports about impending shortages with the FDA as soon as they become aware. They must also provide the reasons for shortages and their expected duration.

There are dedicated offices in various FDA centres that handle product shortages. However, the most prominent is the Drug Shortage Staff (DSS) within the Center for Drug Evaluation and Research (CDER). As per Title X of the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012, the FDA may issue a non-compliance letter to manufacturers who fail to comply with the drug shortage notification requirement. This can lead to serious consequences, including potential legal action and damage to the company's reputation.

At the very minimum, the FDA requires that manufacturers issue a notification at least 6 months in advance to give the agency sufficient time to address the difficulties encountered and, where possible, identify alternate suppliers. Inevitably, sole suppliers would be expected to draw greater attention.

Data Management and Pharmacovigilance

Acquisition and maintenance of quality data is a challenging undertaking. It requires a significant outlay of financing, infrastructure and qualified personnel. Most drugs and medical devices are marketed globally, and managing data acquired from multiple sources can be complicated by differences in regulatory, business, scientific and medical environments. There are also differences in the patient populations. The need to inform the FDA about issues that arise in all markets may run into regional, national and global complexities.

Many firms must also handle the absence of clear delineation of tasks, priorities and communal needs, leading to fragmented or uncoordinated practices. Indeed, the US drug industry needs to catch up in capturing valid clinical safety data, preferring only to disclose the more readily acquired chemistry, manufacturing and control (CMC) data. Managing

post-marketing data in a way that meets regulatory deadlines while satisfying investor goals makes the industry reduce the scope of information captured. This sometimes leads to risk-averting practices that include the following:

- Piecemeal implementation of technology
- Failure to evolve or advance in processes is related to failure to accept and implement new and improved approaches or technologies because of fears of disrupting mature systems.
- Continuation of practices that are based on preconceived ideas and incorrect perceptions
- Misunderstanding and over-interpretation of regulations and guidelines, often in the form of submission of excessive and irrelevant information, failing to achieve actual regulatory intent.

Poor pharmacovigilance practices and post-market study designs yield poor-quality data and unexplained or intractable information, which inevitably leads to citations by regulatory authorities. This can damage the company's reputation and lead to increased regulatory scrutiny. The study protocols are often more complicated than necessary, which diminishes focus and proper resource utilization, ultimately leading to unfulfilled objectives. Clear identification of priorities, would for instance, help reduce the clutter that is often associated with data collection and which distracts from core issues.

Unnecessary quality control and other monitoring bottlenecks could be expunged without affecting the core data. Another common problem is poor risk identification, which regularly leads to poor risk mitigation strategies. Risk mitigation becomes complicated and ineffectual without proper risk management tools, and when risk management is reactive and corrective rather than preventive or simply management of known potential problems. Ideally, a defined product's evaluation and response to risks should be unique and proportional.

Risk Evaluation and Mitigation Strategies (REMS)

There are instances where FDA approval of an NDA, ANDA or BLA comes with an obligation to lay out precise Risk Evaluation and Mitigation Strategies (REMS) to minimize risk and ensure that the benefits of certain products outweigh their risks. This happens when the FDA determines that safety measures are needed beyond professional labelling to ensure that a drug's benefits are obtained. This may happen before or after a product has been approved. The latter applies if the FDA becomes aware of new safety

information afterwards. Drug sponsors then develop REMS programs, which the FDA approves as appropriate. REMS can be required for a single drug or a class of drugs.

Each REMS has specific safety measures unique to the safety risks associated with a particular drug or class of drugs (i.e., no two REMS are exactly alike). Sometimes, healthcare professionals must follow specific safety procedures before prescribing, shipping, or dispensing the drug. The risks under consideration must be severe and documented in the drug's label. A standard REMS contains 1) a medication guide or patient package insert, 2) a communication plan, 3) elements to assure safe use (ETASU) and 4) an implementation system.

ETASU requirements form the core component of a REMS program by stating the measures to be taken to reduce a specific serious risk listed in the labelling of a drug. Depending on the specific indication, they may, for example, require that: 1) prescribers receive specific training or certifications, 2) the drug be dispensed only in specific healthcare settings or with evidence of safe-use conditions such as laboratory test results, 3) each patient using the drug be subject to monitoring, and 4) each patient using the drug be enrolled in a registry.

There is no single one-size-fits-all strategy to manage all manner of risks in the drug industry. Instead, there are a series of good practices that can be helpful. First, there needs to be continuous risk identification, either following a pre-planned periodic review or one that is fully adaptable to specific changes. Second, the relevant parties must review the information gathered, and corrective and preventative action must be designed and implemented. There are immediate and long-term actions depending on the nature of the event. The critical focus always remains the patients' well-being, and in order to satisfy this aspect, their exposure must be limited as much as practicable, and there has to be a system to track them. Third, appropriate communication must be maintained with consumers, regulators and other stakeholders through progress reports and other updates. Lastly, there may also be a need for internal and external training with healthcare providers and conducting audits to ascertain that proper standards are maintained.

Post-Market Activities: Registry Studies and Physician Focus Groups

Pharmacovigilance activities must be conducted throughout the product lifecycle, starting from approval and as long as it is in the market. Risk documentation needs to be assessed individually and cumulatively. Full disclosure of pertinent information must be made to the regulators to maintain effective collaboration between regulators and the industry. Consumer liaison, on the other hand, needs to be handled cautiously with

measured but adequate response. Depending on the product in question, a global pharmacovigilance plan may be needed to cover all markets.

In any case, the sponsor must anticipate adverse events based on the approval package. A plan must also be laid out to deal with populations that were not included in the clinical trials, such as children, pregnant women, patients with relevant co-morbidities like renal or hepatic disorders, patients carrying a relevant genetic polymorphism, and patients belonging to ethnic groups that were absent or under-represented in the clinical trial. Attention may also need to be paid to patients with the indicated ailment but to a more severe degree.

Other major post-market undertakings include registry studies. These are observational and ideal for obtaining adequate data and identifying off-label uses of a product. They also include Section 522 studies, which are specific to medical devices. Comparative effectiveness data is needed to help insurance organizations, including Medicare and Medicaid programs, decide whether to cover a medical product's use.

However, since the comparator products are often older and cheaper, the sponsor may need to reimburse patients for the extra costs incurred to prevent them from dropping out of the study. On the other hand, off-label use studies arise because products are not necessarily used as indicated. These studies are, therefore, critical as they may provide valuable marketing data, initiate hypotheses for future studies, and indicate possibilities that can be pursued for future regulatory submissions.

Unlike clinical trials, which have patient inclusion criteria, registry studies consist of the general population in clinical practice and, therefore, allow the inclusion of patients with confounding complications and who have differing ages, socioeconomic backgrounds and healthcare attitudes. Lastly, some medical device approvals may require that the sponsor carry out studies under Section 522 of the Food, Drug, and Cosmetic Act. This typically applies to Class II or III devices whose failure could lead to serious adverse health consequences, which are implanted for more than one year or used in pediatric populations. It also applies to life-sustaining or supporting devices used outside a designated user facility.

In general, registry studies are not markedly different from clinical trials because they contain similar design, planning, and project management elements. The same ethical, privacy and data ownership principles also apply. However, they are often plagued by poor statistical design and data management.

There have been concerns that sponsors often have a hidden intent of creating a market by providing discounted or free drug products and by promoting off-label uses. There is also the issue of incomplete reporting, whereby the final study disclosure is in the

form of a publication rather than a full report, in addition to failure to register on clinicaltrials.gov.

