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The roles of a process development group in biopharmaceutical process startup

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Abstract

The transfer of processes for biotherapeutic products into final manufacturing facilities was frequently problematic during the 1980's and early 1990's, resulting in costly delays to licensure (Pisano 1997). While plant startups for this class of products can become chaotic affairs, this is not an inherent or intrinsic feature. Major classes of process startup problems have been identified and mechanisms have been developed to reduce their likelihood of occurrence. These classes of process startup problems and resolution mechanisms are the major topic of this article. With proper planning and sufficient staffing, the probably of a smooth process startup for a biopharmaceutical product can be very high – i.e., successful process performance will often be achieved within the first two full-scale process lots in the plant. The primary focus of this article is the role of the Process Development Group in helping to assure this high probability of success.

Introduction

During the 1980's and early 1990's, plant startup problems were very common for biopharmaceuticals (i.e., the products of cells). It became an expectation that plant startup problems and delays for these types of products were inevitable, and that time must be allotted to use the plant as the venue for the final stage of process development (Pisano, 1997).

Delays in plant startups for biotherapeutic products are costly in several ways. Plant startups typically occur on the critical path to licensure, and delays in plant startup translate into day-per-day delays in licensure. The current cost to develop a new pharmaceutical has been estimated at on the order of $400,000,000 (Pisano, 1997). Thus, most products require projected annual sales of at least $100,000,000 to justify this expense. Plant startup delays can rapidly accumulate many millions of dollars of lost future revenue, and often lead to lost competitive advantage.

Poor plant startups also have lasting effects on the morale and relationships within the process development and manufacturing groups of a company. Individual careers are affected.

Finally, there is also a moral dimension to the problem of plant startup delays for biotherapeutics. Often, we are developing products that have the potential to save lives or improve the lives of thousands or millions of people.

Given these financial, career and moral dimensions, there is tremendous incentive to examine each of the factors that could contribute to delays in plant startup, and determine what can be done to improve the probability of rapid plant startup for biotherapeutics. The concept of using a plant as a venue for a final stage of process development is usually to be avoided if at all possible. The premise of this article is that plant startup of biotherapeutic products is not inherently chaotic. A detailed, retrospective examination of plant startup problems will usually conclude that the causes of a poor plant startup could have been anticipated with more careful planning and experimentation. Clearly, many of the problems with biopharmaceutical plant startups in the 1980's and 1990's arose from a

lack of appreciation of the complexity of plant startup. And, many of these startups undoubtedly suffered from the lack of a playbook for plant startup preparations, and from lack of appreciation by management of the number of process development and manufacturing personnel who must be committed to a process startup to assure rapid success.

A number of rules, guidelines, and mechanisms have begun to emerge over the past decade to facilitate rapid plant startups for biotherapeutics. And, there has been recognition by upper management that the time and resources spent to implement these plans can substantially increase the probability that the process startup will be successful within the first two lots.

The playbook for a successful plant startup has at least three key parts. One part describes the sequence of events in the development of a scaleable process that will match the marketing and clinical needs for the proposed product.

A second part is the overall vision of how the Manufacturing, Process Development, Engineering, Facilities, Quality Control, Quality Assurance, and Regulatory Groups will work together to assure timely success. This vision includes a detailed statement of the sequence and timing for information exchange and management decisions leading to a successful plant design and startup, process startup and product/plant licensure. This part of the playbook also describes the management structure (e.g., a Technology Transfer Team) that will monitor and assure the success of this overall process. This topic has been recently discussed by Gerson and colleagues (Gerson et al., 1998).

A third part of the playbook provides more specific guidance of how each group in the startup can be optimally managed at different stages in the plant startup process.

This article can be viewed as just one piece of Part 3. That is, this article focusses on the management of a Process Development Group during the months just before and during the startup of the process in the plant. This article presumes as a starting point that a process has been previously developed that should meet the requirements of the Marketing and Clinical Groups, and this information has been transferred to the Manufacturing and Engineering Groups to assure plant readiness. The specific goal of this article is to describe how a Process Development Group can best be managed to assure rapid, successful process startup in the plant.

The Manufacturing Group obviously plays many important roles in the plant startup process. It is not the intention of this article to discuss these roles in a comprehensive manner. Rather, roles of the Manufacturing Group will only be discussed as necessary to distinguish and clarify the different responsibilities and accountability of the Process Development and Manufacturing Groups.

In recognition of these broad responsibilities of the Manufacturing Group, the term ‘plant startup’ will be used from this point forward to reference the comprehensive set of events that must occur in parallel for a successful startup. The term ‘process startup’ will define those specific activities related to the successful operation of the process in the plant equipment – that is, successful process startup represents one facet of a successful plant startup.

It was certainly true in the 1980’s that many significant holes existed in our basic understanding of process scale-up for production of biotherapeutics. As examples: Could genetically-engineered mammalian cells withstand the stresses of agitation and aeration in very large, stirred tank bioreactors? (Birch et al., 1985) How would protein post-translational modifications be affected by bioprocess variables during scale-up (Goochee and Monica 1990).

