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Placing Patient Safety First: Developing A Disaster Plan To Reduce Risks From Covid-19 Stability Program Impacts

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ABSTRACT

Scientists and regulators have warned the industry about the importance of creating a Disaster Plan for over three decades. We have experienced industry disruptive weather events like Hurricanes Katrina and Maria, geological events including Fukushima, industrial accidents like Deep Water Horizon and Chernobyl, and now a global pandemic like COVID-19. Still, too many healthcare companies are taken by surprise and are unprepared for the disruption to the critical Stability Program, thus significantly increasing impacts on the product expiry, as well as other risks. The question urgently at hand is: Can you shut down your operations and reopen unchanged after the pandemic? [1]

Without a pre-approved stability- specific Disaster Risk Reduction (DRR) Plan, organizations are simultaneously forced into significant patient safety, efficacy, and regulatory exposure when samples suddenly cannot be pulled or tested to fulfill the stability commitments. This type of impact occurred on March 23, 2020, when India implemented a country-wide 21-day lockdown due to the COVID-19 Pandemic with a 4-hour notice. As noted by Langerman and Elson, “It is easier to turn off something than it is to start it up again.”[2]

This discussion will guide readers through the process of creating a DRR Plan for the stability program that will be both robust enough to cover all the major disaster types and flexible enough to adjust for externalities. Additionally, risk mitigation approaches will be discussed, along with regulatory exposures to consider. Without a Stability DRR Plan, organizations will struggle with protecting patient safety and efficacy while recovering business continuity from any disruptions such as COVID-19.

INTRODUCTION

Pharmaceutical and Medical Device Stability Programs are essential to support the expiration dating of healthcare products and fulfill the regulatory commitments made with the product. Globally harmonized ICH guidelines Q1A (R2) requires multiple studies of different lots of drug substance and drug product to be placed on stability to establish an expiration dating period. Commitments must be made to conduct stability testing in order to market new products and to monitor the quality of the product through its lifecycle [3, 4, 5].

The current pandemic urgency is diverting significant resources to develop treatments and vaccines for COVID-19. Fabrication of life-sustaining medical devices such as ventilators, PPE, diagnostics, and the testing peripherals are also consuming priority resources in the healthcare industry. While the focus and urgent need cannot be overstated, there is also a need to ensure the business continuity of existing products as well as the advancement of other quality of life or life-sustaining programs. Continuing to progress treatments and maintain current programs supporting commercial products is vital to global health. Unfortunately, during COVID-19, many companies have found themselves underprepared for either the level or duration of the disruption.

The preparation plan to handle disaster should be developed and implemented prior to the occurrence of any disruption. The best decisions are those driven by available data using a risk-based approach. Once the disaster strikes, it is significantly more challenging to simultaneously access, interpret, and evaluate decades of stability data to assess the risk to patient safety and efficacy from any stability program disaster. Especially when there are decisions relate relating to optimizing stability testing output versus laboratory capacity. Healthcare industries need to leverage the power of data, analytics, and remote engagement at scale to prevent having to rely solely on stability Subject Matter Experts' (SME) intuition. No matter that our intuition is well-founded, data must supersede any disaster approach. Figure 1 lists examples of possible stability disruptions that may be caused by a disaster.