Physician focus group studies are also an essential post-market activity. FDA deems the focus group valuable because it can be a flexible tool for exploring respondent awareness, behaviour, concerns, beliefs, experiences, motivation and operating practices at a more in-depth level. They also yield unforeseen insights or additional nuances of existing information. They are most informative when the studies are blinded. The FDA and other regulatory agencies do not consider them promotional as long as they do not directly involve patients.

Proper structuring is critical to extracting usable data, allowing the sponsor to get an accurate glimpse of the potential product market and design the appropriate product label. It also allows the sponsor to understand the prescriber's and patients' unbiased opinions of the product and, as a result, design fitting marketing plans and advertisements. They may also aid in designing clinical trial programs by identifying clinically relevant endpoints and potential trial sites.

Chapter 5:

Regulatory Crises during the Investigational Phase of Development (IND/IDE crisis management)

Multiple potentially problematic issues arise during the investigational phase of medical product development. They revolve around matters such as clinical trial management, recruitment of clinical trial subjects, clinical trial design, high placebo effects, and interaction with regulatory agencies around the globe, including FDA meetings. The issues at hand vary greatly with specific tasks, with those faced by the product sponsor distinct from those faced by the clinical trial site, the manufacturer or the contract research organization (CRO), as discussed separately below.

Key Challenges Faced by Sponsors

Starting with the sponsors they need to forecast and review spending to meet budgetary constraints. A CRO firm to carry out some of the clinical development work has to be identified, which requires establishing qualifying parameters followed by defining expectations, assigning responsibilities and engaging in continuous review or monitoring processes. Similar tasks have to be conducted for all vendors providing services.

In other words, all contracts covering differing scopes of work must be negotiated and aligned to the provision of necessary and reasonable services. Any ongoing projects must be managed entirely by qualified personnel, and the decision-making process must be adequately defined and adopted. There is also the matter of standard operating procedures (SOPs) – self-developed and contracted - which must properly track the creation of documents and their maintenance to satisfy audit requirements.

Clinical Trial Site Challenges

The clinical trial site needs to be adequate for the study regarding personnel, equipment, and space. Patient recruitment is a critical component of any study; decisions have to be made whether to go for small or large practices, use the referral process, or adopt active recruitment. This is all in addition to addressing the patient training component. It is also essential that the location of a trial site be sufficient to assure patient safety through easy access to emergency treatment centers and ready availability of the PI and co-PIs. The site must also demonstrate its ability to create, maintain and store auditable records and offer training in handling source documents.

Contract Research Organizations (CROs) Obligations

Contract research organizations (CROs) must satisfy a wider range of obligations. Firstly, for a CRO to adequately monitor clinical trials, it must recruit the right clinical research associates (CRAs) and establish standard policies and practices for in-person and remote monitoring. Safety monitoring is incredibly vital and involves the setting up of a safety database, independent tracking and active patient eligibility review. Remote monitoring and all computerized systems need to be validated. They must comply with Part 11(i.e. Title 21 CFR Part 11) regulations, which define the criteria under which electronic records are judged to be equivalent to paper records in the eyes of the FDA.

Secondly, if some functions are to be contracted out, then the qualification and selection criteria of the sub-vendor must be defined. This is on top of monitoring and auditing practices, which are often legally mandated.

Thirdly, regarding regulatory affairs support, procedures must be laid out for documenting reviews and submissions, and troubleshooting typical issues such as protocol deviations and amendments, informed consent hitches, safety reporting and site compliance problems. These sorts of problems can be handled internally within the CRO, or they may need the help of external consultants. Interactions with the FDA also fall under the support of regulatory affairs.

Lastly, quality assurance protocols, including SOPs, personnel training, and internal and external audits, must also be well defined and ready for execution and review.

Manufacturing Crisis

Manufacturing crises can be extensive and highly disruptive. They range from production and stability issues with the investigational product (IP) through logistical challenges to labelling and packaging problems. Product stability problems can arise from storage failures power outages, amongst other causes leading to loss of IP integrity even before its projected expiry date. Logistical challenges are extensive and can involve failure along the product processing pathway, disruption of materials supply, and the loss of traceability of product ingredients, in addition to social upheaval and natural calamities. Labeling and packaging often vary with regulatory jurisdiction, and failure in this dual aspect can be surprisingly disruptive, with serious consequences such as nullifying trial blinding processes.

Protocol Design and Good Clinical Practice (GCP) compliance issues

Other significant problems faced during the development phase include difficulties arising from the study protocol design and Good Clinical Practice (GCP) compliance issues. Within protocol design, organizations must determine the feasibility of having a particular number of sites, arms and patients vis-à-vis the level of involvement required of the principal investigator (PI).

The protocol must also state the basis and conclusion of any risk-benefit evaluation, especially in situations of the first ever usage of a drug product in man, and in the context of risk information from previous studies, primarily if related. The protocol must also state the rationale for conducting the testing. Eligibility criteria also need to be debated, particularly where they involve vulnerable populations and when the objectivity of related assessments is unclear. GCP compliance issues usually revolve around the informed consent process, defining procedures for adverse events reportage, and addressing any concerns with data recording and reporting processes.

Insurance, Statistical Issues, and Clinical Study Reports

Because of the uncertainties inherent in business, one has to plan for insurance coverage, as well as statistical issues and problems with the clinical study report. Insurance covering the clinical trial site, including the investigator and the facility, and clinical trial insurance, is important. It is also wise to seek CRO and other vendor insurance. In order to avoid statistical anomalies, the initial analytical plan must anticipate the occurrence of site, subject and protocol variations and devise approaches to manage the problems. It must also define the sample sizes and the relevant parameters for data analysis. The clinical study report, on the other hand, must be developed by qualified medical writers and must satisfy the criteria demanded from scientific, regulatory, clinical, and statistical reviews.

Special Considerations for Biologics, Medical Devices, and Botanicals

Finally, the drug or medical device product can have its own problems. To a degree, these problems segregate according to the nature of the compound or device in question. Biologics face issues that are similar to those encountered in traditional drugs, and these have more or less clearly defined regulatory requirements. On the other hand, medical devices can be unique in some profound ways.

A good illustration of this aspect would be in applications where their use is irreversible, even under investigational settings. This aspect alone can be of significant

concern in the execution of informed consent forms (ICFs) and the granting of Institutional Review Board (IRB) approval. By their very nature, medical devices also encounter a larger share of blinding complications.

There is, finally, a category of unique products comprising botanicals and non-regulated products (e.g., cosmetics and dietary supplements), which face distinct challenges in the form of unclear intellectual property rights in the former and IRB dependency coupled with a lack of clarity on questions of safety versus efficacy, and fidelity in the latter.

Meetings with the FDA

The FDA strongly recommends meetings, and sponsors are entitled to one or more in part because they expedite the approval process by providing clarification to a variety of issues and serving as a forum for dispute resolution. Besides, their cost is covered by the hefty user fees. Pre-submission meetings (e.g., pre-IND, EOP2 and pre-NDA) are considered critical by the FDA compared to mid-cycle meetings (mid-Phase III and mid-review). The meetings may not be granted if the FDA perceives an IND is not planned. The meetings always have a stated agenda, which can range from clarification of what a sponsor should plan on submitting to dispute resolution.

The sponsor must send the questions they would like discussed in the form of a tentative agenda when filing a meeting request. The FDA usually responds with their comments, which can be pretty detailed, a few days before the proposed meeting. Once the sponsor confirms the agenda, the meeting then stands scheduled. Because the FDA follows an ongoing review process, the meetings can be held before or after any defined phases as the medical product approval process progresses. The diagrams below illustrate this, and they depict the expected scenario for drugs, medical devices, and biosimilars.