However, by the mid-1990’s, these and many other problems had been largely understood and resolved, and bacteria, yeast and mammalian cells were routinely cultured at production scales from 1000 to 10,000 L (Hu and Aunins 1997). During the 1990’s, relatively few cases emerged of process ‘scale up problems’ that could not have been anticipated based on laboratory scale experiments. One notable example was the observation and investigation of oscillatory process behavior in large-scale E. coli fermentations by Jim Swartz and coworkers at Genentech (Swartz, 1994; Swartz, 1996; Swartz, 1997; Andersen et al., 2001).

Currently, most industrial and academic bioprocess development scientists and engineers subscribe to the notion that it will usually be possible to develop a small-scale process model that will predict process performance at large-scale. Process surprises are still possible at large scale, but these process scale-up surprises are becoming much less frequent.

Having a representative laboratory model for a process plays an important role in preparations of the Process Development Group for successful process startup, but it is not a guarantee of startup success. Differences between manufacturing and process development protocols can and do lead to process failures. Incompatibility of the process with the produc-

tion equipment can doom a large-scale manufacturing process. These and other classes of typical process startup problems are summarized in Table 1. Dozens of unanticipated problems may emerge in the plant, and the experience of process startup can become chaotic. This article will focus on the rules, guidelines and mechanisms to reduce the likelihood of these problems.

Different organization models for process startup

A critical early decision affecting process startup is the choice of the mode by which process information will be transferred from the Process Development Group to the Manufacturing Group. Three general models include:

- Technology Transfer by Phone or Mail
- Technology Transfer through an Intermediary
- Direct Transfer from the Process Development Group into the Plant.

Some companies have attempted Technology Transfer by Phone or Mail, usually with very poor results. In this scenario, the Process Development Group prepares a detailed written protocol describing the process – i.e., based on their small-scale experience. This is forwarded to the Manufacturing Group, who translates this protocol into manufacturing documents. Problems begin to arise almost immediately as the Manufacturing Group begins to 'adjust' the process and in-process assays to match the equipment and procedures at the plant. It is almost inevitable that serious process problems will arise during process startup. At this point, the Process Development Group will disavow the process ('The Manufacturing Group made so many changes that we don't recognize this process'), and the Manufacturing Group will throw up their hands and say, 'But the Process Development Group gave us a process that made no sense in our plant setting'. At a moment when both groups should be working together, they will instead be pointing fingers at each other.

Technology Transfer through an Intermediary involves declaration of a group of process transfer experts within a company. The Process Development Group transfers the process to a Technology Transfer Group, who subsequently translates the process development information into a workable manufacturing plan. This intermediary group may have laboratories in which they can practice and learn the process. This approach can be successful if the right chemistry and communication exists between the Technology Transfer Group, the Process Development Group and the Manufacturing Group. This approach may be desirable in the scale-up and transfer of traditional pharmaceutical products, where an intermediary chemical engineering group may provide much-needed expertise in 'traditional' chemical process scale-up problems – e.g., problems related to heat transfer and mixing issues in large-scale operation.

However, for biopharmaceutical products the sources of plant startup problems are only infrequently related to such traditional scale-up problems, and there is little merit to the use of an intermediary process transfer group under these circumstances. In fact, it is inherently inefficient and undesirable to transfer such a process twice, as much process information can be lost along the way. Process transfer problems frequently occur at organizational interfaces. The use of an intermediary Technology Transfer Group in process transfer creates an additional interface.

The most efficient mode of process transfer for biopharmaceutical products is a direct transfer of the process from the Process Development Group into the Plant. The organization of such a transfer is described in the next section.

Establishing responsibilities and accountability for the success of process startup

Roughly nine months to a year prior to plant startup, it is important to identify the process development and manufacturing leaders of the startup, and establish a clear written agreement of their individual responsibilities before and during the startup. This agreement should then be approved in writing by their respective managements.

There can be some tension surrounding the completion and approval of this agreement – e.g., if there is disagreement between organizations concerning the primary responsibility for certain activities. However, following completion of this agreement, it is generally the case that both the Process Development and Manufacturing Groups will become much more comfortable about their respective roles in the startup, and will begin to work in parallel and together to assure process and plant readiness for startup. In contrast, failure to complete this written and approved agreement will cause inter-division and/or inter-departmental differences of opinion to smolder, resulting in a steady diversion of energy away from the hundreds of fine

