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Research Overview

Manufacturing a Rapid Biologic Response

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Strategy, Management and Health Policy				
Enabling Technology, Genomics, Proteomics	Preclinical Research	Preclinical Development Toxicology, Formulation Drug Delivery, Pharmacokinetics	Clinical Development Phases I-III Regulatory, Quality, Manufacturing	Postmarketing Phase IV

ABSTRACT There are two major components in making new biologic medical countermeasures available for bio-defense and pandemic response: (1) the detection/discovery of effective countermeasures, and (2) their subsequent Process Development (PD) and manufacture. PD and manufacturing, however, are often the most costly and time-consuming parts of the process, potentially taking years and costing hundreds of millions to billions of dollars. To address these long timelines, governments have historically stockpiled countermeasures for known biothreats. Unfortunately, this kind of stockpiling is very expensive, and does not provide protection against novel threats. Fortunately, there currently exist many new technologies that, when combined strategically, have the potential to significantly reduce the time and cost associated with the PD and manufacturing of biologic countermeasures. Drug Dev Res 70 : 288–295, 2009. © 2009 Wiley-Liss, Inc.

Key words: biologics; manufacturing; rapid response

INTRODUCTION

Shortcomings in the Current System

It is generally recognized that Process Development (PD) and manufacturing for biologics are too expensive and time consuming for rapid response protection of entire populations. Recognizing this, in 2006 the Defense Advanced Research Project Agency (DARPA) launched a new program, Accelerated Manufacturing of Pharmaceuticals (AMP), designed to accelerate production of critical biologic medical countermeasures. The AMP calls for medical countermeasures to move from the initiation of PD through manufacturing of three million doses in 12 weeks (www.darpa.mil/dso/thrusts/bwd/act/amp/index.htm). In actual practice, for a civilian population, the dosing demand might be closer to 300,000,000 doses. As seen in Figure 1, if the medical countermeasure were a monoclonal antibody (mAb), traditional approaches would require at least two years, and possibly much more, to achieve the goal.

Given the implications of a biothreat emergency for which a medical countermeasure has been developed, but cannot be made generally available for more than two years, stockpiling selected biologic medical countermeasures certainly has an important role in our national defense. In the United States, efforts have focused on specific countermeasures. In 2006, the Department of Health and Human Services (DHHS) awarded contracts for $199.45M worth of flu vaccine (2.7M doses of a planned 20 M doses), and announced a $1B program to shift to cell-based influenza vaccine manufacturing (DHHS Press Release, Nov. 20, 2006. HHS Buys Additional Vaccine for Potential Use in an Influenza Pandemic www.hhs.gov/news/press/2006pres/20061120). In 2007, DHHS awarded contracts worth $132.5M to retrofit existing facilities to maintain a warm base for surge capacity in a pandemic emergency (DHHS Press Release, June 14, 2007. HHS Awards Two Contracts to Expand Domestic Vaccine Manufac-

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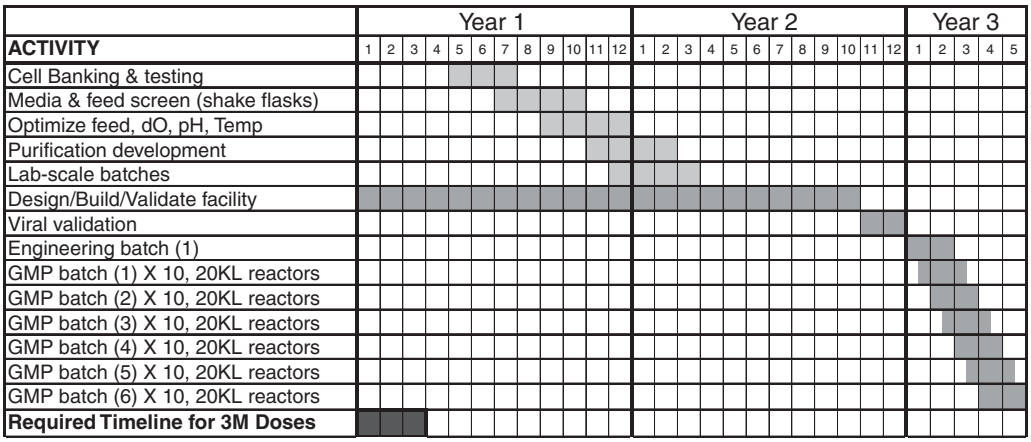