FDA meetings are meant to be informal scientific discussions on an equal footing, so electronic recording is strongly discouraged. The meetings usually involve clarification and discussion rather than interrogation. It is not helpful to bring along lawyers as this eliminates any informality. The meetings are a continuous process and can be arranged, with reason, even after product approval. Ideally, an informational meeting such as the pre-pre-IND one should precede any commencement of the approval process because it provides an opportunity to obtain information and advice from the reviewers on what is required. This helps the sponsors gauge their readiness and odds for success.

The FDA only requires that the sponsor provide a product concept at the initial meeting. Such a manageable restriction is beneficial with biosimilars and medical devices,

where meetings often lead to reduced regulatory demands and, hence, significantly lower costs. This happens, for example, when the FDA rules that there is no need to conduct non-clinical trials when a product has already been approved for a separate or very closely related indication.

In other instances, however, the expectations are clear enough to render such meetings unnecessary. Where clarity is not in doubt, meetings may be unhelpful and may not even be granted. Indeed, a lot of the information often sought is available online in the form of guidance documents and regulations that a sponsor could simply reference.

However, gathering an accurate reading of what the reviewers expect before beginning the approval process is generally helpful. Informal advice may be provided during a meeting. However, the best approach is to propose what the sponsor wishes to carry out and, following the inevitable push-back from the FDA staff, settle on a well-defined set of studies. It is essential that one does not commit to conducting a study and then fails to do so. The expectation is that one must meet all commitments made. As a rule, a sponsor should refrain from asking questions whose answers would be unhelpful.

Further, the questions should be specific rather than open-ended. They should only seek to obtain concurrence and commitments rather than directions and considerations. By clarifying any issues beforehand, the aim ought to be to avoid implicit acceptance of unstated or unnecessary responsibilities. This is especially so because many meetings sought by sponsors are aimed at reducing the number of studies they need to conduct.

Therefore, the sponsor must always have a well-supported rationale for seeking any commitments (or indulgence) from the FDA. The agency, on its part, is required to provide specific objections and possible solutions to any request sought by the sponsor, along with a clearly defined timeline stating the expected progression of events.

Remembering that the agency has total jurisdiction in this field is always important. If any disputes arise, the FDA prefers internal resolution using its officers, rather than pursuing such matters through a court process or external arbitration. The primary reason for this is the maintenance of confidentiality. Suppose any disagreement remains unresolved between the reviewers and the sponsor. In that case, one additional internal option is mediation through the FDA Ombudsman office, which cannot force reviewers to change their minds.

It is important to remember that concurrence amongst reviewers is the overriding factor in any decision to approve or disapprove, and no entity, including higher-ranking executive officers, can force the reviewers to change their decisions. The most that the FDA leadership can do is rule against their reviewers' advice. This intellectual independence is an essential factor in having an objective approval process.

The requirements that must be met to schedule a meeting vary with FDA review divisions. However, generally, and excluding the initial meeting, there has to be some relationship between the sponsor and virtually all centers within the agency before a specific category of meetings can be granted. The FDA is, for instance, unlikely to discuss R&D questions if an IND has yet to be filed. In the case of devices, it is essential to have a prototype ready.

With biosimilars, the drug product must have been purified and characterised regardless of whether it is a protein or some other macro-molecule. The mode of production must also be clearly defined and reproducible. A drug master file (DMF) –usually type I or II - may be provided at this juncture. It is important to note that DMFs are reviewed for completeness and not for the accuracy of the contents.

So, when is one ready for a pre-IND/IDE meeting? This would be when the whole idea of a "final product" has been developed in the form of a finished formulation or prototype and a target indication(s) and population(s) identified. The CMC information must be ready with a well-characterized active pharmaceutical ingredient (API), its manufacturing and packaging information (which must comply with cGMP), and stability studies. A sufficient amount of GMP-compliant investigational material must be ready for use in clinical trials once the FDA grants a go-ahead for clinical trials. A set of representative basic non-clinical studies (preferably GLP compliant) carried out in animal models and *in vitro* must also be ready.

These would contain acute and sub-acute toxicology, pharmacology and *in vitro* toxicity tests. A minimum set of genetic toxicity studies comprising in *vitro* Ames and micronucleus assays neemust be. These pre-clinical studies must define the maximum tolerated dose (MTD), no-observable-effect-level (NOAEL) in a model animal species and the major expected adverse events. It is also helpful (but not required) to have determined the primary mechanism of action for the product. Lastly, a draft clinical protocol must be ready with a complete synopsis of the proposed clinical development plan.

In order to request a meeting, one has to identify the division that will most likely review the application, which depends on the product's classification. Building a rapport with the relevant division director and project management staff is helpful. If other divisions might be involved, it helps to have a good idea of the hierarchy and decision-making process within them and to follow any division-specific instructions that have been put in place.

The meeting request process is two-step, beginning with a 6-7 page initial abbreviated request based on a standard regulatory format. Once the agency has reviewed the request, it responds within 14 days, either agreeing to hold the meeting on a specified date or denying a meeting with a detailed explanation of its reasoning. Depending on the

type of meeting requested, the date can be 30-75 days after the initial request to the FDA. If the request has been granted, the sponsor prepares a more detailed package that includes the full agenda and submits it approximately 2 to 4 weeks before the meeting.

The FDA responds with their preliminary comments 2-3 days before the meeting. The meetings can be held over the phone or in person and last about one hour. The in-person meeting must be justified for it to be granted. The only people who should attend a meeting have something to say. A list of attendees is provided beforehand s strictly followed during admittance into FDA campuses. The decision-makers (e.g., the CEO or COO) and relevant subject matter experts should attend. If the subject of the discussion is clinical trial design, the clinical experts and statisticians must be present. Likewise, regulatory experts would be needed in any strategy meeting.

The presence of legal experts, investors, bankers and people without a specific role in the discussions should be avoided whenever possible. The tone during the meeting should be appropriate and as informal as a scientific discussion. The sponsor or their agent is expected to forward meeting minutes to the FDA within 10 working days following the meeting, as the project manager at FDA considers these during preparation of the official meeting minutes. The official minutes prepared by the FDA are released within 30-40 days of the meeting.

Preparing for an FDA Meeting

It is imperative to prepare well for an FDA meeting. During a meeting, a sponsor can put forward a proposal that differs from what is deemed to be the agency's expectation and provide rational support for it. In order to do this and also address the meeting's agenda comprehensively and within the short time allotted, it is considered good practice to hold preparatory mock discussions.

It is also good practice to schedule the meetings appropriately within the product development cycle to obtain full benefit. Different meetings require different preparation, but specific issues need to be reviewed against possible responses. For instance, while pre-NDA and PMA meetings are heavy on data, pre-IND/IDE meetings tend to dwell more on strategy and less on data. Typically, pre-IND/IDE meetings discuss the entire clinical development program (CDP) and are heavy on regulatory planning and strategy to initiate clinical studies.

The meetings focus on defining the commitments of the sponsor and the agency. They are considered the most important by the FDA, and on average, holding them triples the odds of IND approval without delay. The end-of-phase II and pre-NDA/PMA meetings

discuss the available results and their impact on the application. Holding them doubles the chance of first-cycle approval. Mid-cycle meetings are also data-intensive but tend to be highly tissue-specific. They are often not granted, but written responses are still provided.

Meetings provide an insight into the concerns of FDA reviewers and a platform for receiving feedback on ideas. It is essential to have well-prepared subject matter experts to discuss and justify the scientific rationale of any given proposal and try to understand the subtext of the agency's views because it usually has more information than it is ready to disclose. Unrelated matters must be avoided, with the focus solely on obtaining answers or clear directions. It is not necessary to commit to new suggestions on the fly during the meeting. Instead, all new ideas the agency projects should be considered carefully after the meeting. Still, tunnel vision must be avoided since discussions can sometimes lead to exciting developments.

