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White Paper

Business Continuity Management: The Benzonase® Endonuclease Success Story

The need to ensure continuity of business operations reached what was perhaps a new level of importance during the COVID-19 pandemic. Supply chains were put under intense pressure and, in many cases, significantly disrupted while the demand for materials critical to the production of vaccines soared.

One of the products facing unprecedented demand was Benzonase® endonuclease. On the market for more than thirty years, this nuclease is used to digest host cell DNA during manufacturing of viral vaccines and viral vectors for cell and gene therapy applications. Use of Benzonase® endonuclease enhances process yield, limits fouling of downstream equipment, and helps to ensure patient safety. Demand for this enzyme increased by five-fold within three months during the pandemic and remained high, ultimately being used to manufacture more than two billion doses of COVID-19 vaccines.

This white paper describes our business continuity planning process, how it enabled an uninterrupted supply of Benzonase® endonuclease during the pandemic, and the continued evolution of this process, informed by lessons learned in recent years.

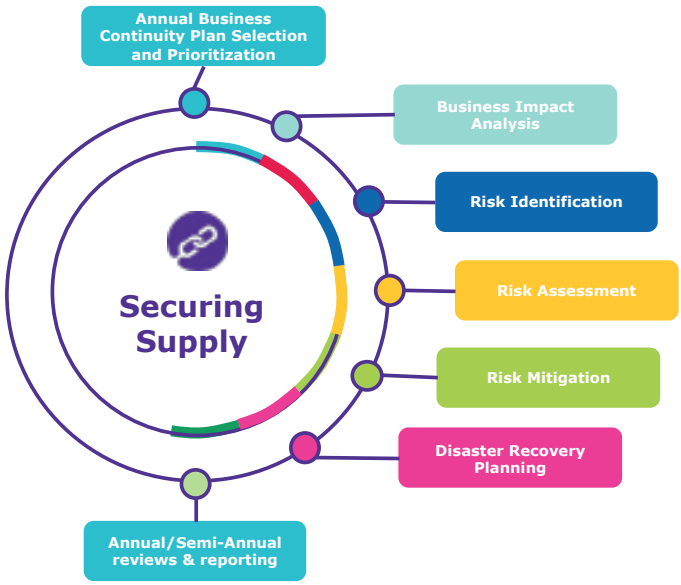

Figure 1. Key steps in the business continuity management process.

Business Continuity Principles

Development and implementation of business continuity plans are an important part of the overall enterprise risk management landscape. It is part of a wide-ranging process that includes initiatives to address risks related to suppliers, raw materials, logistics, distribution, and information technology (IT), as well as crisis management.

The business continuity management process used by our organization to secure product supply is based on ISO Standard 22301 and was established in 2011. Elements of the process are shown in **Figure 1**. The process begins with an annual prioritization of business continuity needs, followed by an analysis of the business impact. The formulation of a business continuity plan for a particular product, process, or location includes risk identification, assessment, and mitigation. Annual and semi-annual reviews are conducted to ensure the plans reflect the current environment and market conditions.

Risks related to demand, manufacturing, materials, facilities, and systems are first identified and may include forecast accuracy, capacity and maintenance, sole sourcing, buildings, water and power, and the enterprise resource planning (ERP) system. The vast majority of high risks across more than 120 business continuity plans are related to manufacturing equipment, utilities, and raw materials. Examples of assessment criteria related to these risks and possible mitigation actions are shown in **Table 1**.

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Equipment and Utilities	Raw Materials
Assessment Criteria	**Assessment Criteria**
• Availability of backup equipment • Age • History of breakdowns • Capacity load • Scrap/yield • Maintenance and spare parts • Recovery time • % of volume impacted	• # of qualified sources • Lead time variability • Market capacity • Quality/defects • Supplier relationship • Time to find alternative source • % of volume impacted
Mitigation Actions	**Mitigation Actions**
• Purchase backup • Qualification on alternative equipment • Cross-training • Training on manual alternatives • Increase in spare parts • Increase in preventive maintenance • Audit of vendors (spare parts lead times, loaners)	• Qualification of second sources • Qualification of alternative materials • Increase of inventory positions • Audits of suppliers (manufacturing locations, capacity, risk programs) • Continuous monitoring of supplier performance and inventory levels

Table 1. Examples of assessment and mitigation action for equipment, utilities, and raw materials.

The step following risk identification, assessment, and mitigation is disaster recovery planning in which two scenarios are considered – a more probable, less catastrophic situation and a less probable, highly catastrophic incident. A recovery timeline is created for each possibility and details the steps and time required to achieve a series of milestones in the path toward a return to full capacity. The timeline considers factors such as what would happen at "zero hour"; how long would it take to return to any level of capacity; whether another plant be leveraged; and whether outsourcing is an option.