Fig. 1. PD and manufacturing of 3 M doses of a mAb would take more than 2 years using traditional approaches, assuming that the facility can be built and validated within 22 months. This falls far short of the DARPA AMP goal of 3 months. (P. Latham, 2006)

turing Capacity for a Potential Influenza Pandemic. www.hhs.gov/news/press/2007pres/06/pr20070614a.html) and in 2009, DHHS awarded a $487M multiple year contract to Novartis Vaccines and Diagnostics, Inc. to build the first domestic facility to manufacture cell-based vaccine for pandemic and seasonal flu (DHHS Press Release, January 15, 2009. HHS Awards $487 Million Contract to Build First U.S. Manufacturing Facility for Cell-Based Influenza Vaccine. www.hhs.gov/news/press/2009pres/01/20090115b.html). While this provides protection for the potential pandemic flu threat, it does little to address the capital flexibility necessary to manufacture countermeasures for other emerging or engineered biothreats.

According to Dr. Lee Feldman, Chairman and Chief Scientific Officer of the Scian Institute, "An effective policy must be balanced. Right now, there is a lot of money going to stockpiling with little attention paid to a broad-based rapid response" (Telephone Interview with Dr. Lee Feldman, February 6, 2008). Why the focus on stockpiling? Perhaps because, to date, a broadly useful, rapid response capability has been nonexistent and generally thought to be impossible to achieve. Traditional biotech PD and manufacturing technologies have not focused on the "need for speed" required for rapid response, primarily because the years of clinical trials required provide time for relatively time consuming PD and scale-up programs.

Some of the key limitations of the existing PD and manufacturing systems include:

- *Process development time*. The discovery of new therapeutics results in lab-scale processes that generate small volumes of material needed for basic research and pre-clinical testing. The development of manufacturing-scale processes to generate the volume of material of the quality required for clinical trials, and eventually for general distribution is a time-consuming and expensive part of the total drug development process. Typical cell line and media development, for example, can take months and cost millions of dollars using rooms full of roller bottle or shake flask bioreactors. Companies are currently looking at the use of well-plates and robotics to automate this process, but much of the work to date has been limited to achieving higher titers in mammalian cell culture systems.
- *Facility construction time*. Once a manufacturing process has been developed, it can take more than 4 years to design, construct, and validate a new large-scale manufacturing facility.
- *Capital costs of new facilities*. New, large-scale facilities require significant clean room and utility infrastructure and can cost more than several hundred million dollars to construct. The building and maintenance of controlled environments within which one must operate also contribute significantly to capital and operating costs, and facility inflexibility. Suites must be designed and controlled to clean room conditions ranging from class 100,000 to class 100 depending upon the manufacturing step. Typical capital costs jump from around $\$250/ft^2$ for uncontrolled clean space to $\$3000/ft^2$ for Class 100 clean room space. These costs are apportioned as shown in Figure 2.
- *Facility Operating costs*. Manufacturing facilities require highly trained people, and acquiring and maintaining that base of expertise "warm" is very expensive. In addition, staff, who work in clean rooms, must go through expensive and time-consuming gowning and de-gowning operations. The cost of gowning and de-gowning to move from