The agenda should remain within FDA's realm and avoid financial or time constraints associated with conducting suggested studies and business matters, such as what a competitor may or may not have been required to provide. It is not essential to hold all possible meetings, especially because there are alternate ways to get FDA feedback. Moreover, some meetings can turn unhelpful, forequesting dataat is beyond the sponsor's comfort or is needed for an actual technical reason. The responses obtained may also be unspecific or ambiguous, resulting in a confused strategy.

The classification of a product is only sometimes clear since it can be a combination, bringing together a drug and a medical device, for example. This is a critical matter because submissions assigned to the wrong office can give rise to a variety of challenges and delay market approval. When faced with this dilemma, a sponsor can petition the FDA to make a ruling on a product's classification and determine the division or office within the agency that would be responsible for its review.

Sponsors may give their opinion, which they can formally describe when filing a request for designation (RFD) with the Office of Combination Products (OCP). FDA decides by applying the statutory definitions of a drug, device, biologic or combination product in the FD&C Act, guided by the scientific data available concerning the product when the classification determination is made. If the FDA fails to provide a written response within sixty days, the sponsor’s recommendation regarding the product's classification is considered the final determination.

The FDA may not modify a determination of a product or of the component of the FDA that will regulate a product, except with the consent of the sponsor or for public health reasons based on scientific evidence. It may, however, be appropriate to change the determination when, for example, there is a change in the composition or intended use or

component of the product or if new information reveals a mechanism of action that differs from what was initially described in the RFD.

Developing a regulatory strategy is essential in successfully navigating the pathway to market approval. In principle, an effective strategy customizes one's needs. The initial step involves analyses of regulatory trends, which can help define the actual expectations of regulatory agencies. This refers to awareness of current practices, past trends and future expectations. Based on these trends, a gap analysis can be executed to help identify what information is available and what is needed. The information generated from the two exercises is then used to prepare a development plan during FDA meetings. Each stage of product development requires a separate plan, with early periods being more exploratory while the later stages focus primarily on pivotal data. The post-submission plan is grounded on precedent.

The regulatory environment changes rapidly as new regulations are implemented, investigational issues crop up and public policy changes. New regulations follow when designations change, as happens when a breakthrough pathway for approval is granted. They also follow when RiskMAP (Risk et al.) strategies or expectations regarding safety reporting change. Investigational issues can develop with IRBs, clinical sites and from difficulties surrounding trial subject recruitment. Such changes ought to be expected when an adaptive trial design is adopted.

In recent years, the social media phenomenon has led to a more rapid evolution of public policy issues compared to historical trends. In order to maintain some advantage, a means for obtaining regulatory intelligence must be found. This entails looking beyond FDA and other government regulations and guidance documents for un readily apparent information. One possibility would be maintaining an eye on the US and WHO clinical trial registries to track ongoing studies and their stage of development.

Tracking precedence, including approvals and rejections (which, being private, are more challenging to obtain), is also informative. Information is also available on regulatory websites belonging to other key organizations, such as the EU's European Medicines Agency (EMA) and Health Canada, press releases from private and public organizations, patents and market exclusivity filings and reports from safety databases. Tracking regulatory precedence with Health Canada and the EMA can, , sometimes, be difficult because, unlike the US FDA, the two bodies do not post much of their information online. Still, guidance documents remain the primary source of regulatory information.

Guidance is defined as a current understanding of a particular topic, which is not legally binding. This designation means that regulatory authorities have the flexibility to accept or reject a petition that is based on guidance on a case-by-case basis. In other words, any information derived from a guidance document must be adapted to the appropriate

rationale. Guidance documents typically address significant concerns and scientific methods based on experience with similar products. They, therefore incorporate elements of precedence information. With information from these sources, it is possible to identify deficiencies in current data more readily and develop a plan for obtaining any missing and vital information. That is what underlies competent gap analysis and strategic planning.

Precedence looks at the regulatory review of products similar in chemical constitution, population and medical indication, and handled by the same department within a regulatory agency as new candidate product. Such reviews serve as a learning tool, a starting point for strategy development, or a means to update the knowledge base in addition to justifying the rationale behind a subsequent application. In other words, an earlier review can be viewed as a regulatory snapshot at the time of decision based on applicable legislation and regulations, science and acceptance criteria.

The information can be obtained from presentations made by leading health agencies, past approvals, minutes from official interactions with health agencies (including proceedings of advisory committee meetings), and product labeling, amongst other sources. By law, presentations made by FDA personnel must be made available to the general public either online or in another archival format. It is essential to keep in mind that information that is more than 10 years old may not be relevant. However, if information is still posted on the FDA's website as a guidance document, then it can be considered to be still applicable.

As alluded to earlier, a gap analysis and strategic planning system is particularly useful. It is anchored to a minimalist philosophy and entails the application of any available information that can inform the fastest, most efficient and cost-effective way to develop a product and obtain its regulatory approval. It follows scientific and statistical rationale and demands skillful troubleshooting and risk assessment. When drawing up a plan, the right product classification must be identified.

Priorities also need to be defined in terms of what needs to be addressed early in the development process and what can be deferred or run in parallel. For instance, it is much more cost effective to gain approval to conduct a clinical trial for one indication and then request approval for modifications or additional indications after that. This is because the rate for denial following the initial submission is 80%, double the 40% rate for supplemental approvals.

Depending on the product, choices may have to be made on whether animal testing is required and to what extent. There is also value addition to the product through proper positioning. Common mistakes include targeting blockbuster indications, meager scientific background (e.g., unknown mechanism of action), incomplete pre-clinical and clinical

testing, excessive or insufficient development costs and failure to take advantage of incentives.

In order to preclude costly oversights, comprehensive searches for information that is in the public domain must be done. The most reliable information comes directly from the regulatory agencies themselves which makes it essential to review the source documents of any information provided by third parties. This is an important qualification to bear in mind because reviews and third-party analysis are routinely used to deconstruct the sometimes-confusing regulatory information. In this field, as in many others, experience does indeed pay dividends. In sum, however, a unique product demands a unique plan.

Chapter 6:

Dispute Resolution with the FDA (Disputes with FDA reviewers)

Disputes will inevitably arise with the FDA regarding various issues, from review decisions to procedural differences and patent disagreements. There is no universal advice on handling disputes because their nature usually informs the specific procedure for resolution. However, there are multiple guidance documents, FDA staff presentations, and precedent analyses available online, with advice on procedures and tips for navigating the dispute resolution process, both formally through the centres and informally through the ombudsman's office.

Disputes can be broadly classified into three categories:

1. differences of opinion;
2. compliance issues, and
3. procedural differences.

Differences of opinion are related to the scientific content of submissions made to the FDA and the corresponding decisions made on that basis. The differences may concern the necessity of specific animal or clinical studies, the clinical relevance of the data, the acceptability of study designs, And the testing and characterization required of a product.

Compliance issues usually relate to non-conformity with standard quality guidelines or practices, i.e. GxP where "x" could refer to laboratory, manufacturing, clinical, documentation or other process. Disputes over patents and market exclusivity decisions would also fall under this category. Procedural differences often involve allegations of improper or unprofessional interactions, such as unreasonable decision changes, lack of clear direction and unjustified or overly burdensome requirements.

Differences of opinion are commonly resolved through face-to-face meetings or discussions. The provision of additional data and analysis, particularly by the sponsor, and clear communication of the rationale behind study designs and conclusions are usually helpful. If the situation favours it, the views of key opinion leaders within a speciality can lead to desirable outcomes.