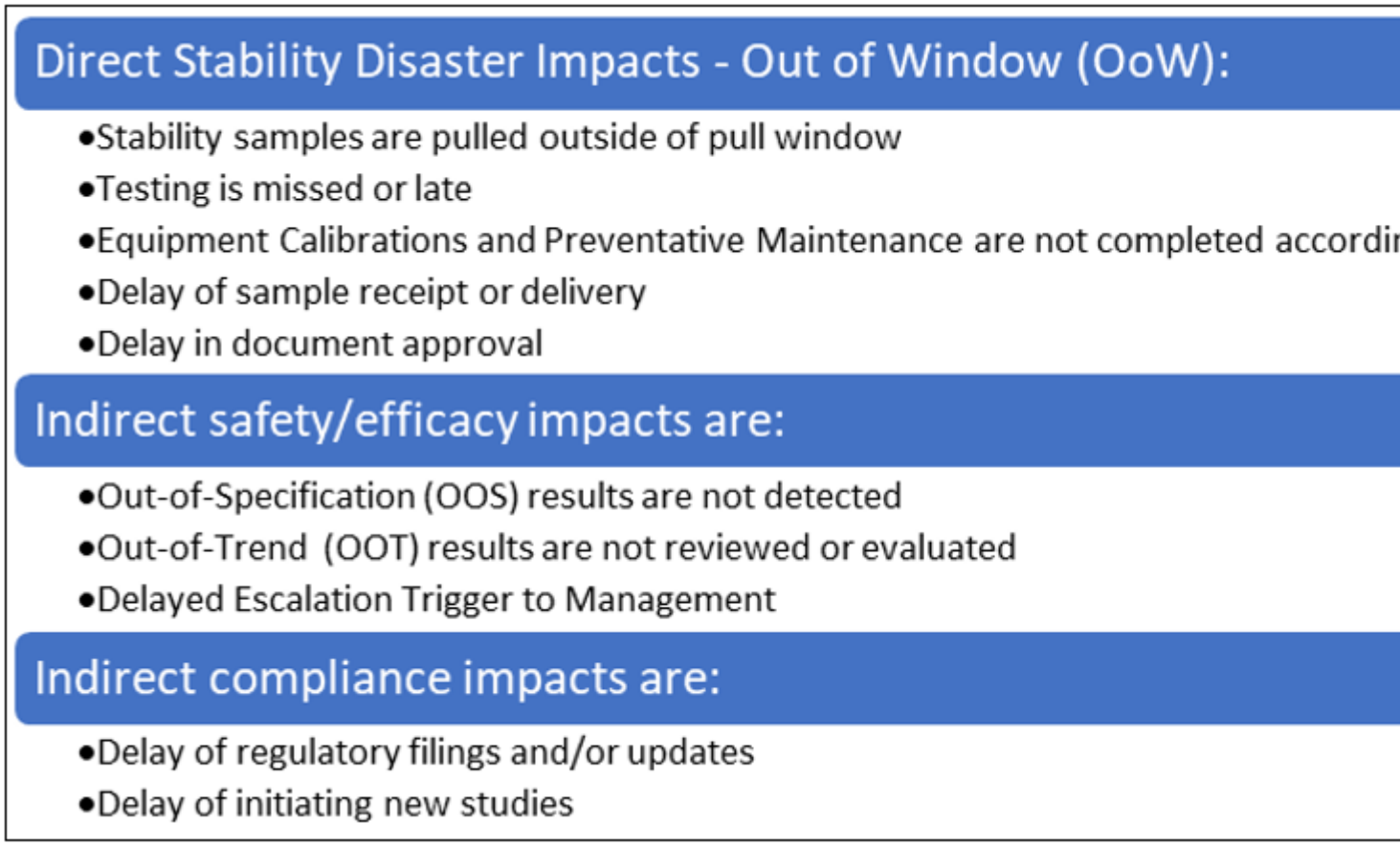

Figure 1- Possible Stability Disruptions Caused by Disaster

DEVELOPING A DISASTER RISK REDUCTION (DRR) PLAN

The concept of DRR Plans is not new. They have been recommended by the US Agency for International Development Office of US Foreign Disaster Assistance (USAID) for decades to facilitate community resilience in the case of a disaster. The information for getting started can be accessed via the web links listed in the body of the document or in the references. Organizations can tailor the depth and breadth of the document to the specific applications. USAID/OFDA has issued hazard-

specific DRR sheets to help vulnerable communities and industries to become better prepared to cope with the hazards around them. It also includes development activities that will be critical for building resilience, even to recurrent crises, over the long term [6]. These proposed activities should either reduce the risk, frequency, or severity of a specific, recurrent shock or shocks over time and help to recover more quickly [6,7]. The Philippines' implementation of actions and measures for mitigation in catastrophes aims to ensure the timely, effective, and coordinated response for all eventualities of disaster within their boundaries [8].

As previously stated, regulating agency experts have been warning companies to prepare for business continuity during a disaster. The data has have been available and seems to fall victim to the loss of urgency and support after the immediate crisis. Many references supporting disaster planning case studies are discussed in references [8,9,10]. Notably, even though the 2009 H1N1 Influenza Pandemic caused the US Government to spend subsequent years developing, refining, and regularly exercising response plans at the international, federal, state, local, and community levels, the COVID-19 Pandemic quickly overwhelmed medical facility capacity and broke PPE and testing supply chains which, 5 months later, have still not recovered [10]. The current COVID-19 pandemic has proved that the global industry was not prepared to handle a pandemic of this magnitude. The economic effects are being felt globally. Organizations were forced to take unprecedented steps to halt the spread of COVID-19, including severely restricting staff access to laboratories, or even shutting down the entire laboratories, buildings, and work sites for weeks at a time [10].