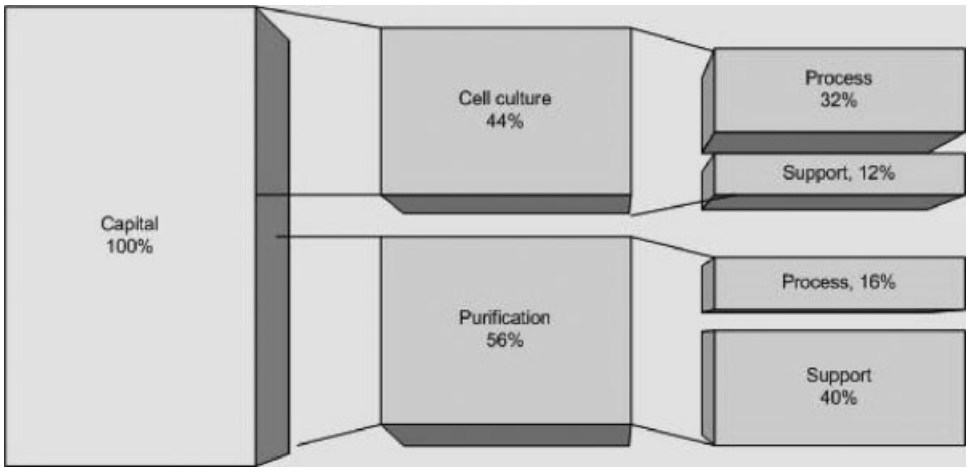

Fig. 2. Over 50% of the capital cost of a traditional facility is in the support systems [van Reiss, 1999], which are dramatically reduced in modular, single-use facilities.

suite to suite is so high that to avoid them large companies often employ entirely separate teams for up-stream, down-stream, buffer prep, and media prep manufacturing areas.

- *Lack of manufacturing flexibility.* Current bio-manufacturing plants are designed as fixed facilities and require substantial capital infrastructure. Process and support equipment are hard-piped together and are supported by large water generation and processing systems. This results in high cost, long construction times, and almost no flexibility. Facilities are generally designed and hard-piped for a specific class of product and can take years and hundreds of millions of dollars to be adapted to different types of therapies or vaccines.
- *Location limited distribution*. Current bio-manufacturing plants are designed as fixed facilities and require substantial capital infrastructure. Additionally, there are substantial economies of scale in bio-manufacturing. As such, capacity is generally centralized and immobile making relatively easy targets.
- *Inadequate or no knowledge and data management systems*. There is a lack of sophisticated knowledge/data management systems in today's PD and manufacturing operations. This results in time-consuming tech transfer and scale-up. Additionally, companies routinely operate with "after the batch" quality control and quality assurance assessments that can only be implemented once the paperwork is filled out and after the manufacturing batch has already been completed. As a result, manufacturing errors are often not detected as they happen and not revealed until months after the batch is produced and all the paperwork has been reviewed. In a rapid response environment, there is no time for complex technology transfer or to use a system where errors are not immediately found and rectified.

The implementation of a biodefense response capability using the typical approach would, therefore, not be flexible enough to manufacture responses for the wide variety of potential threats. In addition, new capacity that was initiated today would not be available for response until 2013 or later. Finally, the capacity would have to be large-scale and centralized, limiting distribution and scale-up while residing in a fixed location thereby making it an easy, less secure target. In addition to the development and infrastructure issues, there are also major regulatory hurdles to any rapid response system. While much effort is focused on the regulatory approval of countermeasures using the Food and Drug Administration (FDA) Animal Rule (http://www.fda.gov/Cber/rules/humeffic.htm), there is a parallel effort that must be addressed in manufacturing. Facilities are currently validated and approved to manufacture specific therapeutics, a difficult and time-consuming process. For any rapid response capacity to work in the United States, there would be a lot of work required up-front with the FDA to define the requirements and determine what work can be done in advance. This would be required in any case where one hopes to facilitate rapid validation/approval for a novel countermeasure in an existing facility. Hopefully, the use of a "standard" but flexible facility and better knowledge management systems could help to facilitate this effort.