Regarding compliance issues, there are effectively only compromises if the least burdensome procedures are followed. It is critical to tackle compliance issues early enough to avoid warning letters and execution of other administrative constraints by the FDA.

Some issues, such as those related to standard quality practices, usually require follow-up meetings to resolve completely.

Most importantly, it is good to remember that compliance issues are only considered closed once the FDA formally does so. Lastly, resolving procedural or professional conduct disputes is usually done internally within the agency despite being accusatory. There are finite possibilities for appeal within the agency in the event of disagreement with decisions made, beyond which any unresolved matter must go to the courts for resolution. Written submissions should be filed with the FDA as process records in all cases, including meetings.

As indicated above, differences of opinion are tackled through meetings with the reviewers. A single meeting will generally handle one topic, although additional meetings may be arranged when additional information becomes available. When meetings are problematic to arrange or unnecessary, all matters can be resolved via written submissions and responses. Resolutions should be based on common sense and follow a give-and-take approach. While the sponsors are expected to justify and defend their reasoning and study design, the FDA, on its part, is required to consider all data presented before making a decision.

This is well illustrated in the case of (*TM-name here-*), a promising drug developed for a nephrology indication. According to the interim analysis, the drug's performance was equivalent to a placebo, and the product was headed towards failure. However, a closer look at the data revealed that patients with specific pre-existing renal and cardiac problems showed remarkable improvement from the drug. The sponsor, therefore, closed the initial study and applied and received a fast-track designation from the FDA to target the population subset that responded to the drug. Another illustration would be the drug *TM-yyyy*, an anti-HIV drug which failed to show any significant effect when used in combinatorial cocktails that are common in anti-HIV therapy.

However, mono-therapy using the drug resulted in very significant improvement in patients. In this instance, the sponsor subsequently applied for and received a breakthrough designation. In both these illustrations, thoughtful analysis of clinical data was sufficient to convince the FDA to look favourably at the drugs and fast-track their approval to help fulfil critical unmet needs.

Key opinion leaders may sometimes carry sufficient clout to sway the FDA's opinion, especially on scientific or analytical issues that need to be understood. Per precedence, the agency seldom reverses its opinion based on prominent opinion alone. However, it respects knowledgeable views and is open to adopting new technology and procedures. An arrangement that the FDA frequently uses to assemble opinion leaders is the FDA Advisory Committee.

These committees are put together by the FDA and provide the agency with independent, expert advice on complex scientific, technical, and policy issues related primarily to the development and review of products that it regulates. The FDA currently has 48 technical and scientific advisory committees and panels.

Each committee has 10-12 members, but notable non-voting experts may be invited to participate, depending on the matter. Extra members are often incorporated to replace those with a conflict of interest over a specific issue. The members are usually appointed exceptional government employees (SGEs) for their engagement. Committee membership consists of recognized experts and includes physician-scientists, statisticians, epidemiologists, pharmacologists, nutritionists, nurses, and animal or pre-clinical studies experts. It also includes industry, patients, and consumer representatives who, it is assumed, add different perspectives that give balance to the discussions and final recommendations.

While legally non-binding to the agency, advisory committees carry substantial soft power because they consist of acknowledged authorities within a given discipline and are well-qualified to evaluate critical issues independently. Therefore, the committee's opinion is routinely considered a basis for public and policy support for an application or other issue under discussion. By default, Advisory committee meetings are public proceedings that anyone can attend, ask questions about, and even record so long as it is not disruptive. Preparatory committee meetings are often held behind closed doors for FDA staff, usually only a day or two before the official meeting.

As a matter of strategy, it is best to avoid placing critical decisions like the approval of a product in the hands of advisory committees because they have a very high rejection rate. Like most committees, they prefer to err on the side of caution and sometimes exceedingly so. It is, therefore, imperative for the sponsors or their representatives to prepare thoroughly for the meetings. Essential homework would include a review of the professional background of committee members to learn their likely opinions on applicable scientific and policy matters. This involves poring over CVs, publications and presentations, including past recordings of advisory committee meetings, particularly on related subjects.

It also helps to consult with past committee members to build an idea of their questions and develop a Q & A summary. Experts in the core areas of the proposed medical indication, statistics, consumer protection, and the industry itself would be essential to have, and they should be as knowledgeable as the Advisory Committee in order for them to contribute effectively during the meeting. In addition, alternative plans for responding to the actual trajectory that an actual meeting takes would need to be developed in readiness for any unfolding scenario.

During preparation for the meeting, team members in the sponsor's corner need to come up with a list of critical questions that are as complete as possible. It is equally important to identify weaknesses in the responses and to think of alternative analysis as applicable. A minimum of 3 to 4 mock advisory committee meetings are advised, preferably with video recordings to help review and internal discussion.

The mock sessions should be spaced out well enough to allow sufficient time for retrospection. External "reviewers" can be included to add an independent aspect to the evaluation. Private meetings with the FDA usually need a single mock session, although the preparation should be as comprehensive. During the meeting, there should be a readiness to admit shortcomings and provide possible corrective measures. Regardless of how many analyses the data has undergone, it is helpful to be ready to conduct additional ones on the spot and discuss any issues that might arise. This reinforces the importance of having knowledgeable people on board for the meeting.

The FDA has about 19 different written processes in addition to multiple regulations regarding dispute resolution. The disputes themselves can be internal between reviewers, reviewers and their supervisors and between centres. External disputes are between the agency and sponsors. Regardless, virtually all processes describe a hierarchical system for dispute resolution running from the Branch through the Division and Office to the Center.

Ultimately, unresolved disputes end up on the FDA commissioner's desk. Somewhat counterintuitively, internal FDA disputes can be very costly for sponsors. This is well illustrated in the dispute involving Fulyzaq® (crofelemer), the Salix Pharmaceuticals' product for treating diarrhoea associated with some anti-HIV drugs. Its approval was famously held up, and consensus within the agency was awaiting. In this instance, the section responsible for reviewing botanicals approved the drug. However, the CMC section hesitated owing to concerns about the characterization of the API and consistency of the manufacturing process. Salix had to work with the agency to develop a novel procedure to test the pharmaceutical consistency among different manufactured batches to salvage the situation.

The multiple FDA documents that dwell on dispute resolution have a common underlying theme: they generally seek amicable decisions following a consultative approach free of bias and retaliation. The initial contact for the sponsor is with the personnel and group that handled the review or matter at hand. If the issue remains unresolved, it is escalated step by step up the FDA hierarchy. As mentioned earlier, advisory committees may become involved, but the final decision rests with the FDA.

Complainants always have the option of litigation. It is preferable to avoid litigation, but in some instances, that can be challenging. Litigation occurs with far greater

frequency in patent disputes, particularly concerning generic drugs. As a matter of policy, the FDA grants a 30-month stay whenever a brand name drug maker (the innovator) raises a formal objection to the approval of an ANDA because of patent issues. This stay can now be invoked only once after it was determined by the Federal Trade Commission (FTC) that drug manufacturers were seeking a series of 30-month stays to block generic drug manufacturers from the market effectively. This practice was interpreted as a misuse of the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Act. Under this law, generic drug manufacturers must not repeat expensive clinical trials to gain market approval.

Instead, they are only required to demonstrate that their drugs are bioequivalent to the brand-name drugs, which means that the active ingredient in the generic drug and the brand-name drug must be identical, have the same bioavailability, follow the same quality manufacturing standards, and have similar labelling. One hundred eighty days of marketing exclusivity is awarded to the generic drug firm that is the first to submit a complete ANDA to the FDA as an incentive to challenge any patents that the generic manufacturer believes it does not infringe or that it considers invalid.

