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Preparedness for Pandemic Flu Outbreak: A Case for Business Continuity and Technology-Transfer Planning

Biopharmaceutical companies should come together to create an efficient business continuity plan that would be effective in a pandemic.

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ABSTRACT

Kim Steele/Getty Images

To succeed in a pandemic flu outbreak, the biopharmaceutical industry must unite, disregard proprietary and competitive issues, and forge a preparedness plan to ensure adequate vaccines. A business continuity plan is essential. Such a plan must address three key areas: maximum tolerable disruption period, recovery-time objective, and process resilience. Technical and regulatory hurdles must be overcome, in part through the pursuit of new vaccines, including those that use cell-culture and recombinant manufacturing techniques. An effective pandemic preparedness plan would involve manufacturing scale-up, production optimization, and shared capacity among organizations.

During the last few years, efforts to develop a preparedness plan for an avian flu pandemic have galvanized the world community. Though health experts worldwide may feel relatively well positioned to detect such an outbreak early, support international efforts to contain it in its earliest stages, and limit its spread, the reality is that its impact could be devastating. As the world shifts its focus away from other potentially catastrophic outbreaks such as severe acute respiratory syndrome (SARS), we cannot drop our guard against any pandemic.

The real challenge in preparing for a pandemic outbreak involves putting in place a process by which the biopharmaceutical industry can respond quickly and effectively. The obstacles normally associated with vaccine production are exacerbated in a pandemic. If the industry is to ensure public safety, tasks such as indentifying the strain rapidly, compressing vaccine-development and process-development timelines, and translating global regulatory standards must be executed flawlessly. To meet the expectations of the global community, the industry must invest heavily in developing a well-defined business continuity plan that goes beyond normal business continuity and includes the task-compression activities required in response to a pandemic.

A History of Pandemics

A brief overview of the past emphasizes the magnitude of the current challenge. The initial outbreak of the Spanish flu was recorded as early as 1918, and this pandemic is generally considered the most lethal of the 20th century. The outbreak began simultaneously in France, Sierra Leone, and the United States, and it swept around the globe. The World Health Organization (WHO) estimates that during the Spanish flu's lifecycle, nearly 25% of the world's population fell ill (approximately 500 million people), with an estimated fatality rate of 40 million people. The Spanish flu was just one of several flu pandemics in the United States in the last century.[1] Table 1 summarizes the various types of viral strains and the impact of each on US population. In each case, the pandemic was caused by a different subtype of the influenza A virus.

Table 1. Viral strains and their impact. Spanish Flu affected nearly 25% of the world population.

Pandemic years	Estimated US fatalities	Influenza A subtype	Populations at greatest risk
1918–1919 Spanish flu	>500,000	H1N1	Young, healthy adults
1957–1958 Asian flu	70,000	H2N2	Infants and elderly
1968–1969 Hong Kong flu	34,000	H3N2	Infants and elderly

Table 1. Viral strains and their impact. Spanish Flu affected nearly 25% of the world population.

Table 2. Attributes of the three viral strains—influenza type A, B, and C.

Influenza type A	Influenza type B	Influenza type C
• Antigenic shift and drift • Epidemics and pandemics • Humans and animals • 15 H and 9 N antigens	• Antigenic drift • Milder epidemics • Humans	• Antigenic drift • No epidemics • Humans and swine

Table 2. Attributes of the three viral strains—influenza type A, B, and C.

Influenza viruses are characterized as type A, B, or C. Table 2 summarizes the attributes of each of the three types. The key challenge in pre-paring a vaccine to combat these three involves influenza A's ability to morph as it develops. This attribute is called "antigenic shift" and "antigenic drift."

The first of these changes in the virus, antigenic drift, is a minor modification in an antigen on the surface of a pathogenic micro-organism. This circumstance is typically the result of natural selection, in which the virus mixes with a partially immune population. Immunization against the original virus may provide some partial protection against the modified virus, but an epidemic could result if the situation is left unchecked.

The second of these alterations, antigenic shift, is a more lethal and abrupt change in antigenic composition. For example, the hemagglutinin (H) or neuraminidase (N)

spikes from a human influenza virus could be replaced with a spike from a nonhuman animal, or an adaptive mutation could result in a major antigenic change. This type of change is called "re-assortment." In re-assortment, humans can become the "mixing bowl" in which a non-human virus strain, such as an avian strain, can mix or re-assort with a human influenza strain, resulting in a new strain that is immuno-logically unique, readily trans-missible, and consequently, much more effective as a human patho-gen. The 1918 Spanish flu virus began as an avian flu, and then it mixed with a human influenza virus to form the H1N1 influenza A virus subtype that attacked a quarter of the world's population.

