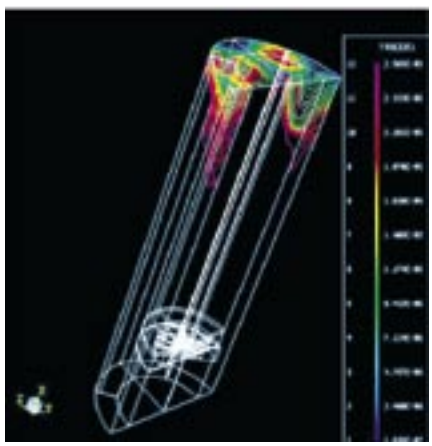
Manufacturing Process Development for High-Volume, Low-Cost Vaccines

Donald F. Gerson and Bhawani Mukherjee

Vaccine development follows two major parallel paths. One path is from discovery research to clinical evaluation and proof of efficacy. The other is from experimental methods making small test quantities of a putative protective antigen to process development for manufacturing a useful product. The second path involves manufacturing process optimization, chemical engineering, and application of pharmaceutics, packaging development, and many other practical activities. Both paths — and others — are required to convert a putative antigen into a vaccine for worldwide use.

Vaccine development undergoes two major transitions: the transition from research to development shortly after a putative antigen is found, and the transition from development to manufacturing once there is a fairly high expectation of efficacy. In development, and through the transition to manufacturing, many disparate objectives must be met and many disciplines must converge. To successfully and simultaneously develop, specify, and design manufacturing processes and equipment, to finalize process-engineering parameters in preparation for scale-up, to ensure product bioequivalence at all scales of manufacturing, to refine QC methods, and to solve unexpected problems requires the concerted effort of a highly skilled process development and industrialization team (1).

Low-cost manufacturing for the developing world requires balancing cost and need. Even though the need is urgent, the ability to pay for vaccines is low in locations that are often regions where other health risks are high. So there is still no reason to encourage or allow ineffective, inconsistent, inefficient, or low-quality manufacturing. The criteria for good manufacturing practices, product quality, and regulatory compliance can no longer differ around the world. Product and manufacturing standards required for the developed world must also be used for the developing world. Vaccine and pharmaceutical standards are converging worldwide, and long-term planning for vaccines for tuberculosis (TB), malaria, and human immunodeficiency virus (HIV) must take this into account.



View of a computational fluid dynamics model of mixing in a bioreactor DONALD F. GERSON (AXENIC, INC.)

Given the constraints, the best approach to maximizing success and reducing the cost of new vaccines for the developing world is to apply additional time, resources, and skill into perfecting highly efficient, reproducible manufacturing processes that minimize unit costs in vaccine manufacturing. The three major approaches to cost minimization are to manufacture at the largest practical scale; to use a well-understood, robust, and highly reproducible process; and to use the best possible facilities, equipment, and automation to minimize consumption of raw materials and energy, personnel requirements, and the consequences of uncontrolled effects on the product or its testing. Emphasis on process development is a major success factor in being first to market with new biopharmaceuticals; inadequate process development is

PRODUCT FOCUS: VACCINES

PROCESS FOCUS: SCALE-UP TO HIGH-VOLUME MANUFACTURING

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the most frequent cause of late-stage product development failure (2).

Any effective vaccine for TB, malaria, or acquired immune deficiency syndrome (AIDS) will be brought into widespread use as quickly as possible, putting pressure on process development. Improved regulatory environments allowing for controlled continuous improvement after licensure — such as that promised by the US FDA's process analytical technology approach (PAT, 3) — will help balance the urgent need for vaccine use with the need for cost improvements achieved through incremental process improvements.

From Method to Manufacturing

Process development begins with a satisfactory laboratory process for producing test quantities of vaccine. Once preclinical testing and phase 1 or 2 clinical trials have proven that a vaccine candidate is potentially efficacious, process development starts in earnest.

Figure 1 diagrams the progression from laboratory method to large-scale manufacturing on both product and process development tracks, indicating the appropriate facilities in which to perform the work at each stage. Once a protective antigen is found, increasingly detailed, systematic, and repetitive approaches slowly transform the original laboratory-scale vaccine production method into a practical, highly reproducible, and robust large-scale manufacturing process to make the new vaccine available to the world.