Business Continuity Management for the Supply of Benzonase® Endonuclease

Prior to the pandemic, our business continuity and crisis management plans and simulations considered the possibility of a regional epidemic and the impact on materials for the vaccine industry; it did not, however, consider the possibility of a global pandemic. Strong, existing supplier relationships and resilient supply chains were already in place across the organization. As demand for products surged, however, a reduction in the overlap of production shifts and localized outbreaks of the virus led to reduced capacity as the safety of employees was prioritized. Distribution was also challenging due to border closings and the effect of the pandemic on shipping channels.

Fortunately, a comprehensive business continuity management plan designed specifically for Benzonase® endonuclease had been established in 2019. At that time, there was a single manufacturing site located in Denmark.

The time from the start of manufacturing to batch release was roughly 8 weeks and the product shipped on dry ice at -20 °C. As part of the business continuity planning process, a series of risks were identified:

- Manufacturing know-how was concentrated in a single location
- Lead times could cause backorders in case of unexpected demand
- Demand could change largely overnight
- Shipment issues could damage the product
- Raw material variation could alter the product quality

The first three risks were managed with the business continuity plan while the last two were addressed with updates to standard operating procedures. Samples of critical raw materials are now tested prior to the bulk product being delivered to our organization and temperature strips are used to track possible variation that may affect product quality.

As outlined in **Figure 1**, the continuity plan started with an analysis of the potential business impact. This process included the capture of a variety of information including:

- Critical product details (revenue, growth, etc.)
- Maximum expected period of disruption
- Maximum tolerable period of disruption
- Market and quality criteria
- Critical supply chain maps

The subsequent risk identification step was based on a full list of all items relevant to the production of Benzonase® endonuclease including:

- Manufacturing equipment
- Site utilities
- Software applications
- IT hardware
- Raw materials (direct & indirect)
- Distribution capabilities

Following an in-depth risk assessment, several risk mitigation steps were enacted including:

- Purchase of backup equipment
- Replacing old equipment
- Validating alternative pieces of equipment
- Qualification of second suppliers
- Inquiry and partnership with suppliers
- Increase of inventory
- Cross training

An evaluation of likely disruption scenarios was undertaken to develop a recovery timeline and identify actions to improve that timeline. While there was a lower overall risk due to the location of the production facility in a politically and environmentally stable country, risk would be further minimized by opening a second production facility with the same manufacturing capabilities. The duplicate site, located near the original facility in Denmark, is used only in the event of an emergency and allows resumption of Benzonase® endonuclease production without delay.

Preparing for the Future

While the business continuity management plan for Benzonase® endonuclease enabled our organization to meet surging demand during the pandemic, this unprecedented global event drove additional improvements as outlined in **Table 2.** Changes have been enacted to address factors that can impact continuity including the approach to crisis management, suppliers and raw materials, manufacturing capacity and operations, inventory planning, distribution, and logistics.

Among the key action steps are the development of step-by-step plans for multiple scenarios, annual simulations, and plans that can be deployed across global sites. Maintaining a clear view of how suppliers manage risk is essential, as is supply chain mapping, which now includes the use of third-party software to monitor global political unrest and environmental events in real time. Increased manufacturing capacity and building surge demand into inventory safety stock calculations are essential, as is a sharper focus on ensuring labor continuity. Distribution and logistics are strengthened with flexibility in terms of the use of multiple distribution lanes and running tests and simulations.

Elements of Continuity Planning	Actions Taken
Crisis Management Plans	Need step-by-step plans for multiple scenarios
	Annual simulations for plans
	Leverage plans that can be rolled out across sites
Suppliers and Raw Materials	Expanded supply chain mapping
	Increased surveys of suppliers' crisis management plans
	Review of inventory levels
Manufacturing Capacity	Expanded capacity
	Deeper insights into labor as constraint
	Surge capacity simulation
Manufacturing Operations	Improved plans for labor continuity
	Test safety measures
	Continued tie with capacity planning
Inventory Positioning	Surge demand to be added to safety stock calculations and algorithms
	Early tracking system to ramp up production
	Leverage understanding of vaccine market to plan for specific product increases
Distribution and Logistics	Split transit lanes in advance
	Improve visibility to transit nodes, border closures, etc.
	Tests and simulations

Table 2. Improvements to the business continuity management planning process.

Conclusion

Global business operations and supply chains supporting the biopharmaceutical industry were tested like never before as a result of the COVID-19 pandemic. Demand for products to support the development and manufacturing of new vaccine and therapeutics rose sharply, requiring companies providing those materials to rely on existing business continuity plans or scramble to react. Our business continuity plan for the supply of Benzonase® endonuclease was already in place when the need for this critical reagent in the vaccine manufacturing process increased rapidly to an unprecedented level. Proactive continuity planning enabled an uninterrupted supply, supporting production of billions of vaccine doses.

Our business continuity management plans have continued to evolve and improve. These plans position our organization to address changes in demand more effectively and efficiently, anticipate events that may affect supply chains and business operations, and respond more rapidly to changes in the operating environment, if and when the need arises.

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