Pandemic preparedness activity is currently focused on the H5N1 influenza A virus subtype, a bird-adapted strain, which is known as avian flu. To date, the H5N1 avian flu virus has been found in birds in 48 countries, and in pigs in China, felines in Thailand, and civets in Vietnam. When the first fatalities were recorded from the outbreak of avian flu, the US Centers for Disease Control and Prevention (CDC) estimated the fatality rate worldwide could range from 80 million to 100 million people if a pandemic outbreak were to occur. Since 2002, more than 385 cases and 243 deaths have been reported from the avian flu virus.[2] Because of its ability to mutate and to be rapidly transmitted, the global community has focused on this virus.

Pandemic Preparedness Planning

Health oversight organizations around the world have developed pandemic preparedness guidelines. The World Health Organization (WHO) has published its Global Influenza Preparedness Plan, which serves as the foundation for national and local authorities to define their own plans. The WHO plan divides a pandemic outbreak into six major phases, shown in Table 3.[3] To address the specifics of each community's readiness activities, 11 technical areas have been designated for a pandemic preparedness plan. These areas are shown in the sidebar (Pandemic Preparedness Planning: Technical Areas of Focus).

Table 3. The World Health Organization plan divides a pandemic outbreak into six major phases.

The Industry Approach

Although there has been significant activity concerning the steps necessary to combat a pandemic outbreak from the perspective of isolating and managing its impact on the general population, the biopharmaceutical industry's ability to rise to the challenge remains unclear. In May 2006, the WHO convened a meeting of key stakeholders from national immunization programs, national regulatory authorities, vaccine manufacturers, and the research community to develop a strategy for combating a pandemic. The recommendations of that committee were published as part of WHO's Global Pandemic Influenza Action Plan to Increase Vaccine Supply, in which the organization identified three major approaches:[4]

1. Increase seasonal immunization programs against influenza for countries with immunization programs.

2. Increase production capacity among the largest vaccine manufacturers.

3. Invest in research and development of new, more rapidly developed vaccines.

The industry's ability to support all three initiatives will determine the ability to respond to an outbreak.

Responding to the Call

Pandemic Preparedness Planning: Technical Areas

A. Communications
B. Epidemiology surveillance
C. Community disease containment
D. Infection control
E. Clinical issues
F. Healthcare planning
G. Antivirals and vaccines
H. Laboratory
I. Poultry worker health
J. Care of the deceased
K. Environmental public health

Pandemic Preparedness Planning: Technical Areas

The challenges facing the biopharmaceutical industry in the event of a pandemic outbreak are multifold. To meet WHO's pre-paredness plan requirements, the industry must invest in a carefully considered business continuity (BC) plan. Unlike most BC plans, this one must go beyond merely restoring operations in the event of a disaster such as a pandemic outbreak; it must focus on the industry's ability to effectively handle the timeline and technology hurdles created by the antigenic shift potential of H5N1. The question must be asked: Do the technology and regulatory requirements involved in manufacturing a vaccine inhibit the biopharmaceutical industry from effectively responding to such a fluid and shifting threat as that posed by the H5N1 avian flu virus?

Business Continuity

The UK's Business Continuity Institute defines business continuity management as a holistic management process that identifies potential effects that threaten an organization, and provides a framework for building resilience and the capability for an effective response that safeguards the interests of its key stakeholders, reputation, brand, and value-creating activities."[5] A number of guidance documents—including NFPA1600 (US and Canada), BS25999 and FSA (UK), and HB221/APS 232 (Australia)—describe a process and framework for creating and implementing a BC plan.

These plans are divided into three phases: business impact analysis, risk assessment, and final analysis. In each phase, they focus on three fundamental parameters that are central to establishing business continuity: maximum tolerable disruption period (MTDP), recovery-time objective (RTO), and process resilience.

MTDP measures the maximum allowable time a business could tolerate an interruption in operation for each key work center or operation as it pertains to the business's product. Understanding the interdependencies among operations is essential to determine the MTDP. Identifying the MTDP for technology transfer, manu-facturing, regulatory, and supply-chain processes would be central to pandemic preparedness.

The RTO sets the metrics for responding to the disruption. An organization must define early in the process whether survival of the business is the base acceptance criterion for the continuity activity or, in the case of a pandemic response, for

countering the fluctuating demands of the out-break. Having a clear definition, based on recent or forecast data as they pertain to a pandemic's impact on operations, is essential to defining realistic RTOs.