To summarize, regulatory consideration of drugs and medical devices reviews all available and relevant data. Therefore, any regulatory history associated with a given product is cumulative and will be considered during reviews. Human experience data is regarded as the most informative and relevant and should always be provided (assuming it is available). As indicated earlier, it is essential to hold periodic discussions with the FDA to address the agency's concerns and avoid costly wastage of resources in performing unnecessary studies. Still, any commitments made to the agency must be kept.

In the event of a conflict, the resolution should be pursued systematically and amicably to provide the agency with information supporting the approval of the product under review. Before escalating any dispute, it is worthwhile to consider the facts about the dispute, the history of the dispute, including the contribution of the drug or device company in the matter, any attempts made to work out a compromise with the FDA and whether the agency has exhausted its internal processes. Finally, it is worthwhile to mull over the utility of picking a fight with the FDA, given the high likelihood of failure.

Chapter 7:

Negative Findings from an FDA Audit (Dealing with FDA audits)

In carrying out compliance audits, the FDA implements its mandate under the Federal Food, Drug, and Cosmetic Act (FDCA). Besides warnings and imposition of fines and other civil sanctions, the agency can prosecute corporate officials in positions of responsibility or authority for liability crimes for violations of FDCA under the so-called Park Doctrine. The Park Doctrine originated in a 1975 Supreme Court ruling allowing the federal government to seek a misdemeanor conviction against a company official for alleged violations of the FDCA without having to prove that the official participated in or was even aware of the violations. The government is only required to show that the official was in a position of authority to prevent or correct the alleged violation. Despite these possible costs,

FDA audits do not have to be the strenuous tasks they often become if manufacturers, clinical investigators, CROs, IRBs, and other parties that are subject to the agency's regulatory oversight adopt and implement a well-defined array of best practices. Moreover, there are guidance documents and multiple online resources that can help individuals and organizations prepare effectively for audits, handle the actual audit, and respond to audit findings.

Scope Of FDA Audits

A majority of audits are manufacturing-related. However, the integrity and sufficiency of other germane issues such as personnel, facilities, documentation, information systems, laboratory, and clinical procedures, amongst others, can be scrutinized as well. Curiously, audits can also inspect the use of funds provided by the

Center for Medicare and Medicaid Services (CMS) to cover approved patient reimbursement costs in some clinical trials to prevent fraudulent use. Even with this broad mandate, the FDA still requires the involvement of internal quality audit departments within organizations that it regulates, as they can help spot and address problems more readily than external inspectors from the agency.

Further, the FDA recommends that sponsors or owners of drug products draw a Quality Agreement between themselves and their contractors, establishing their respective responsibilities. Whereas ultimate responsibility remains with the owner, the FDA considers that such an agreement can help to delineate responsibilities and assure the

quality, safety, and effectiveness of drug products. The agency assumes that the owner must have conducted a comprehensive assessment to verify the suitability and competence of the contractor to provide the outsourced services before establishing a contractual relationship. The owner is further expected to continuously monitor and review the performance of the contractor.

Before the FDA conducts an audit, a notice of inspection, formally known as Form 482, is issued a week or two in advance. A fortnight can seem very brief when one is unprepared. There can be surprise audits, but these are rare and will typically have a precipitating cause, such as whistle-blower allegations or reported incidences of safety violations. Most audits are safety-related and tend to be study or application-specific.

Roughly 80% of them are, however, routine inspections, and selection for audit by the FDA does not, therefore, imply fault on an organization. Because the agency cannot audit every single site worldwide or even nationally, it looks for tell-tale signs of problems. These include evidence of inadequate or suspicious documentation, sloppiness, training deficiencies, poor publicity, and complaints. Some actions can also raise red flags, as happens when manufacturers, for example, submit perfect scores in quality specifications or records that have unusual patterns of variation, which are often indicative of falsified data.

Good Manufacturing Practice (GMP) Audits

As pointed out earlier, GMP audits comprise the major part of FDA audits. Accordingly, manufacturing plants are audited once every three years for US-based manufacturers and every 2 years for foreign firms. Because of the global nature of modern drug manufacturing, the harmonization of GMP standards in the pharmaceutical industry through the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) has been hugely beneficial. PIC/S had its beginnings within the EU zone but now counts many major national drug agencies in its membership ranks, including the FDA.

Unlike the FDA, PIC/S offers training on GMP inspection procedures to national inspectorates and helps maintain high standards by ensuring that members comply with PIC/S standards at all times through the assessment of new applicants and reassessment of existing members. Industry benefits by having standardized guidelines that do not vary across national borders.

FDA auditors are the enforcement arm of the agency. They work under the Office of Compliance within the Division of Scientific Investigations. Besides GMP auditors,

there is the Bioresearch Monitoring (BIMO) Program. BIMO specializes in inspecting clinical investigators, IRBs, nonclinical (animal) laboratories, and bioequivalence analytical laboratories to ensure the safety of human research subjects and the quality and integrity of data submitted to the agency.

Frequent triggers for BIMO inspections include conducting a large volume of clinical trials, conducting clinical studies outside of one's field of specialization, reporting significantly better efficacy or fewer AEs than other investigators studying the same drug, patient or sponsor complaints and unusual data patterns such as having too many patients with a particular disease state in a defined locale than would be statistically expected. In all, about 1,000 auditors are working from both the agency headquarters in the Maryland suburbs of Washington, DC, and the regional offices. They are trained in the FDA auditing manual and compliance expectations and have absolute authority to review and critique on the FDA's behalf.

It is illegal to refuse an FDA audit as it indicates non-compliance with US regulations. Sanctions can include suspension of all activities at a given production site and even raids by the FDA with the backing of federal agents and local law enforcement. When the refusal involves a facility domiciled in a foreign territory, it typically leads to the prohibition of product export to the US. In order to coordinate audits, the FDA has 16 regional and eight international offices.

International audits take more time to arrange largely because there has to be some form of authorization from the host nation, in addition to hitches in the issuance of travel visas. The FDA has attempted to get a handle on this in China, where the need for audits is enormous due in part to the large volume of products manufactured there. However, its endeavor to increase the number of auditors has not been successful.

Handling FDA Audits

Upon receiving a notice of inspection (Form 482), all relevant personnel should be informed and principally, the QA department. Depending on the anticipated scope and general preparedness of the organization, the need for a consultant should be evaluated. Either way, a plan must be drawn on how to handle the inspection. This should include a thorough check of documentation to organize and clean up records, as well as a review of the documentation procedures and all internal audit findings (both QC and QA). Next, in order to prepare the staff, mock interviews are strongly encouraged.

These basically consist of answering two questions (i.e., what do you do? and how do you do your work?) and obliging to a request to demonstrate performance of the stated

tasks. Importantly, the staff responsible for interacting with the inspector must be assigned, and a private operating office with easy access to a copier ought to be provided. Lastly, it is generally helpful to engage in some troubleshooting in order to identify other potential issues and possible solutions.

Once the auditor arrives, he (or she) is received at the reception by previously designated personnel. The auditor is obliged by law to present his (her) official credentials for formal identification, but these cannot be copied. During this opening interview, the auditor also presents Form 482 for signature. Senior management needs to be present during the opening and closing presentations and should also be kept informed about progress made. It is essential to provide the auditor with an escort at all times for facilities access control. It is equally important to control access to personnel.

Further, the files or information provided should comprise only what has been requested. Documents typically sought include SOPs, manuals, raw data files, study reports, and training files. Facilities usually inspected include laboratories, clinics, manufacturing plants, storage areas, and equipment suites.