The FDA Guidance for Industry on Planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug Products recognizes that in a disaster such as an influenza pandemic, a widespread illness could result in high absenteeism [10]. This type of incident may hinder normal production activities and cause supply chain shortages of drug products, packaging materials, drug components, and excipients. It also recommends that the industry prepares for an emergency by developing plans to ensure operational continuity during emergencies when a significant number of employees cannot report to the workplace. [10]

Each company should have a Stability DRR plan to address emergencies and support business continuity. For a company that has multiple sites, the DRR plan must be specific enough to address critical impacts at each location where it is to be implemented to be effective. This plan must be developed and reviewed periodically to provide flexibility and current information to adjust operations, resources, and personnel as needed. Plans must include approaches for things that will go wrong such as resurgent outbreaks [2]. Authorized people should also be available to make decisions on activating, deactivating, making changes and decisions before, during, and after the emergency. This team must be established and trained with backup to handle the execution of the DRR plan such as shipping samples, activating stability tests at different sites, etc.

It further recommends that companies prioritize products based on medical necessity because using a tiered approach provides useful insight into how best to manage and shift resources to meet public health needs for the most critical products. The general considerations from the FDA guidance conclude that companies must have detailed critical considerations for plan implementation during a period of high absenteeism. The threshold for plan activation should also be considered because not all disasters are created equally. Table 1 is a list of questions that may be found helpful for starting the discussions for the Stability DRR Plan in any stability organization [2,10,11,12,13,14].

1. How should efforts to resume processes suspended during the emergency be prioritized?
2. What is the most efficient method to address delayed activities such as sample analysis and equipment calibrations?
3. How should issues resulting from the execution of the Plan (e.g., out of specification test results, deviations, unusual complaints) be reported to the regulatory authorities?
4. What mechanism is most appropriate to review and summarize activities taken during DRR Plan activation?
5. What is the trigger (milestone) for initiating business resumption?

Table 1-List of Questions to Start Developing a Stability DRR Plan

It is essential to define your organization's common terms and acronyms. Include the terms Disaster, Disaster Risk Reduction

(DRR) Plan, Essential Functions, and any other Stability jargon specific to your organization to avoid delays and confusion about the necessary functions during the crisis. The DRR Plan must list the essential functions to keep the stability program operational. Minimally it should include an Inventory Team, Testing Team, and Shipping/Receiving Teams if the sample storage is different from the testing laboratories.

Each company should also secure the Essential Function Certification Letter on the local site company letterhead with a local site approval signature, especially if sites are in different countries. Without the certification, team members are at risk of citation or worse from local regulating authorities. This web-link to a template can help in the creation of the letter.

ESTABLISHING STABILITY PRODUCT RISK AND IMPACT LEVELS

The DRR Plan should be based on risk- and data-driven strategies. Therefore, Stability Product Risk Levels must be defined and well evaluated. Several factors should be considered in this determination. The most crucial factor is the degradation kinetics of the drug substance, drug product, or medical device as this will impact the chemical and physical stability profile. The shelf life of the product is also a critical contributor. For those products that have a short shelf-life, testing is critical. Figure 2 provides some insights for the discussion to define the risk levels of the stability program.