The incremental steps on the manufacturing pathway are as follows. The discovery laboratory develops a lab-scale process for the vaccine that can make quantities suitable for proof-of-concept and laboratory testing. That process is transferred to a GLP small-scale process development laboratory for production of phase I clinical materials. A small-scale process is developed from the lab-scale process and transferred to a cGMP production facility for the intermediate-scale production of phase 2 and phase 3 clinical materials. Finally, that process is transferred to a GLP large-scale process development laboratory for development of procedures and engineering parameters required for designing and defining the large-scale process to be used for ultimate manufacturing in a regional manufacturing facility.

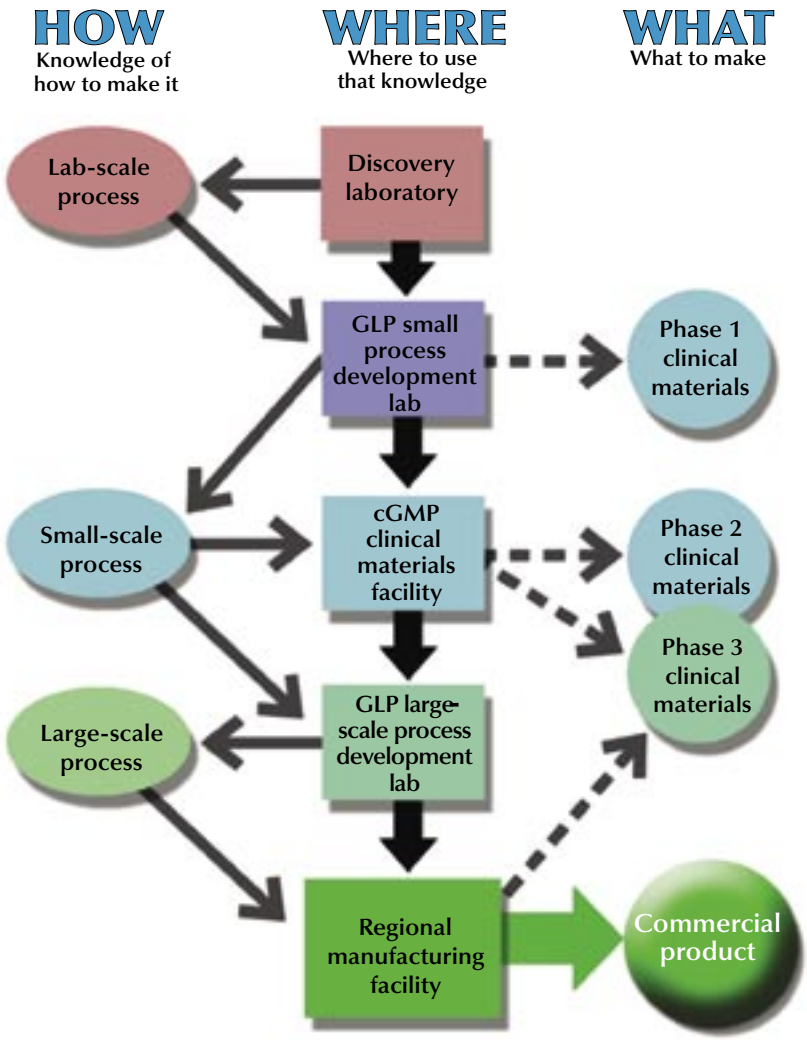


Figure 1: The scale-up of process, facility and quantity of vaccine required during product and process development

Two problems must be overcome during those transitions: One problem is to meet regulatory requirements at each stage; the other is to redesign the process so that at each desired scale it makes the same product as was made originally in the laboratory.

A host of new activities arise in vaccine development — each requiring detailed study, specification, and resolution. Proper emphasis on those three steps enables a candidate vaccine to be developed, tested, and produced on a large scale for successful distribution following licensure. At each step of process development, economic considerations (of less importance during product discovery) must carefully shape the decision-making process so that the manufacturing can produce effective vaccine economically at large scale.