Table 1. Nine classes of process startup problems for biopharmaceuticals

Problem	Problem avoidance mechanism
1. Insufficient time was spent developing a laboratory-scale model of the large scale process, and challenging that laboratory process to confirm the robust range for process operation.	The Process Development Group develops a laboratory-scale model of the final manufacturing process and performs experiments to challenge the process for four to eight months prior to process startup in the plant.
2. The process delivered to the plant is incompatible with the process equipment at the plant.	The Process Development Group takes responsibility for understanding the plant equipment, and takes responsibility for assuring that there will be no process mismatch.
3. Differences in the process protocols between the manufacturing plant and the process development lab lead to unexpected, adverse events.	The Process Development Group takes responsibility for understanding the manufacturing environment, and for modifying the laboratory-scale model to match this environment.
4. Slight differences in the analytical protocols between the manufacturing plant and the process development lab lead to incorrect process decisions or incorrect interpretation of process performance.	The Process Development Group takes responsibility for assuring that the analytical procedures used to characterize the small-scale laboratory process are identical to those that will be employed in the plant. In-process reference samples are prepared and sample storage conditions are evaluated prior to process startup.
5. Previously installed plant equipment does not operate as intended during process startup.	The Manufacturing Group reviews the maintenance records of each piece of process equipment prior to process startup, and performs prudent preventative maintenance as necessary.
6. Newly installed plant equipment does not operate as designed during process startup.	The Manufacturing Group assures that the Installation and Operational Qualification of Plant Equipment (IQOQ) is performed under realistic process conditions.
7. The process is not operated as intended in the plant due to a mistake in a manufacturing document.	The Process Development Group takes responsibility for assuring that the final manufacturing documents accurately reflect the desired manufacturing process.
8. The process is not operated as intended in the plant due to incomplete, misleading, or ambiguous instructions in a manufacturing document.	The Process Development and Manufacturing Groups perform a 'Walk-through' of the process in the plant prior to startup to check the clarity of manufacturing documents. The Process Development Group monitors every key process operation in the plant during startup, assuring that the process is operated as intended.
9. The process is not operated as intended in the plant due to an operator error.	The Manufacturing Group provides adequate operator training, with Process Development Group assistance as required. The Process Development Group monitors every key process operation in the plant during startup, catching errors before they impact the process.

details that are necessary for rapid process success in the plant.

The written agreement should begin with a clear statement that the Manufacturing Group is the customer in this process startup. The Manufacturing Group will have to live with this process for years. The process must be compatible with the equipment, procedures, and operating environment that exist at the plant. The Process Development Group must actively listen to the needs of the Manufacturing Group, and adjust the process as necessary to be compatible with Manufacturing Group needs. *The mantra of 'Manufacturing is the Customer' must be repeated almost daily by Process Development Team members in the period preceding process startup.*

A second clear statement in the agreement is that all of the groups will benefit from a successful process startup. The bright light associated with a successful process startup illuminates the careers of everyone who is involved. Everyone must understand that team harmony is critical.

It is very important to divide the startup responsibilities within the Startup Team and establish the clear written accountability of one person or group for each distinct activity in the startup. A fairly detailed example of this division of responsibility is presented in Table 2. However, the bottom line is as follows.

The Manufacturing Group assumes responsibility that the manufacturing systems at the plant will be ready for process startup – e.g., that equipment will operate as designed, and that approved documents, released raw materials, and trained operators will be available for process startup.

The Process Development Group assumes complete responsibility that the process will succeed in the plant, provided that the process is implemented according to the manufacturing documents and the plant equipment operates as designed. *'Process Development is Responsible for the Process' is the second key mantra in a successful startup plan.*

This division of accountability can be clarified as follows to the Manufacturing and Process Development Groups. 'Let's imagine that the first startup lot has failed. If the equipment operated as designed and the manufacturing documents were followed, then the Manufacturing Group is off the hook. The accountability for this failure lies completely with the Process Development Group'.

Once the magnitude of this responsibility sinks in for the Process Development Group, they will realize the importance of immediately spending time at the plant to understand the environment of equipment, people and procedures in which the process must succeed. After they have understood the needs of the Manufacturing Group as Customer, the Process Development Group should update their written description of the final manufacturing process, and seek Manufacturing Group feedback to assure that details of process equipment operation and timing have been captured.

The responsibility for the process includes responsibility for delivery and robust operation of the in-process analytical procedures that will be employed to control or monitor process performance.

The importance of stressing this comprehensive process responsibility of the Process Development Group can not be underestimated. It is this responsibility that will assure that there will be no unexpected differences in the process or in-process analytical protocols between the process development experiments and the final manufacturing process, and that the particulars of production equipment and procedures have been considered.

The Process Development Group should review every piece of equipment in the plant and trace every process-related line with the Manufacturing Group to assure that no fine detail of process operation or timing is ignored (e.g., the performance of process feedback control loops, warm-up and cool-down characteristics of process tanks, etc.).

A classic example of process-equipment mismatch is the case where a fed-batch fermentation is being performed during process startup, and it is found to the horror of all that the initial liquid level in the fermenter doesn't rise up to the level of the lowest fermenter impeller. It is the complete responsibility of the Process Development Group to have identified this issue early in the technology transfer process, leading to either an adjustment of impeller location or a modification to the process.

The Process Development Group may require access to the plant for experiments to characterize the performance of process equipment – e.g., to determine whether heat transfer will be adequate for the process given the particulars of jacket design for a particular tank at the plant. The prior written agreement between Process Development and Manufacturing Management will help to assure that reasonable requests for plant access by Process Development will be honored. The process development group must in turn understand that their schedule is secondary to the schedule of plant personnel (the Customer), and these experiments may need to occur on evenings or

weekends. Alternatively, it is possible for the Process Development and Manufacturing Group to work out a plan for equipment characterization. The plan can then be implemented by the Manufacturing Group at their convenience, and the data provided to the Process Development Group.

The Process Development Group is responsible that the process will succeed in the plant equipment, *as designed*. If there is a flaw or omission in the equipment design, it is the responsibility of the Process Development Group to find it. As an example, a warm room may have been designed to meet the stated specification of steady-state temperature control of 37 ± 2 °C. However, that specification may not guarantee sufficient air circulation in the warm room to meet process needs for heat transfer. It is the responsibility of the Process Development Group to identify potential design problems that could lead to process problems. Then, they can work with the Manufacturing Group to assess the risk. This activity of the Process Development Group must be given high priority early in the preparations for process startup, since equipment modifications can require months of lead time to implement. In summary, the Process Development Group must review the design and operational history for all equipment that will be employed for the process and reach a high level of assurance that the process will be successful in this equipment.