TECHNOLOGIES THAT FACILITATE A RAPID RESPONSE

It is easy to see why the current manufacturing base is not appropriate for rapid response. Fortunately,

there are new technologies that begin to address these issues. The first set of technologies is the platform vaccine and therapeutic technologies. "A lot of people are looking for the one drug/many bugs solution" says Dr. Robert House, President of DynPort Vaccine Company. "If you can discover therapies that address multiple threats simultaneously, increase the long-term stability, or develop adjuvants that dramatically increase efficacy, you may have a major impact on the requirements for stockpiled countermeasures" (Telephone interview with Dr. House, February 6, 2008). While these approaches show promise, there are also new technologies that address the PD and manufacturing issues of rapid response.

Manufacturing Using Novel Expression Technologies

Novel expression systems from multiple species could represent a significant part of any rapid response solution. They promise dramatically higher efficiency and a corresponding reduced manufacturing time to produce the doses needed. They have the additional benefit of reduced capital and operating cost, and in some cases much more rapid scalability. Although the product must still be purified via additional "downstream processing" (DSP), advances in purification processes like continuous chromatography have also shown promising results.

These new ways of expressing biologics have met fairly heavy resistance in traditional biopharmaceutical manufacturing in the commercial sector. The two reasons for this are risk and cost. Many of the most promising technologies are also the ones that require the most development, and therefore present the greatest risk. Also, in a world where the margin for a product can be greater than 80%, any radical change to the manufacturing process that introduces risk into the product supply is generally not readily adopted, even if cost savings are substantial. For these reasons, most biologics today are made in traditional bioreactors using standard mammalian or microbial expression systems. Despite major potential benefits, innovations like transgenic plants and animals, and novel expression systems have seen limited adoption.

The cost/risk calculus changes dramatically for using these novel expression technologies if the scenario is bioterrorism or a pandemic rapid response. Against this backdrop, technologies like transfected or fast-growing transgenic plants and novel, high-producing fungal, microbial, or even mammalian manufacturing strains become more viable. There is a need for additional work targeted at the development of rapid and powerful PD technologies and manufacturing systems that can use these new expression technologies.

Automated, Rapid, Robotic, High-Throughput PD Labs

One way to decrease the time required for PD while generating high yield processes is through the implementation of highly automated labs with high-throughput screening technologies. Fortunately, much of the evolution to high-throughput process development is already taking place across the biopharmaceutical industry. Robotic equipment is either commercially available or being internally developed. The two great challenges that remain in building a high-throughput robotic process development laboratory for rapid response include: knowledge management and application of technologies throughout the entire process.

Knowledge Management

A major challenge associated with integrating the PD labs is one of managing and translating the information required to transfer the process into the manufacturing facility (tech transfer). Current PD organizations lean heavily on spreadsheets, text files, and paper to collect and store the data generated. This translates not only into time lost, but into inefficiencies where an average of 8% of experimental work must be repeated because data cannot be found; an average of five hours per employee per week is spent looking for data or reports [Morris et al., 2005]. In a laboratory where automated equipment is collecting and storing data constantly, there is a requirement for a central knowledge management system to process and manage the information. There are several companies working on developing these systems, but at present there is nothing that can collect this data and prepare a standard scale-up and technology transfer package for the time-effective transfer of a process into large-scale manufacturing. Further development of such a system will be a key element to any future rapid response capability.

Application of the Technology Throughout the Entire Process

Current systems are focused largely on the "upstream processing" (USP) development of clones, cell lines, and fermentation processes. To develop a full process in the timelines required, additional development must be made with respect to high-throughput purification/DSP development tools.