Responding to Audit Findings

Personnel within the organization should keep calm throughout the inspection and remain courteous and professional towards the auditors. It is always helpful to be relaxed, defensive, or to make unsubstantiated comments. Staff should only say what they know and not what they believe. It is important to take good notes and record all activities. Once the inspection is complete, an exit interview is held to summarize any findings, clear any misconceptions, and document the formal discussion. The organization is, by law, allowed to clarify any issue before a report is compiled.

The inspector has two options: no findings, which is great for the organization, or findings of some violations or problems. The issuance of FDA Form 483 accompanies a finding. Findings that usually result in the issuance of Form 483s include documentation problems (e.g., inadequate SOPs, poor records), inadequate CAPA, deficiencies in vendor qualification, safety reporting violations, inadequate training records, deviations from stated procedures (e.g., clinical protocol subject inclusion/exclusion criteria and other violations of study processes). Note that some of these findings relate specifically to either marketed products or investigational products. When a 483 is issued, it does not help to argue or become defensive. Instead, it should be reviewed calmly and a response issued later on after some reflection and additional communication with the FDA.

Following an inspection, the auditor compiles an Establishment Inspection Report (EIR) and submits it to the head office. Upon evaluation, an organization may receive one of three possible letters:

- A no-action indicated (NAI) decision followed when no objectionable conditions or practices were found or when the significance of the objectionable conditions fails to justify further FDA action.
- A voluntary action indicated (VAI) decision follows when objectionable conditions are found and documented, but the FDA deems it unnecessary to take or recommend further regulatory action because the objectionable conditions are few and insufficient to impact subject safety or data integrity.
- An official action indicated (OAI) decision follows when regulatory violations uncovered during the audit are repeated or deliberate or involve the submission of false information to the FDA or the sponsor.

In response to an OAI, the 483, and with reference, as applicable, to any informal comments made during the audit, an organization must take Corrective and Preventative Actions (CAPA) to address all findings, both major and minor. A formal response must also be made to the FDA within a reasonable time frame (30-60 days) and followed up with the agency roughly 60 days after the submission for their feedback. Care must be taken not to over-commit oneself.

Importantly, a finding can be contested, especially when it is clear that an error has been committed. A good illustration of this would be one case where auditors questioned a protocol that FDA reviewers had approved. In this particular incident, the company requested and was granted a tripartite meeting with auditors and reviewers. The reviewers sided with the company arguing that protocol design was not a territory for inspection, and the most the auditors could do was establish whether an approved protocol was followed.

Escalation To Warning Letters

Form 483 and an organization's response to it is public information. However, because there are a vastly greater number of 483s compared to say, Warning Letters, the former are not as readily available as the latter. Further, the FDA does not maintain an up-to-date online tracking system for 483s. It typically takes several months without any progress for an actionable 483 to be escalated to a Warning Letter. A Warning Letter is a formal notice of significant violation of statutory obligations under FDCA. It is the principal means by which the FDA achieves prompt voluntary compliance with the Act. If

the documented violations are not promptly and adequately corrected, it can lead to an enforcement activity. It is, therefore, a serious escalation.

All warning letters must be reviewed internally before they are issued. Some violations require mandatory review by a specific FDA Center as per issued guidelines. When two or more Centers are required to conduct a review, a lead Center is designated by the FDA Office of the Chief Counsel (OCC) to streamline any ensuing correspondence.

Organizations are usually given a short time to respond, but it is often too late to do much. Warning Letters are irreversible decisions and are always made publicly available on the FDA's website. This can be problematic due to the ensuing bad publicity and associated commentary in the media, use in case studies, and potential for use by consumers and lawyers for litigation purposes. It is, therefore, helpful for organizations to have adept legal and public relations policies (including social media approaches) to deal adequately with any possible fall-out.

Chapter 8:

Off-Label Uses, Off-Label Promotions, and Whistle-Blowers

Off-Label Use of Drugs and Medical Devices

Off-label use of a drug or medical device refers to any use of an FDA-approved product in a way not described on its marketing label. The FDA will not have reviewed such use and may, therefore, pose safety risks. The term is mostly used in reference to prescription products that need a doctor's supervision, but the term still applies to over-the-counter products. The FDA considers off-label usage particularly important because it can lead to the discovery of new uses during clinical practice, which would be of great benefit to patients.

The agency's public support for off-label use rests on the premise that doctors ought to have the freedom to prescribe as they are best placed to make educated judgments based on clinical experience and state of the art. Further, it is a fundamental fact that a given product can have applications beyond those approved by the FDA or any other regulatory agency, and such use can be an important therapeutic option or even constitute a medically recognized standard of care.

Challenges of Off-Label Promotion

In practice, patent issues and commercial considerations can force or induce companies to convert off-label uses to on-label especially for products with a potentially large market. However, in many cases, the off-label market is too small to justify incurring the extra cost necessary to obtain regulatory approval.

A good example of an off-label use that successfully made the transition would be Rogaine (Minoxidil), which Upjohn originally developed for the treatment of hypertension. It, however, had the unusual side effect of causing unwanted hair growth in patients, which prompted Upjohn to begin testing it as a treatment for hair loss. Upjohn discovered that a topical application to the scalp of a mild solution of Minoxidil prevented hair loss and induced hair re-growth in some patients. The product is now off-patent and available over-the-counter for the treatment of hair loss, including severe conditions such as *androgenic alopecia*.

Another example would be Viagra (Sildenafil), which Pfizer initially studied for the treatment of hypertension and angina pectoris but discovered during clinical trial to have little effect on angina but a marked ability to induce penile erections. Aspirin, on the other hand, is an old analgesic that is now frequently taken as a primary prophylaxis for coronary heart disease.

Regulatory Enforcement and Legal Consequences

Whereas no law prohibits a physician from prescribing an approved medication for other uses besides the specific FDA-approved indications, pharmaceutical companies are themselves not allowed to promote a drug for any other purpose without formal FDA authorization.

Indeed, the United States federal government and multiple state authorities regularly pursue criminal and civil cases against pharmaceutical companies and their employees for promoting off-label uses of prescription drugs. The cases are usually settled out of court with the payment of hefty fines, such as the $2.3 billion fine against Pfizer for off-label marketing of Bextra and three other drugs. The case related to allegations that Pfizer paid bribes and offered lavish hospitality to healthcare providers to encourage them to prescribe *Bextra*, an anti-inflammatory drug; *Geodon*, an anti-psychotic drug; *Zyvox*, an antibiotic; and *Lyrica*, an epilepsy treatment.

While more useful, there have been few discussions of the regulatory strategies for legal off-label promotion. Instead, there has been some push-back against FDA regulations, which are considered too restrictive by some sections of private industry, particularly on the grounds that they impede the basic constitutional right to free speech. This view was upheld in the United States v. Caronia case of December 2012, where the US Appeals Court decided that the First Amendment protected the defendant's truthful promotion of a drug for indications not approved by the FDA. The defendant, Alfred Caronia, was a pharmaceutical sales representative for Orphan Medical, Inc.

At first glance, the decision appeared to limit the government's aggressive enforcement of the criminal misbranding statute, in addition to having wide implications for the way drugs are marketed in the United States. However, unlike individuals, corporations are not well suited to wage battles against the federal government that can potentially lead to felony indictments. Instead, the drug industry still prefers to admit to misdemeanor misbranding charges alleging truthful off-label promotion and pay huge fines to resolve such cases. This approach avoids bad publicity and protects corporations from potential loss of government contracts that, by law, accompany criminal convictions.

Guidance for Legal Off-Label Promotion

Because this is a complex subject, the FDA has published guidance documents about investigational studies of off-label use of approved drugs and off-label promotion. Using these guidelines, along with reviews of case studies from the unsuccessful and successful promotion of off-label uses, it is possible to draft practical criteria to inform the development of regulatory strategies for converting off-label uses to in-label uses. The information can also be helpful in developing practical tips for the training of sales and marketing teams in off-label uses of products and for developing procedures that would encourage internal dispute resolutions and reduce the emergence of events worth whistle-blowing.