The Process Development Group is also responsible for learning about the practical constraints placed on the process by labor environment at the plant. Process timing must be compatible with the typical plant operating schedule and procedures.

This comprehensive responsibility of the Process Development Group for the process reaches to the finest details of process startup. If a typographical error occurs in the typing of process details into a Manufacturing Document, it is the complete responsibility of the Process Development Group to find and correct this typo to assure that the process is operated in the desired manner.

Even without this process responsibility, the Manufacturing Group still faces a daunting challenge in preparing the plant for process startup – e.g., to assure appropriate documentation of equipment installation and qualification, operator training and so forth. There are literally hundreds/thousands of such details that must be addressed to fulfill all of the regulatory and process pre-requisites for successful startup and licensure. These many important challenges will not be further discussed in this manuscript. Likewise, this manuscript will not further discuss the parallel activities of analytical development groups in assuring that validated release assays have been developed to assure final product characterization.

Rather, the focus of the remainder of this manuscript will be on the activities of the Process Development Group in the period prior to the startup and during the startup. (Additional comments about team organization and accountability are provided in the endnotes[1,2,3,4]).

Developing a scale-down model for the final manufacturing process

It is essential for the Process Development Group to implement a laboratory-scale manufacturing process in the process development laboratory to mimic details of plant operation. It is most valuable if the Process Development Group has at least four to eight months of lead time prior to plant startup to develop this laboratory-scale process, and gather data about process performance. (The duration of this experimental period will be largely dictated by the complexity and duration of the process – e.g., processes based on bacterial culture can often be characterized in less time than processes based on mammalian cells). Management should understand that US and European Regulatory Authorities are requesting to see increasing amounts of historical laboratory data demonstrating process robustness. The laboratory data gathered during this period will form the core of the process validation documentation.

In developing the laboratory-scale process model, it is generally wise to adopt the attitude that no detail of plant operation should be assumed as insignificant. For example, operations in the plant often take 200 to 300% more time than laboratory operations, due to the additional requirements for environmental monitoring, documentation, union work rules, etc. One should not assume that such a difference in process step duration doesn't matter, one must prove experimentally that it doesn't matter.

An appropriate attitude concerning the development and implementation of the laboratory-scale process is as follows. There will be 20 to 30 features of the manufacturing process that each have a 1 to 5% probability of causing process failure in the plant (e.g., duration of a particular hold step or the warm-up rate of a particular process step). Among these many hypothetical process issues are the one or two features

Table 2. A Typical Distribution of Process Development and Manufacturing Accountability for Process Startup

The Process Development Group is responsible to:
• Assure that the process will match the equipment available at the plant
• Assure that the process will operate robustly during startup at large scale
• Provide process information to the Manufacturing Group in a timely manner to assure that process timelines can be achieved.
• Specify the grades of raw materials to be used in the process
• Assure that the Manufacturing documents will correctly define the process, and correctly define the in-process data to assure that the process is under control
• Train Manufacturing supervisors and Technical Support personnel in the operation of the process
• Assure that in-process assays are appropriate for use in the Manufacturing setting, that Manufacturing personnel are properly trained to operate these assays, and that they are operated properly during startup
• Monitor the process startup to assure that the process is being operated as intended
• Recommend and approve any process changes during the startup
The Manufacturing Group is responsible to:
• Monitor the schedule of all preparations for plant startup, including the deliverables of the Process Development Group
• Design, purchase, install and qualify new equipment for the process
• Assure that all installed process equipment works as designed
• Assure that raw materials are purchased, tested and released
• Organize and schedule all activities in the plant associated with startup
• Train operators in the operation of the process
• Implement the process as defined in the Manufacturing documents

that have the potential to cause serious process startup problems if they are not identified, understood, and managed. The goal of the Process Development Group is to explore as many of these hypothetical process problems as possible, to identify those few problems where process failure could actually occur within a reasonable range of process operation. If a process risk factor is identified, then further experimental efforts should address potential constraints on process operation or process modifications for risk reduction.

A partial list of process issues to be addressed experimentally during the period prior to startup are presented in Table 3.

For these laboratory-scale experiments to have maximum value, it is important that they employ the same grades of raw materials that will be employed in the plant. Furthermore, for these experiments to have maximum utility and relevance, they should use the *identical* analytical procedures that will be employed to control or monitor process performance in the plant. Methods of process sample storage in the laboratory should match those to be implemented in the plant. During this period, it is important to develop analytical reference standards for comparison of plant performance with laboratory performance – i.e., retain samples from key points in the small-scale laboratory process that can be compared against comparable samples from the large-scale process during plant startup.