Disposable Manufacturing Technologies

The implementation of "single-use" technologies in bio-manufacturing is rapidly becoming mainstream. These technologies provide a significant advantage in the context of bio-defense because they add a great

deal of flexibility to a facility and allow for more rapid changeovers between products. Many companies currently provide single-use solutions ranging from support operations like buffer and media prep and storage, to single-use bioreactors, pre-packed columns, filters, and membrane chromatography. There is even a trend in the industry for companies to provide single-use products across the entire manufacturing process [GE Healthcare, 2006; Millipore, 2006; Sartorius AG, 2007].

One of the main issues associated with single-use technologies is the question of cost. It has been widely reported that single-use technologies can reduce capital expenditures, but the operating cost trade-offs are not inherently obvious. It has been reported that the implementation of disposables in the buffer and media prep areas alone can lead to total operating cost savings in the range of 17% [Sinclair, 2008]. Nevertheless, these analyses are generally focused on medium- to smaller-scale facilities and the doses necessary to make a countermeasure for the entire population could require a very large-scale capacity. As such, it is important that any rapid response strategy take into account the scale of manufacture when exploring the financial impact of single-use technologies.

The current trend in bio-manufacturing is to use disposables. However, this practice is often limited to individual process or support areas (i.e., buffer prep., media prep, or fermenter seed train). The result of this incremental adoption of disposables has been a capital savings of up to 40% [Sinclair, 2008]. In order to fully realize the value of disposables, however, they should be used across the entire process, thereby completely eliminating elements of the current infrastructure (e.g., SIP/CIP skids, stainless buffer and media prep areas, "hard-piped" connections, etc.).

Flexible Modular Facilities

There are two approaches to the concept of modular facilities. The first is the "pre-fabricated house" concept where the facilities' design and construction are standardized, but they still have the fixed piping and support systems, and the operators remain contained within the individual clean rooms. While this approach can save years and millions of dollars in the construction of a new facility, it unfortunately provides little benefit in the context of the flexibility and operating cost needs of rapid response.

The second approach to modular facility design is to re-think the entire concept of a clean room. Typical facilities have fixed equipment in fixed rooms with fixed air handling systems and fixed piping for process flow, cleaning, and sterilization. In a flexible, modular facility concept, the individual process steps are placed into reduced-size, isolator-like, clean room modules, which can be on wheels. These modules can have their own air handling systems, or be attached to a central air handling system through flexible ducting, and they can be located in a continuous line in a single open hall suite (gray space). Process and support systems fluids and materials flow into and out of the modules through single-use sterile connectors. Operators (the largest source of contamination) are removed from the clean room and enjoy the freedom to move up and down the manufacturing line in the "gray space" outside the modules. Operator interface with the process steps is handled through glove ports.

As with single-use technologies, modular, flexible facilities are somewhat limited in their scale of operation. Nevertheless, the dramatic decrease in capital could facilitate the cost-effective ability to build distributed capacity that is more secure, presents less convenient targets, and allows for smaller countries to build their own capacity. Also, with continued investment in increasing the productivity of the processes through higher yielding expression systems and PD labs, it is likely that smaller facilities will be able to produce the needed doses for many potential countermeasures.

Combining Synergistic Technologies

When the flexible, modular approach described previously is coupled with the use of disposables and automation, the result is a major reduction in cost and a dramatic increase in flexibility. When building a traditional facility, the capital costs are largely driven by the piping and support systems required. With a modular facility, these costs are reduced by 50%. Moreover, the facility can be built within a year. The cost of the disposables does increase the operating costs, but this cost increase is far outweighed by the labor savings associated with operating modules in a single open hall suite (including reduced gowning/de-gowning and eliminating costly steam in place, clean in place operations). Finally, the facility takes virtually no time to shift from shut-down to operation, to relocate, or to re-configure from one product to another. As such, it can provide the necessary flexibility for rapid response or surge capacity.

COMMERCIAL APPROACHES/STRATEGIES: MAINTAINING A "WARM BASE"

Unfortunately, while technologies can address the issues of flexibility, cost, and speed to manufacture, there is no technology that fully addresses the year or more it takes to build and validate a facility. As such, the issue of establishing and maintaining some form of "warm-based" capacity will have to be addressed with commercial strategies like those as detailed below.