Most important, inadequate attention to process development details can result in failure or abandonment of a good product through unforeseen manufacturing difficulties or unnecessarily high cost. In advance of significant process development activities, assumptions or estimates of manufacturing costs are usually wrong. If preliminary production cost estimates are too optimistic,

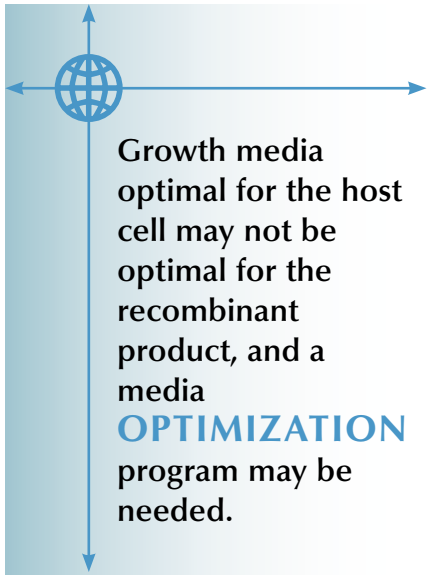
a perfectly good product may be abandoned in the face of actual high production costs; if estimates are too pessimistic, a good product may be abandoned on the basis of incorrectly assumed high production costs. In both cases, costs can almost always be brought in line with expectations if a process is subjected to an appropriate level and duration of process development by those skilled in this aspect of new vaccine development.

To achieve such an outcome, a succession of clinical materials production facilities must be available that are properly designed for the scale of operation and are operated in accordance with appropriate cGMPs. To obtain the desired product at each successive scale of operation, process development research must ensure bioequivalency. Licensure depends on successful proof of efficacy and documented proof of the optimization and reproducibility of the full-scale manufacturing process in the penultimate manufacturing facility.

Biological Process Optimization

Strain development and medium optimization are the best means of improving yield and minimizing cost. As has been seen in hepatitis B vaccine production, migration of the effective genetic sequence to high-productivity hosts can significantly increase volumetric yields during primary production, greatly reducing cost and increasing availability.

One of the most difficult aspects of developing vaccines with recombinant technology is ensuring the stability of constructs and strains. An iterative approach in strain development that checks the growth and productivity of numerous recombinants will select strains that maintain high viability while effectively expressing the recombinant antigen. The location of the insertion element, whether in the genome or on a plasmid, affects expression and growth. Promoter selection may seem logical from a genetic viewpoint, but host-cell physiology can moderate the effect of the promoter on expression, glycosylation, or growth rate. Growth media optimal for the host cell may not be optimal for the recombinant product, and a media optimization program may be needed. In addition, genetic stability and recombinant strain purity are often confounded, requiring multiple limiting dilution experiments to determine whether nonproducers are generated by genetic deletion events or by higher division rates of nonrecombinant cells.



Scale-Up Technology

The fundamental technical problem that must be overcome during process development stems from a very basic but poorly understood law of physics, which says that change of scale is not symmetrical. This is best illustrated by a quote from the Nobel Prize winning physicist Richard Feynman, who describes this problem as follows:

> It is not true that if you build an apparatus, and then build another one, with every part made exactly the same, of the same kind of stuff, but twice as big, that it will work in exactly the same way. (**4**)

The greatest and most common fallacy in the vaccine and biotechnology industries is the notion that large equipment made to look just like successful small equipment will make the same product. That approach leads to failures of processes, losses of products, and interruptions of careers. The only approach that can consistently result in successful scale-up is to determine and measure critical scale–independent process parameters and to design and operate equipment appropriately to deliver those process parameters at a larger scale.

Fluid Mixing: In practice, the main process parameters that do not scale well are fluid mixing, oxygen transfer, precipitations, and filtrations. Of these, fluid mixing is the least scalable and most commonly used unit operation in vaccine and biotechnology process design. Although the two-dimensional view of a small and large bioreactor or process vessel may look similar, and although the shape and overall design of a small impeller may look like those of a large one, their actions in producing fluid flow in three dimensions are remarkably different.