It has been the author's experience that the number of potential startup problems that will be identified (and avoided) will be directed proportional to the number of process development staff that have been assigned to the project. If the Process Development Group is understaffed in these efforts, a significant number of risks will not be addressed. In fact, a significant number of process risks will not reach consciousness, and may come back to haunt the project during or after the startup period. Perhaps it is human nature for the Process Development Team to not consciously recognize more risks than they can reasonably hope to eliminate through experimentation prior to startup. Another manifestation of this phenomenon is that the list of potential process risks never seems to reach zero prior to process startup, in spite of the fact that risks are being continuously eliminated through experimentation. As startup approaches, it seems that one new risk is identified as each old risk is eliminated. Some guidance concerning appropriate Process Development staffing levels will be presented in the final section of this manuscript.

Table 3. A sampling of process issues that should be addressed in laboratory-scale experiments in the months preceding plant startup

• Identification and testing of key process control factors for each process step (e.g., effect of temperature and pH on cell growth and product formation, and effect of load on chromatography column performance)
• CO_2 accumulation or stripping in large-scale fermenters
• Duration of process steps, including worst case conditions
• Duration of hold periods, including worst case conditions
• Warm-up and cool-down rates in large-scale equipment
• Chromatography column resin packing and regeneration procedures
• Equipment cleaning procedures
• Process sample handling and storage procedures
• Impact of different lots of raw materials from the same and different vendors, including different lots of chromatography resin and process filters

Laboratory experiments just in advance of process startup

During the period just preceding process startup it is highly advisable to operate the laboratory-scale process using the exact lots of raw materials that will be employed in the first process startup lots in the plant. The most important reason for this experiment is to largely eliminate raw materials as a hypothetical cause of poor plant performance during the first process startup lots. That is, if there is a problem with the process during process startup, the first question that will be asked is, 'How did this first startup lot differ from previous process development lots?' If one or more lots of raw materials in the process startup differ from previous process development experience, then it will be human nature to focus first in this direction (although there may typically be just a one in ten chance that raw materials are actually the problem). In summary, it is highly advisable to eliminate the hypothesis concerning raw materials in advance.

In the last month before process startup, it is almost inevitable that ideas for process improvement will emerge from the Process Development and Manufacturing Groups. This phenomenon is literally guaranteed to occur, and probably relates to the rising anxiety level associated with the coming startup. *The third important mantra for successful process startups is, 'We Don't do Experiments in the Plant'*. That is, it is generally very unwise to make last minute changes to the process in conjunction with the first full-scale lots in the plant. If a process idea can not be extensively tested in the small-scale laboratory model, it should usually not be implemented in the plant.

Technology transfer documentation

Prior reference was made to a description of the process that should be prepared by the Process Development Group for the Manufacturing Group many months prior to plant startup. The primary purpose of this early process description is to define the process in sufficient detail to assure that plant equipment and facilities will be appropriate for the process, and be ready on schedule. This document should describe what process operations must occur and how they will occur in the plant – e.g., including specific references to the tanks and transfer lines that will be employed to introduce medium into a tank.

Approximately one month prior to plant startup, another version of the Technology Transfer Documentation should be provided to the Manufacturing Group that provides all of the information that is necessary to create the Manufacturing documents for the process. (See Table 4) This process definition includes both setpoints and ranges for controlled variables in the process.

As noted earlier, it is the complete responsibility of the Process Development Group to carefully audit each Manufacturing Document that defines process implementation in the plant, to find and correct all documentation errors that could impact process performance.

The final process walk-through

Approximately two weeks prior to the startup, the manufacturing process documents and SOP's will be largely complete. At this moment, it is highly advisable to have a 'walk-through' of the process attended

Table 4. Features of technology transfer documentation

• Provide a block flow diagram of the process
• Specify the setpoints and acceptable ranges for controlled variables in the process – e.g., the medium should be autoclaved
• Specify process hold times and typical step durations
• Describe how the process should be operated in the plant equipment in sufficient detail for preparation of manufacturing process documents
• Specify the grade and amounts of raw materials to be used to create process solutions, and the order in which they should be added to create solutions for the process – e.g., medium and buffers
• Provide the protocols for the necessary in-process assays and identify the frequency of data collection
• Specify how process samples will be taken, stored and archived.
• Specify the in-process controls that will be analyzed to assure appropriate assay performance and process scale-up performance
• Present example data – e.g., kinetics of cell growth and product formation, UV chromatographs, etc.
• Identify how columns will be poured, operated, cleaned, and regenerated
• Provide information concerning the solutions to be employed for equipment cleaning

by a small, select group of process development and manufacturing personnel. The purpose of this walk-through is to identify any last minute details that must be resolved, and to make sure that the Manufacturing process documents are clear and unambiguous in their description of how the process should be implemented. One effective means of conducting this walk-through is to ask a manufacturing supervisor (who is not yet very familiar with the manufacturing document or the process) to describe each process-related activity based on what he/she reads in the draft Manufacturing process document. This walk-through is best accomplished on the plant floor by literally walking from location to location within the plant, reviewing in detail the individual activities that will occur at each location – e.g., to review the specific manner in which a frozen vial of cells will be thawed and the specific pipette type that will be employed to inoculate the first shake flask in the process. This approach is very effective in identifying deficiencies in the documentation. Another means of conducting this rehearsal of the process and of the Manufacturing documents is to simulate the process operations using water as the process fluid (a 'water run').