Walk-In Rights

There are currently over 1.5 million liters of biomanufacturing capacity (mammalian and microbial combined) in the US (BioPharm Services Bio-Manufacturing Capacity Database. www.biopharmservices.com). So why can't the government simply appropriate this capacity in the case of an emergency? The benefits of this approach are clear: (1) The capacity exists; (2) The resources to operate the facilities are present; and (3) The capacity is widely distributed.

On the surface, this seems like a sensible approach, but the facilities are not flexible and probably cannot be reconfigured to manufacture a novel countermeasure. The challenges of even minor retrofits and technology transfer render the possibility of a 12-week response very low. In addition, the logistics/legal/political issues of working out walk-in rights on the spot would be too cumbersome and there would not be enough time in the case of a bio-event. For a walk-in rights scenario to work, the contractual issues would have had to have been worked out in advance.

Government Owned, Government Operated (GOGO)

One way to ensure the capacity for biological product, and to avoid the obstacles of "walk-in" is for the government to build and own the production facilities (i.e., GOGO). Unfortunately, it is not economically feasible to build and maintain the variety of facilities that would be required to meet all of the potential demand. It is possible that the facility (when not responding to a bio-threat) could be used to manufacture stockpiled products, but the large-scale surge capacity required for emergency response would be prohibitively expensive and idle much of the time. The final and possibly most compelling argument against large-scale GOGO capacity is the potential inability of the government to efficiently manage and operate the facility. In the United States, the government has avoided the scenario where it must provide the management or the capability to cost or time-effectively manage very large-scale biologics manufacturing for even the stockpiled products.

Government Owned, Contractor Operated (GOCO)

If the main shortcoming of a GOGO is the ability (or willingness) of the government to run such a facility, then one possible answer would be for the government to buy/build the facilities and turn them over to a commercial entity for their operation. In addition to the presumed increases in operational efficiency, this approach would open up many more possibilities for facility utilization when there is no national emergency. GOCOs could be operated as commercial contract manufacturers or to make a company's own marketed therapeutics. The issues of control and the logistics of walk-in rights would need to be resolved in advance, and would have to address issues like the consequences of a decision by the government to change management.

Unfortunately, the GOCO concept shares the shortcoming with the GOGO that it is simply not economically viable with respect to the scale and flexibility necessary to provide a rapid response for a wide variety of possible countermeasures. Nevertheless, this approach can provide effective coverage of specific countermeasures against significant threats known in advance (i.e. DHHS and Novartis Vaccines and Diagnostics, Inc. for pandemic influenza) or for a flexible rapid response core capacity to cover limited populations (first responders or military) for high-yield/low-dose countermeasures.

COMBINING TECHNOLOGIES AND COMMERCIAL STRATEGIES

While none of the technologies or strategies above independently solves the problems inherent in establishing a rapid bio-response capability, a combination of approaches could. One possible strategy is described below and combines high-throughput process development, automated data management, highly efficient expression systems, and single-use, modular facilities in a GOCO base with a walk-in right surge capacity. This system could handle rapid response as described below.

Stage I: Process Development

The first step is to build a highly automated, high-throughput process development lab. This could be a GOCO or commercial facility contracted to the government and would be capable of taking novel countermeasures and developing a manufacturing process within weeks. The lab would be equipped to rapidly screen the latest, highest producing expression systems and purification processes. Additionally, the lab would identify process platforms in advance that work across multiple countermeasures, minimizing the exploratory element of traditional process development.

When not addressing emergencies, the facility could be leveraged to develop processes for the many countermeasures currently in development. If these do not fully utilize the capacity, it could be made available for commercial, contract development work. The facility would utilize an automated data management architecture that will allow for rapid, automated tech transfer into a standard, flexible facility platform. Possible processes for such a facility and transition into a flexible manufacturing base are shown in Figure 3.