The complex equations of fluid flow require specially designed and validated numerical integration software. Some years ago, it was hard to use computational fluid dynamics (CFD) programs to solve practical mixing problems, but with today's technology and with specialists in the field readily available, it is easy and inexpensive to use CFD calculations as an integral part of any scale-up program (**5**).

CFD accurately predicts and calculates many mixing parameters. Calculations can use the dimensions of large equipment to find conditions that simulate the actual measured mixing times or oxygen transfer rates of small pilot equipment. CFD results can then be used to assist in the design and specification of large equipment and to calculate large-scale operating conditions that will incorporate correct values for critical operating parameters. Another tool for scale-up is a new instrument that can measure mixing as an operational parameter closely related to the turbulent kinetic energy as calculated by CFD (**6**).

Using CFD to calculate and analyze ways to achieve equivalent

mixing and shear at large scale will resolve many problems currently encountered in oxygen transfer rates and mixing for fermentation technology, viscous fluid blending, precipitations, and blend uniformity. Process development of low-cost vaccines for the developing world should make use of CFD to increase success probability, increase operational efficiency, and reduce costs.

Minimizing Operating Costs

The technological component of process development brings many disciplines together to solve practical issues that are quite different from those encountered in discovery. All aspects of operating costs should be investigated and analyzed during process development for new vaccine development. Energy can make up a significant part of total manufacturing costs and are expected to increase in the future. Operating pure water (water for injection, WFI), clean steam, oil-free process air, and HVAC systems consumes very large amounts of power, so those utility costs should be minimized. Estimating lifetime equipment costs requires analysis of preventative maintenance programs, waste disposal, and maintaining spare-parts inventories. The initial capital cost of a vaccine manufacturing plant for the developing world may be underwritten by international or philanthropic organizations, but ongoing operational costs are typically more difficult to recover. Spending more initially for more reliable units may balance the overall cost of equipment selection and maintenance.

Energy consumption per unit output of supplied utility is an important parameter in process and unit selection. WFI generation comprises two major steps, each with multiple unit operations. The first step is treatment of available water, from a city system or a well, to make purified water meeting either US or EU specifications. Multiple options for water treatment include reverse osmosis, ion exchange, electro-osmosis, and carbon filtration. The contaminant load of local source water must be evaluated, and unit operations must balance capital investment against operating costs while maintaining robust effectiveness in meeting regulatory requirements. Converting purified water into WFI is best achieved by distillation because that ensures a sterilization step. Multiple distillation strategies all produce water of the same final quality but at different energy consumption and water reject rates. Careful consideration of all options to maximize overall effectiveness and efficiency over an extended plant lifetime is critical to long-term success in producing vaccines for the developing world.

Implicit in these calculations is a careful evaluation of process utility consumption. One example is balancing the use of purified water for washing and WFI only for final rinsing against the capital and operational cost of maintaining the two systems. Batch size selection affects the total number of sterilization runs and thus total energy consumption required to make a certain amount of product. Reuse of smaller vessels and equipment items requiring a wash and sterilization cycle needs to be carefully compared with the purchase of one-time-use, presterilized plasticware. In each of those cases, the availability and cost of labor, utilities, and water must be projected over the 20-year lifetime of the production facility to model the consequences of different options and provide a rational basis for decision-making (7).

Overcoming Limitations

Current vaccine development programs for TB, malaria, and HIV are strongly and adversely affected by limitations of process development and cGMP manufacturing capabilities. Process development activities are limited at academic centers and in small companies that design the majority of vaccine candidates for the developing world. Contract manufacturers of clinical materials generally do not carry out any significant process development: They execute laboratory processes with minimal changes under cGMP conditions to make materials for clinical trials, but they produce little process development information for scale-up to manufacturing and minimizing costs. Inadequate process development can delay introducing candidate vaccines to clinical testing. An effective vaccine discovered without parallel process development can easily be lost in the subsequent attempt to transfer it to manufacturing if additional and costly clinical trials are needed to bridge between early experimental materials and the final product.

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