It is important for the Process Development Group to do more listening than talking during the final process walk-through. The purpose of this exercise is not to educate Manufacturing personnel about process details. Rather, the primary purpose is to discern how the process will be implemented in the plant given the description in the current Manufacturing documents. There may be a number of fine details of the process protocol that have become second nature to the Process Development Group, but which are not captured in the Manufacturing documents. These details must be identified for incorporation into the documents. In the same spirit, if a water run is to be performed, the hands-on activity should be performed by the Manufacturing Team, with Process Development Team members present as observers.

Very detailed plant walk-throughs are fairly intense, as each process manipulation and equipment manipulation is carefully scrutinized for the potential to fail. It is best to perform the walk-through in two-hour segments over a period of days. If this is not done, there will be a tendency to place much emphasis on the early process steps and skim rapidly through the final process steps of a complex manufacturing process, resulting in an increased likelihood of a mishap in the later process steps. In general, the final operations of the final process step will be particularly vulnerable to failure in the process startup. If two or more Process Development subgroups are responsible for subsets of process steps, the final operations for each subset of steps will be particularly vulnerable.

Prepare for failure during manufacturing startup

During the last two months before plant startup, it is important to develop a written game plan concerning the possibility of process failure during process startup. This game plan should outline in advance who will take primary responsibility for each type of failure. Following the delineation of responsibilities outlined in the sections above, the Process Development Group should immediately step forward to lead the investigation of process failures, while the

Manufacturing Group should step forward to take the lead for investigation of equipment failures, operator errors, etc.

The game plan should also outline a comprehensive approach to the investigation. One effective three-step approach to problem resolution is to:

1. organize in writing all known facts related to the problem
2. state in writing all of the hypotheses that are consistent with most or all of the facts
3. systematically perform experiments to eliminate hypotheses – until the true cause emerges

Without such a plan, there will be a tendency for the group to focus immediately on a single hypothesis, to the exclusion of all other hypotheses – e.g., 'The failure must be due to this new lot of serum-free medium which we have never tested in the laboratory'. **The fourth important mantra of successful process startups is, 'Avoid Pet Hypotheses during Problem Resolution'**. There is a reasonable chance that the first hypothesis chosen by the group will be incorrect. Valuable time will be lost in problem resolution if hypotheses concerning process problems are pursued in a sequential manner.

The tendency to focus on a 'Pet Hypothesis' may have its emotional roots in anxiety reduction – that is, the wish of the Startup Team to quickly rationalize that the problem cause is understood and the situation is under control. In fact, this sequential approach is not generally effective at either finding the problem or reducing anxiety. At some level, each team member understands the risky nature of this narrow approach. On the other hand, a comprehensive investigation of the problem has a calming effect on the investigation team (and their management), as everyone recognizes that everything possible is being done to identify and solve the problem.

Taking preparations for plant failure one step further – The debug plan

There is no worse feeling than watching a process fail, then realizing that insufficient samples have been collected to permit rapid diagnosis of the problem. If this is the case, then it may be necessary to watch the process fail a second time in the plant in order to gather those samples. This second lot failure is a particularly painful experience for the Startup Team and their management.

An approach to eliminate this situation is called the 'Debug Plan'. The Debug Plan is prepared one to two months prior to plant startup.

The sequence of events in the development of this plan are as follows:

1. Examine each step in the process, imagining that it has failed during the first lot in the plant – e.g., cells did not grow properly at the 10,000-L bioreactor step.
2. Apply the comprehensive approach to problem resolution (outlined in the previous section) to identify each potential hypothesis that could explain this failure – e.g., Hypothesis A) cells were unhealthy before they entered the reactor; Hypothesis B) there is something deficient about the medium in the 10,000-L bioreactor; Hypothesis C, etc.
3. Then, identify the samples and side-experiments that would be necessary to diagnose the cause of this hypothetical process failure

This set of samples and side experiments is the Debug Plan. That is, this is the set of samples and side experiments that should be collected/performed *in parallel* with the first manufacturing lot in the plant! A portion of a typical Debug Plan is presented as Table 5. It is quite possible that the process will be successful in the plant, and the debug experiments and samples will be of no consequence. However, if there is a problem during the first large-scale lot in the plant, the debug plan will facilitate rapid problem resolution. When the cost of staffing for implementation of the debug plan is compared against the cost/risk of having to run an additional lot to identify a problem, the debug plan is readily justified).

It is generally wise for the Process Development Group to practice the Debug Plan in conjunction with the final set of laboratory experiments occurring just in advance of process startup – i.e., the small scale process demonstration employing the same lots of raw materials to be used in the plant. First, this will result in a set of archival debug samples that can be compared against comparable samples from the plant in the diagnosis of problems. Secondly, 'Practice makes Perfect'. It's important to work out the logistics and choreography of debug sampling and experimentation prior to entering the plant.