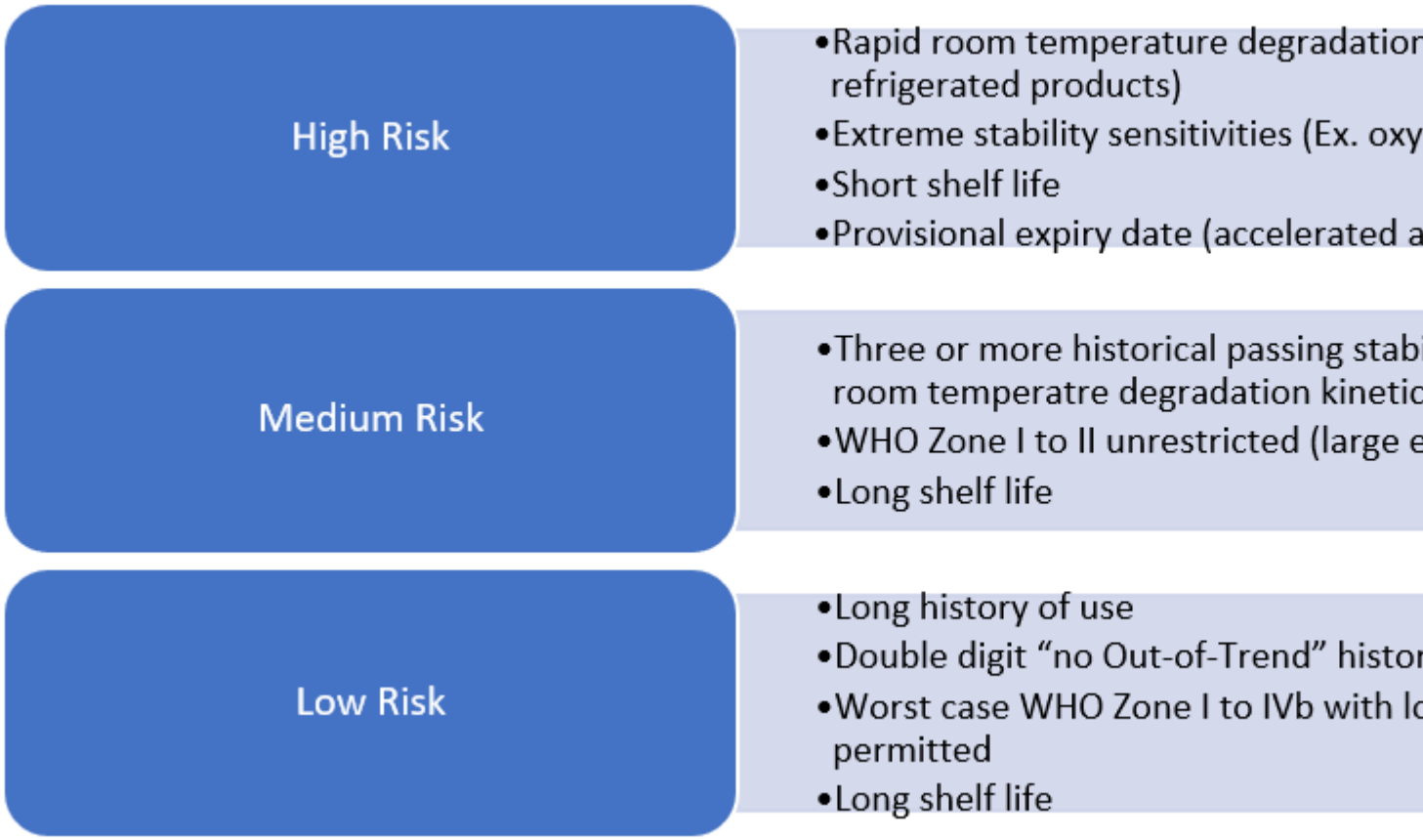

Figure 2- Risk Levels of Stability Products

Once the risk levels are established, the Stability Program Impact Levels must be evaluated. Any DRR Plan should be designed using an impact level principle. Based on the nature of a disaster event, the duration of the likely impact can be forecasted using historical data about similar events on other industries. Since stability testing is time-dependent, event duration becomes the critical differentiation factor for determining the impact level. Figure 3 shows a 2-level program to assess the level of impacts of the Stability Program.