Stage II: Initial Baseline Manufacturing

Once a process is defined, the next step is to manufacture product. By setting up a relatively small ($4 \times 2{,}000$ liter) bio-manufacturing facility, the government can provide capacity that will answer many of the country's rapid response needs. Leveraging single-use technologies and a flexible/modular architecture, the facility would be configurable in days to manufacture virtually any biologic countermeasure. This facility could provide capacity for products aimed at protecting the military or first responders and further coverage for products with either lower dosing requirements or higher manufacturing yields. Finally, when not addressing emergencies, the capacity could be used to manufacture stockpile, countermeasures for clinical trials, or commercial therapeutics as a contract manufacturer. This allows for the cost of the facility to be subsidized through additional activity while maintaining a warm base of operations. Figure 4 shows an existing modular facility.

Stage III: Surge Capacity for the United States

The great challenge with rapid response is the protection of 300M or more people. To accomplish this, there must be a flexible, installed base capacity that is kept "warm" through the manufacture of traditional commercial biologics. The continued operation of this capacity is particularly important as the limiting factor to surge capacity is as much the people as the capital equipment [Langer, 2007].

As modular flexible facility platforms mature, the benefits they provide are becoming more attractive to traditional biopharmaceutical companies. Several of the larger companies are already looking into flexible manufacturing, particularly for their clinical capacity where rapid changeover to a wide variety of different products is most valuable [Menkel, 2006].

There is a projected growth in demand for bio-manufacturing capacity over the next five to ten years with 51% of respondents in a recent survey projecting that they will be capacity constrained by 2011 [Langer, 2007]. If even some of the additional capacity uses a "standard" flexible facility platform, then the ability to scale-up for novel pathogens is facilitated dramatically. With the development of an appropriate data/knowledge management system, technology transfer could be as simple as transferring cell lines and data into the distributed facilities once the process has been demonstrated in the initial baseline manufacturing facility described in Stage ll.

If the government can incentivize industry to build and utilize such capacity for existing commercial purposes, then the only challenge in a true emergency becomes exercising of walk-in rights, the logistics of which can be organized in advance. According to Dr. Feldman, "A model for pre-negotiated walk-in rights already exists where the government has worked with the airlines to pre-arrange for access to their assets in the case of an emergency" (Telephone interview with

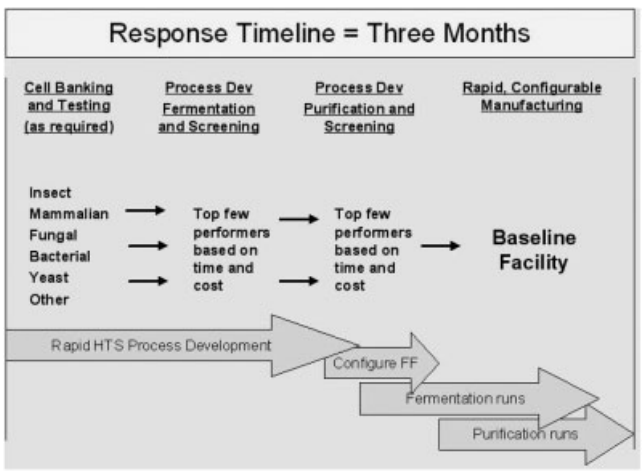

Fig. 3. Using high-throughput screening, novel expression systems, and single-use flexible facilities, the timeline could be reduced from years to months. (P. Latham, 2007)