The greatest value of the Debug Plan is that it forces to Process Development Group to focus in advance on potential causes of process failure in the plant. It is frequently the case that organizing the Debug Plan points out additional experiments that must

Table 5. Features of a Debug Plan for the first step in a cell expansion process[a]

Sample or action	Logic for this sample or action
1. Save 1 L of inoculation medium	Would permit subsequent analysis of medium deficiencies – i.e., should there be a problem with cell growth in the shake flask step
2. Save vial used for inoculation	Inoculate residual cells into a shake flask containing 'process development medium' – i.e., medium that has been previously shown to support cell growth. If there was a problem with shake flask cell growth, this experiment demonstrates that the cells were healthy coming out of thaw. Keep the spent vial in case there is any future question about vial identity.
3. Save a sterile empty shake flask from the same sterilization/cleaning batch that was employed for the first process step	Would permit subsequent analysis to determine if there was a problem with the cleaning or sterilization of this batch of shake flasks first process step
4. Following inoculation of the next cell expansion step, retain a volume of inoculum in the original process shake flask. Use this inoculum retain to inoculate a shake flask containing process development medium	If there is a problem with cell growth in the next cell expansion step, this experiment will demonstrate whether there was a problem with the state of the cells at inoculation

[a] The purpose of the Debug Plan is to proactively take samples and perform experiments during the first startup lot to isolate the cause of potential process problems – i.e., under the premise that such problems could occur during process startup. Some experiments must be performed in parallel with process operations, while many samples can be archived for possible future analysis. If the process step succeeds during process startup, these samples are discarded.

be performed prior to process startup in order to reduce process risk.

Activities of the process development group in the plant during process startup

The purpose of the Debug Plan is to assure retrospective diagnosis of a process problem in the first process startup lot by assuring that sufficient samples are taken and sufficient parallel experiments are performed.

Process failure could also occur in the first lot due to an unexpected action taken by an operator as he/she implements the process according to the Manufacturing documents. The unexpected action could be an incorrect calculation in the document that could lead to a serious process error. Or, the unexpected action could be an incorrect physical manipulation – e.g., opening the wrong valve on a downstream skid. Sometimes these latter 'operator errors' are difficult to uncover retrospectively, and the Process Development and Manufacturing Groups are left with a sense of uncertainty concerning the true cause of process failure.

For this reason, and because the rapid analysis of problems in the first large-scale manufacturing lots is so critical, every process-related operation in the plant during startup should be observed by a Process Development representative. This representative must have sufficient process knowledge to understand how the process should be implemented, to know how the process should behave, and to be able to quickly recognize the types of operator actions that could potentially lead to a process mishap. The Process Development representative must have the authority to pause the manufacturing activity if an action is to about to be taken by an operator that could lead to process failure.

While the Debug Plan is fully implemented for only the first full-scale manufacturing lot, it is wise to continue process coverage in the plant by the Process Development representative until there is very high confidence in operator training and in the manufacturing documents.

The presence of a Process Development scientist on the plant floor during startup has the potential for disruption of the manufacturing routine. In this regard, it is important for Process Development and Manufacturing to develop clear guidelines for Process Development scientist behavior. There should generally be just one Process Development scientist on the plant floor at a given time for a given step, unless there are multiple parallel operations.

Decision-making during process startup

The Process Development Group should communicate to the Manufacturing Group in writing who will be

present at the plant for each process operation, and share lists of cellular phone home phone and pager numbers. Key Process Development and Manufacturing personnel should meet after each key manufacturing operation to discuss process performance, lessons learned, and the need for any manufacturing document modifications.

Unexpected events requiring rapid decisions occur routinely in process startup – e.g., a decision about how to recover from a power outage, an equipment malfunction or an operator error. The lead Process Development scientists should be provided with cellular phones to permit rapid communication and decision-making. All other Process Development scientists should be provided with pagers. The authority for making process decisions should be delineated in advance within the Process Development Team, and the Manufacturing Group should be informed of this decision-making process and who is 'on-call' for process decisions at every moment during process startup.

Communication of process observations and process performance on a daily basis is important within the Startup Team. It can be very effective for the Process Development step observer to construct an email immediately following step operation for distribution within the Startup Team. The Process Development and Manufacturing groups should plan in advance for a regular (perhaps weekly) joint communication to their management(s) about process and plant successes and challenges.

Results

The author has played a leadership role in eight biopharmaceutical process startups at six different plant sites in the US and Europe during the period from 1995 through 2001. Seven of the eight startups were to full manufacturing scale. Six unique processes are represented in this group, with full manufacturing scale ranging from 10,000-L bioreactor scale (for protein expression by a recombinant microorganism) down to a much smaller scale for production of conjugate and viral vaccines. Each of these six processes included both product generation and product recovery/purification operations.

For each of these startups,

- The guidelines outlined in this manuscript were followed.
- Process performance at full scale closely mimicked process performance of the laboratory scale process model.
- There were no unexpected protocol deviations between the process operated in the plant and the laboratory scale process, and
- There were no mismatches between the process and the manufacturing equipment.
- Each of these process startups concluded according to the original manufacturing schedule.

In six of the eight startups, the process was completely successful in the first full-scale manufacturing lot, while in the other two startups, complete process success was achieved in the second full-scale manufacturing lot. In the latter two cases, the causes of problems in the first lot were related to equipment performance – an improper seal installed in an ultrafiltration unit and a malfunctioning on-line dilution system. In each case, the problem was corrected for the second large-scale lot.

On the whole, all of these startups were viewed as very successful by the Startup Team and by their managements. Such a record is a strong testament to the quality of the Process Development Teams and the quality of the Manufacturing Teams with which the author has had the privilege of working. And, this record is also a testament to the overall plans of the Manufacturing and Process Development organizations in the preparation and implementation of these startups.