Resilience describes a process's ability to continue, even in failure. Redundant array of independent disks (RAID) tolerance for an information technology (IT) network is an example of machine resilience. A redundant power stream is an example of site resilience. Organizational responsibility distributed by location is an example of organizational resilience.[6]

Analyzing an organization against these criteria forms the basis for creating an effective BC plan. Figure 1 shows the many considerations associated with an effective BC plan.

Figure 1. Considerations associated with a business continuity plan

Although such a plan represents a significant undertaking when focused solely on maximizing key stakeholder value, the effort required and the far-reaching consequences of a poorly developed and poorly executed plan take on a new level of significance when framed in the context of the inability to respond to a pandemic outbreak.

Technical and Regulatory Hurdles

Figure 2. A conventional vaccine production process requires at least six months for producing an effective vaccine.

A key challenge in preparing an effective vaccine is the issue of developing and stockpiling material in advance. Given the antigenic-shift potential of the influenza A virus, rapid vaccine development soon after the outbreak would probably be critical. Conventional manufacturing processes, which introduce a virus into millions of embryonated chicken eggs, require at least six months for producing an effective vaccine (Figure 2).

Current suppliers of inactivated virus vaccines include Sanofi Pasteur, Novartis, and GlaxoSmithKline. Live virus vaccines introduce a weakened form of the influenza virus to trigger an immune response by the body. A live attenuated virus vaccine manufactured by MedImmune has been recently approved.

The best way around technology hurdles is the pursuit of vaccines that use cell-culture and recombinant manufacturing techniques. Cell-culture processes, similar to those used by monoclonal antibodies manufacturers for decades, could facilitate on-demand production. Solvay has successfully launched a vaccine in Europe based on the Madin-Darby canine kidney (MDCK) cell culture. Novartis has a program in Phase-3 clinical trials using the same cell-culture approach. An effective business continuity plan would require shared capacity among corporations to meet the forecast demand. Currently, the largest cell-culture capacity is held by the 10 largest biotech giants. These companies must be integrated if the plan is to be successful. To serve the public's needs in a pandemic, a vaccine would probably have to be manufactured at multiple sites of different corporations. For this scenario to succeed, the details of intellectual property, cost, and revenue models for the shared response among multiple suppliers must be negotiated in advance.

The Product Transfer Roadmap

Regardless of whether the pandemic response is to shift operations to another site or to another company, the challenges associated with scale-up and production optimization would remain. As with any technology transfer and scale-up exercise, a detailed plan would be required to execute the program successfully. The milestones for the exercise must be driven by the BC plan. A key element in the plan should involve determining the operational interdependencies that must be migrated to meet the MDTP. Unlike in the past decades, the biopharmaceutical industry has now embraced operational excellence tools, such as Lean Manufacturing and Six Sigma, as part of its business model. Leveraging these tools could greatly facilitate the creation of an efficient BC roadmap that would be effective in a pandemic. Leveraging Lean Manufacturing tools—in particular, establishing the value-stream map (VSM) for the vaccine manufacturing process as part of the BC plan establishment exercise—would facilitate identification of bottlenecks and of sources of variation in the process. Complementing the overall business VSM with detailed technical VSMs would ensure that the BC plan reflected the realities of technology transfer and new drug introduction.

Regulatory agencies have already put processes in place for accelerated approval. In the United States, the Center for Biologics Evaluation and Research (CBER) has issued guidelines encouraging vaccine manufacturers to explore cell-culture and recombinant techniques, and to incorporate biological integrators, such as immune response, into their product-development designs.[7] If clinical efficacy using accelerated data can be corroborated by surrogate markets, then the development time for the products may be reduced. In addition, when approval is sought for a vaccine against a pandemic outbreak, and that vaccine is based on one used for seasonal immunization, the review process is expedited. Regulatory complexity increases, however, if the manufacturer of the pandemic vaccine is not the same as that for the seasonal vaccine, as would be the case in a shared manufacturing capacity scenario.

Conclusion

The global community has developed effective processes and steps to respond to a pandemic outbreak. However, the industry's ability to respond effectively remains to be seen. Unless experts accurately anticipate the final form of the H5N1 virus, conventional manufacturing using embryonated eggs will probably not satisfy international demand. For development and approval cycles to meet the needs of a pandemic response plan, innovative vaccines using cell-culture and recombinant techniques, equipped with integrated biomarkers, will be required. The current plan requires industry collaboration in the face of a global threat—collaboration both through allocation of available or allocated manufacturing capacity, and through shared investment in technology transfer and scale-up. Assuming that compensation and intellectual property issues can be managed or set aside, the biopharmaceutical industry must not delay in developing the necessary business contingencies and

technology roadmaps. Although this threat may seem less imminent today than a year ago, the potential for and the consequences of pandemic outbreak remain very real, and they will require cooperation on a global scale.

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