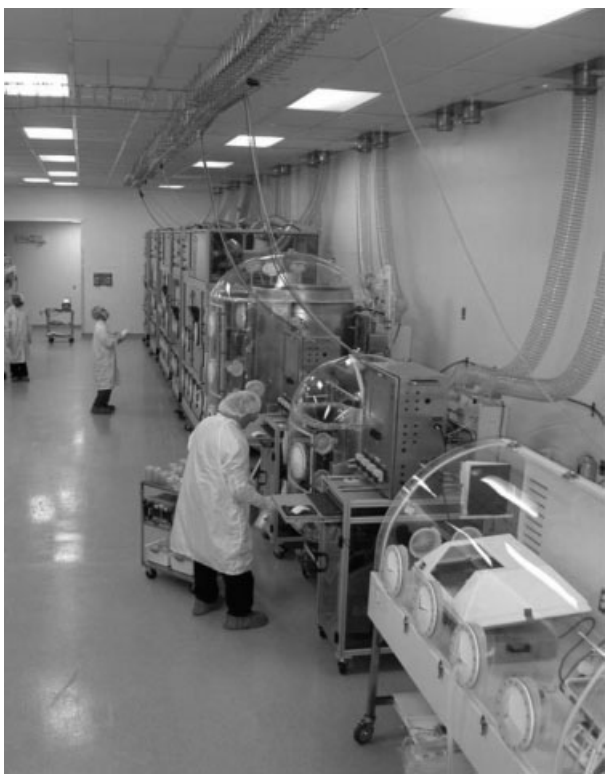

Fig. 4. One line of a multi-line facility that could provide the baseline rapid response. Photo courtesy of Xcellerex, Inc., Marlborough, MA.

Dr. Lee, Feldman, February 6, 2008). Thus, there is a clear precedent for this approach.

What would entice biotech companies to allow such walk-in rights? While no one knows for sure, there are many benefits to the flexible facility concept for commercial bio-pharmaceutical companies and contract manufacturers. The exercise of walk-in rights would only occur in a true emergency (the baseline facility would be the first line of defense). At this point, the greatest challenge to convincing biopharmaceutical companies or contract manufacturers to implement relatively new technologies is in the perceived risk to their (or their customer's) supply chain. Building of the baseline capacity, and leveraging it to manufacture approved stockpiled product, would go a long way towards removing these concerns; it would also demonstrate the benefits.

World-Wide Protection

One of the additional benefits to a distributed, flexible response capacity is that it is consistent with a world-wide network of protection. If, for example, a small country were to build their own flexible facility that mirrors the baseline capacity, then their ability to manufacture their own countermeasures is limited only by another country's willingness to share data files and a few vials of cells. This removes the manufacturing and logistics-chain bottlenecks/risk in the event of a global emergency and allows countries to work together without anyone having to worry about being left without a countermeasure.

CONCLUSIONS

Historically, the ability to protect our first responders, our military, and our population against the threats of novel pandemics, infectious disease, and bioterrorism has been limited. Without a viable solution for rapid response, the government has relied heavily on stockpiling as a means of protecting against projected threats before they become emergencies. Unfortunately, this has been extremely expensive and has left us vulnerable to new or slightly evolved/revised threats.

Advances in process development and manufacturing technology now provide a means for the building of a rapid response system not only in the United States, but world-wide. Leveraging and further developing high-throughput process development, automated data management and technology transfer, high-efficiency expression technologies, and single-use, modular flexible facilities, the government can now enable a cost-effective rapid response platform. By building an initial baseline capacity, then facilitating a broader capacity at commercial sites, we can envision a rapidly configurable, global network of capacity able to meet the surge requirements for virtually any biologic countermeasure.

This effort will require cooperation across government agencies ranging from the FDA to the Department of Defense (DoD) and the Department of Health and Human Services (DHHS), commercial biopharmaceutical companies, and even other countries. Given this cooperation, focus, and resources, it is entirely possible that a network of rapid response could be in place within two years and at a cost to the government of less than stockpiling 2.7M doses of influenza vaccine. There is no single "silver bullet" solution. However, by combining the latest process development and manufacturing technologies with a creative strategic approach, the world no longer needs to rely solely on stockpiling for emergency biologic response.

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