Summary, including comments about staffing levels

The four key mantra of the Process Development Group for rapid process startup are summarized in Table 6. The first two mantra bespeak an underlying philosophy of process startup preparations that focusses on clear accountability for activities between the Process Development and Manufacturing Groups, *and the complete responsibility of the Process Development group for assuring process success in the plant*. The third and fourth mantra focus on key rules-of-thumb for activities during the stressful periods just before and during the startup.

The are many types of problems that can emerge during process startup (Table 1, Column 1). To avoid these problems, the mechanisms described in this manuscript provide a clear and effective structure for

Table 6. The four mantra of successful process startups

Mantra	Interpretation
1. 'The Manufacturing Group is the Customer'.	The Process Development Group must develop and deliver a process that is robust and convenient to the Manufacturing Group.
2. 'Process Development is Responsible for the Process'.	The Process Development Group assumes full responsibility for process success in the plant, presuming only that the process is implemented as described in the manufacturing documents, and manufacturing equipment functions as designed.
3. 'We Don't do Experiments in the Plant'.	The Process Development and Manufacturing groups must resist the natural tendency to make last minute process changes that have not been tested extensively in the small-scale process model.
4. 'Avoid Pet Hypotheses during Problem Resolution'.	Investigations of process problems before before and during startup are conducted in a comprehensive manner. Potential causes of process problems are systematically addressed in parallel.

the Process Development Group and Manufacturing Group activities (Table 1, Column 2).

A typical cell culture or fermentation process has 3 to 5 cell expansion steps culminating in product expression, and a typical downstream purification process for a biopharmaceutical product has 3 to 5 steps. For such a process, approximately one dozen Process Development staff are necessary to accomplish the activities outlined in this manuscript, starting about 6 months prior to process startup and continuing through completion of process startup period. This would include at least 2 or 3 Ph.D.-level staff.

For a ball-park calculation of the expense of these startup preparations, let's assume that the cost of each of these twelve staff is approximately $300,000 per year, including overhead. Thus, over a six month to eight month period, the expense of this team on the order of $2,000,000. For a typical biopharmaceutical on the critical path to licensure, the loss of future revenue is at least $2,000,000 per week of delay in plant startup. Given the increased probability of rapid process success that is possible by employing the mechanisms outlined in this article, this commitment of twelve staff is money well spent.

Situations may exist where there is commonality between a new process and an existing process that has already been implemented in the plant – e.g., common media, common cell expansion steps, common in-process assays. Under those circumstances, the number of process development staff can be reduced. In the infrequent case where the plant is available off the critical path for large-scale 'experimentation', the number of process development staff can also be reduced.

Many of the in-process and release assays associated with biopharmaceuticals are themselves complex 'biological processes'. And, there has been a tendency for the transfer of these assays from Assay Development Groups to Final Product Release Groups to be problematic. It seems likely that some subset of the mechanisms outlined in the manuscript could help to increase the likelihood of assay startup success.

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End Notes

[1] In the delineation of accountability between groups, there may be situations where it is difficult for management to decide which group or person should have responsibility for a given activity. The two groups in question may be the Process Development Group and the Manufacturing Group. However, it is also often the case that there may be some difficulty in assigning responsibility for an activity within two subgroups of the Process Development organization – e.g., assignment of responsibility for the success of the hold step at the interface between the 'upstream' process development subgroup and the 'downstream' process development subgroup. It can be a natural tendency for management to settle on a compromise in which two groups or individuals are designated as mutually responsible for the activity in question. This is generally not advisable. This tact does not double the chances for the success of that activity. Rather, the chances for success are probably somewhat reduced due to the uncertainty created by such dual assignments. It is best to have one clear assignment of accountability for each activity in the process startup. Having said this, exceptions to this rule are possible, but they require a very strong working relationship, a common vision, and a lot of communication between the two parties.

[2] In some companies, there is a group within the manufacturing organization that will take responsibility for process support after the process startup period has concluded. This Technical Support Group will typically play several vital roles during the period leading to the startup. Frequently, they will assume responsibility for new equipment installation and qualification – that is, it becomes the primary responsibility of this group to assure that new process equipment will work as intended. In addition, this group may be responsible for assuring timely completion and approval of manufacturing documents. The close partnership between this group and the Process Development Group before and during the startup is particularly important. During this period, the Technical Support Group should be viewed by Process Development as one of its most important Manufacturing customers, and much time should be devoted to their training in process details. In transferring process insight, it is highly advisable for the Technical Support Group to spend time in the Process Development laboratories learning to operate the small-scale process prior to plant startup.

[3] During the early phases of process development for a biopharmaceutical product (e.g., in support of Phase 1 and 2 clinical trials), scientists and engineers who don't work well in teams can never-the-less be very successful contributors to development projects on the basis of their outstanding creativity and/or technical skills. This is not the case for process startups, where the need for individual talent is at least matched by the need for team harmony. This harmony is particularly important in the plant during full-scale plant operations where there must be no distractions from the fine details of plant and process operations. Thus, it is important to avoid placing abrasive individuals on startup teams.

[4] It is generally wise to assign someone from the Manufacturing Group to maintain a checklist with due dates for the hundreds of details of plant startup, including the deliverables of the Process Development Group.

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