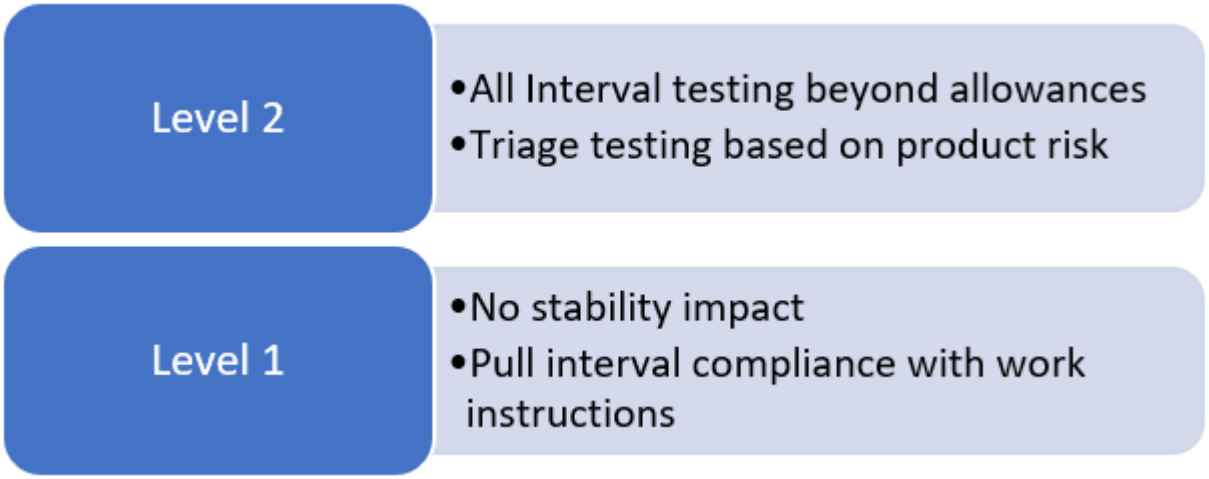

Figure 3 – Development Levels for DRR Plans

Generally, disasters can be considered to have three Out of Window (OoW) stability pathways. Figure 4 shows this decision flow and escalation triggers graphically. When disaster strikes, the first activity is to designate a champion who will evaluate the risks and priorities with regards to the locations where samples are stored and the laboratory where testing is done. Depending on the outcome, the triage plan will be executed, and notifications to the regulatory agencies as necessary. These activities must be performed as soon as possible with all available information. It is necessary to understand that this plan must remain flexible. For example, the COVID-19 pandemic arrived causing the site to be shut down. The duration for the site to resume normal operation was highly variable and externally driven. Corporate management had minimal options until cases of infection decreased to some acceptable level. Therefore, timelines will be flexible and readjusted as needed.