The FDA expressly prohibits the commercial promotion of off-label use. It does, however, make a distinction between scientific exchanges and promotional activities. Thus, the sharing of peer-reviewed published results and other scientific data devoid of promotional material (including the perception of promotion) is allowed. The scientific material shared must consist of all that is available, including both supportive and negative information.

The information must also be current and related to a specific question. It is important to clearly include the rider that the agency still needs to approve the application. There is an FDA guidance on the distribution of medical journal articles on unapproved new uses of approved drugs, biologics, or medical devices that was revised in Feb 2014 to include books and other scientific or medical reference texts. Other recent releases include the Misinformation Guidance and the Twitter Guidance, which were both released in June 2014.

Firms routinely encounter requests for off-label information from various sources. The sources can be platforms that the firms control, such as product websites, discussion boards, and other chat rooms. They could also be third party sites that they do not control, and public venues such as scientific conferences. How the firms respond to these requests defines their intent. The goal is, therefore, to respond in a manner that does not convey any intent to promote off-label use. Some difficulty may arise in determining how exactly to define intent.

In practice, narrowing down the question and providing unbiased and complete information without the input of marketing personnel is a useful rule of thumb. This applies both to a private request where an individual calls or emails seeking information or a public request made during a live presentation at a conference or posted on an online product-specific site. Following a private request, information should be provided only to the requestor and contain an approved label and indications, a disclaimer and safety information, and a list of peer-reviewed publications and abstracts.

It is important to maintain details of the request, including information about the requestor, a copy of the information provided, and any follow-up inquiries. Crafting an acceptable response to a public request is trickier. This is because of concerns about the wider distribution and longevity of information provided as it is heard or seen by a larger number of people and usually remains available on websites for prolonged periods. As a result, the proper response should convey that the question pertains to an unapproved use, and the prudent approach would be for the individual to contact the scientific/medical staff with the specific inquiry.

In other words, the public response should be limited to providing the firm's contact information without any reference to off-label usage. It is, therefore, necessary to train marketing personnel on how to handle such matters, given that they are a common occurrence during conference or meeting presentations. In essence, public and broad responses should be avoided, and sales and marketing staff should be excluded from all activities, including any training and awareness forums. Meticulous records of any response or discussion must also be kept to ensure an effective response to any potential probe by a government agency.

Solicited Vs. Unsolicited Requests

Solicited requests occur when a company invites comments on off-label use. Solicited requests indicate intent to promote off-label use and are, therefore, illegal. They happen when a sales representative mentions off-label use to a physician and asks for a formal request.

They also happen when a company representative or paid agent presents off-label data at a company-sponsored promotional event and asks attendees to submit formal requests for additional information or instructions. Any such material disclosed by a firm to bloggers, consumer reviewers, websites containing questionnaires on off-label usage, or its Twitter feeds is considered solicited material.

Online videos discussing off-label usage posted with the encouragement of a firm and any other material soliciting comments would also fit in this definition. By default, a company can be held liable for any information generated and disseminated by a person under its pay. This can be in the form of consumer complaints, doctor/prescriber complaints, and class action lawsuits. Because of the seriousness of the matter, the perception of solicitation is sufficient for the FDA to fully exercise its mandate, which can include severe penalties.

Navigating Social Media

In the present-day social media age, companies must adhere to strict rules or guidelines. Some platforms, such as Twitter and paid blogs, should be avoided completely. The 140-character limit on Twitter is simply insufficient for complete information disclosure. Facebook is acceptable but has to be reviewed by regulatory affairs staff for acceptability, and company staff must be trained on the appropriate handling of posted comments.

YouTube videos that are posted should contain complete safety information and exclude solicited off-label material. Product-specific websites are acceptable, but they should not have a public commentary or discussion section. Posting comments on other websites or product placements on television and other media ought to be evaluated on a case-by-case basis as these are generally considered promotional activities.

Acceptable Sources of Off-Label Promotion

There are well-defined categories of published literature that a company can use to provide information on off-label use. These include original research based on well-controlled experiments, journals with editorial boards that have demonstrated subject matter expertise and well-defined peer-review process, and reference textbooks with semi-peer review processes. Review articles are generally not acceptable.

The material must be generally available in bookstores and other independent distribution systems. The literature provided cannot be a special supplement sponsored by the firm whose product is mentioned. Nor can it be a solicited article by the journal publisher to the firm or edited or significantly influenced by the firm. Markings, highlighting, summarization, or characterization of any sort are not acceptable. Lastly, the material has to be current, accurate, and un-abridged and must be accompanied by the approved label and a comprehensive bibliography.

Post-Marketing Studies and Investigator Trials

The FDA's interest in regulating off-label use largely stems from concerns about omission or minimization of the risk unapproved usage can pose to patients. There is also the prevalence of misleading or unsubstantiated superiority claims and overstatement of efficacy. Off-label promotion also tends to omit material facts and broaden indications by, for instance, stating that a product can be used to treat cancer. At the same time, it is only approved for a specific form of cancer.

As per federal regulations, all advertisements and promotional labeling for a given drug product must be submitted along with Form FDA-2253 at the time of initial publication or dissemination. This rule applies to all manner of promotional activities, including investigational drugs.

In order to comply, a firm can hire the services of an opinion leader or a few physicians to conduct post-marketing studies with the intent of gaining exposure to the product. Under this arrangement, the physicians are supported by grants or other fees, and the firm plays an active role in the design, analysis, and reporting of results.

The studies are designed to find "new" uses for an approved product. This is a conventional IND study and is formally known as an Investigator Lead Study (ILS). The other alternative is the Investigator Initiated Trial (IIT) where a physician starts his/her trial using a company's product. The product may be requested from the manufacturer for testing purposes or purchased from the market. The drug/device manufacturer has no role in the design, analysis and reporting of results. This study is again designed to find "new" uses. It is formally known as an investigator-initiated IND study.

The Future of Off-Label Promotion

Looking into the future, the drug development and regulation industry should prepare for heavy use of social media, including increased use of Wiki sites, crowd-sourcing of drug information, and increased awareness of off-label uses. Consumer-driven off-label use will likely become more common with the explosion of readily accessible information exchange platforms. This may, however, bring about increased liability to companies for unknown risks to off-label use of their products. Surveillance by the FDA and the FTC will likely increase along with clearer definition of Do's and Don'ts to cope with what will arguably be a more risky safety environment.

Conclusions

Crises are complex events that require a clear and strategic approach to manage. In the medical product industry, crises can arise from various sources—like product safety issues, regulatory challenges, or sudden market changes. While it's hard to predict specific events, companies can reduce risks by studying industry trends and spotting potential warning signs.

Crisis management in this industry shares core principles with other sectors: quick response, clear communication, and decisive action. However, it must also address unique challenges. Medical product companies operate under strict regulations, with bodies like the FDA playing a crucial role. This means crisis management here involves not just solving immediate problems, but also ensuring all actions meet regulatory requirements.

A multidimensional approach is key. Companies must juggle several factors at once: regulatory compliance, public safety, communications, financial impact, and reputation management. By blending general crisis strategies with industry-specific knowledge, medical product companies can better prepare for and manage crises.

Although predicting specific crises is tough, learning from past trends—like regulatory delays, product recalls, or safety concerns—can help companies develop stronger plans. Proactive crisis management allows companies to respond quickly, minimize damage, and maintain trust with regulators, customers, and the public.

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