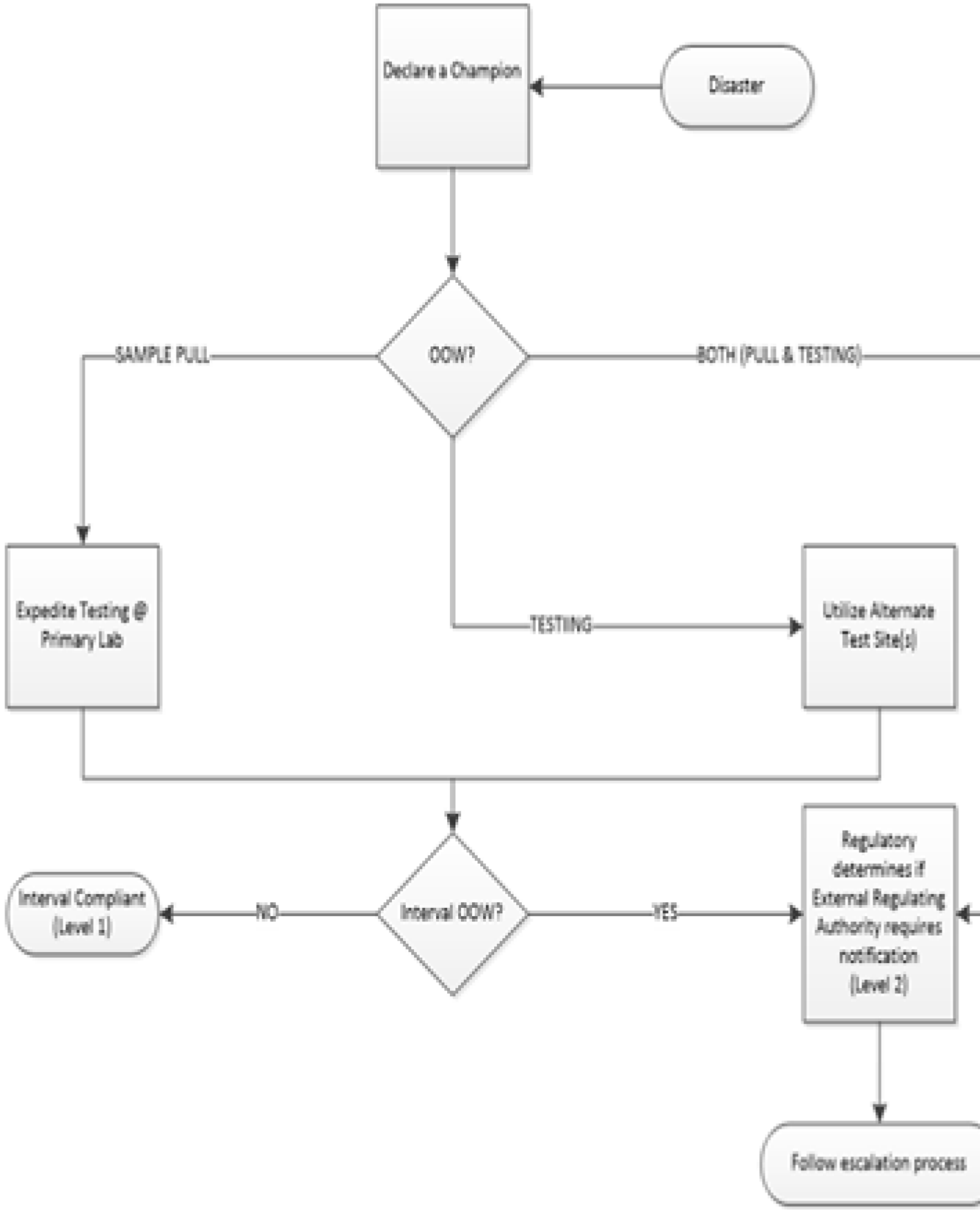

Figure 4 –Stability Disaster Impact Flow

DEFINING THE TRIAGE PLAN FOR STABILITY TESTING

Triage is a process of determining the priority of patients' treatments by the severity of their condition or likelihood of recovery with and without treatment. It is necessary when resources are insufficient for all to be treated immediately, influencing the order and priority of emergency treatment, emergency transport, or transport destination for the patient [16]. In extreme situations, the medical authorities may have to make a decision who would receive the care depending on the likeliness of success. As previously noted, stability testing is essential to support patient safety and efficacy, and it is also a part of company obligations to market medical products [17,18]. As we experienced with India's contract laboratories impacted by COVID-19 restrictions, there are circumstances beyond company control, and access to the laboratory facilities that are equipped and staffed to perform stability related activities may be restricted. In force majeure circumstances, such as government-mandated restrictions, stability triage protocols may be permitted to ensure the continuity of the supply chain [15]. The triage should consider multiple, scientific, dependable approaches, based on the out-of-trend risk levels and the technical value of the stability interval (e.g., expiry date, real-time versus accelerated testing, early phase development or late phase development.)

The Stability DRR Plan should address the use of alternate test lab sites for the Stability Program. It can include a prioritization ranking such as an internal company alternate facility, an external Approved Supplier Laboratory (ASL) site, or even an external credentialed (non-ASL) testing site for a consensus standard method if the missed/late test versus non-ASL risk warrants. Specifically, it is better to determine in advance if data from a consensus standard method from a non-ASL regulated lab is better than no data when all the normal approved labs are disaster-impacted. Discussing in the "heat of the moment" could result in emotion-based logic (i.e., we must do something!) instead of objective reasoning. If the other lab is not feasible, an alternative set of stability samples could be stored at an alternate site to reduce the risks of a stability disaster [18,19].

Another critical element is to define the Risk Priority Level Confirmation Process. When a company is using Triage Process Flows to support the Stability Disaster Risk Reduction, it may be appropriate to utilize a streamlined Stability Protocol Change Control Process to facilitate compliant documentation and execution [15].

A Robust And Flexible Plan To Support Business Continuity

Every DRR Plan should be designed with a robust yet flexible target to assure the continuing support to the business during a disaster. The magnitude of the COVID-19 pandemic has surprised many companies and even driven some that were unprepared for permanent closure. Having a DRR plan is critical. The DDR Plan is not expected to foresee every possible impact. This plan is a guidance document that can be modified for specific events as they come. Any deviations will be documented via the company's nonconformance or escalation processes [18,19]. Table 2 lists the activities that should be part of the DRR plan for the Stability program.

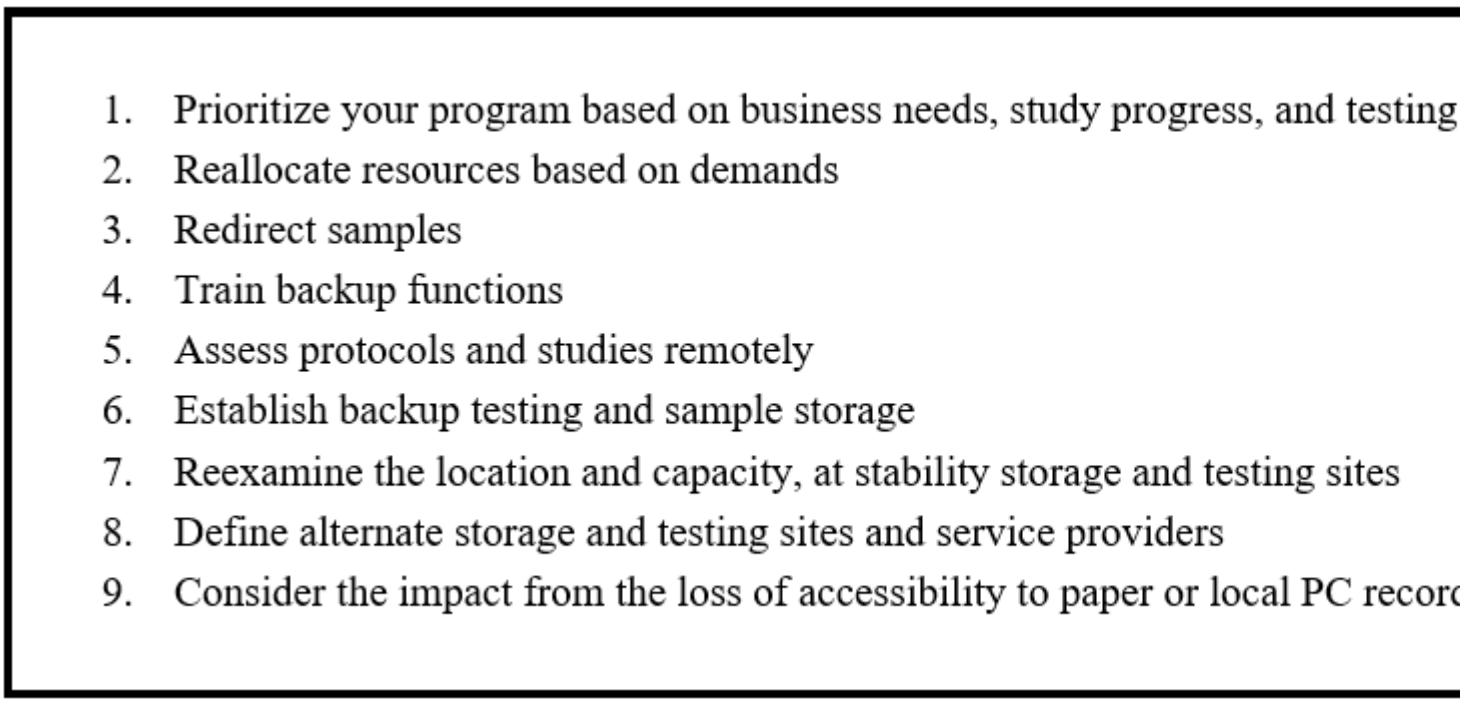
1. Prioritize your program based on business needs, study progress, and testing
2. Reallocate resources based on demands
3. Redirect samples
4. Train backup functions
5. Assess protocols and studies remotely
6. Establish backup testing and sample storage
7. Reexamine the location and capacity, at stability storage and testing sites
8. Define alternate storage and testing sites and service providers
9. Consider the impact from the loss of accessibility to paper or local PC record

Table 2 - Activities to be included in the Stability DRR plan

CONCLUSION

COVID-19 has urgently reemphasized the need to ensure business continuity. The stability program supports life-saving medicines and equipment on a global scale. The phrase “Never let a good crisis go to waste” has been attributed to Winston Churchill. Once again, amid a great crisis, it is imperative that all companies carefully develop a disaster risk reduction plan for the stability program to minimize the disruptions. An appropriately developed Stability DRR plan will provide a framework for actions and prompt response to support the supply chain of the product lines. It can also be extended by subsequent program or guiding principles to assure a continuous process of enhancement, modification, and optimization as needed. This program must be maintained and challenged periodically to ensure all functions can be effective at the time of need. It is critical to a company’s objectives, including the provision of quality products supporting the goal of saving lives and satisfying regulatory commitments.

DISCLAIMER

The views and opinions expressed in this publication are the authors’ own and do not necessarily reflect the views or policies of their respective employers.

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