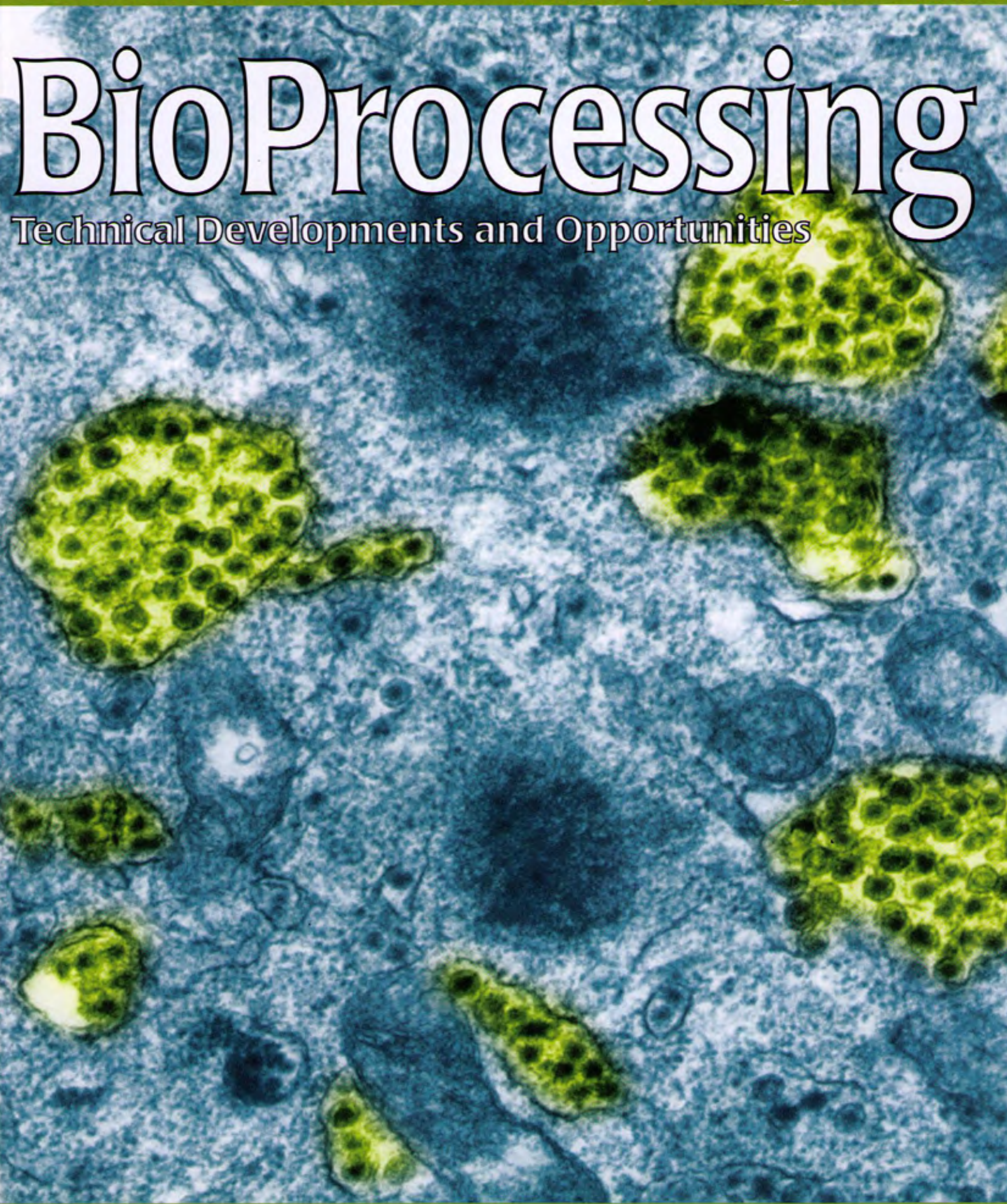
PREMIERE YEAR www.bioprocessingjournal.com

BioProcessing

Technical Developments and Opportunities



A publication of
The Williamsburg BioProcessing Foundation

Fall 2002

Risk Management Tools for the Management of Critical Raw Materials

BY ROBERT M. KENNEDY

Portions of this article were presented at the Williamsburg BioProcessing Foundation, Raw Materials Conference, Newport Beach, California, July 2001 and Salt Lake City, Utah, June 2002

Risk management deals with planning for, and reacting to, hazard or loss. The regulatory authorities are focusing on the issues associated with establishing alternative sources of raw materials, especially as they are noticing a number of related quality problems in biopharmaceutical manufacturing. Supply chain management for critical raw materials used in biopharmaceutical manufacturing is an appropriate subject for risk management. This paper analyzes five important areas in risk management as it applies to the supply chain for critical raw materials.

The first area includes production planning, and the marketing efforts needed to make accurate forecasts for raw material demand. Second is generation and application of a production master plan. The third is adoption of an appropriate inventory policy, and the fourth area is use of a site operations team for situations that involve more than traditional operations. It is useful to involve this group in supply chain management, particularly in planning and training. The last, and fifth, area consists of adoption of a supplier certification program, which is intended to assure a reliable supply of high-quality raw materials.

The FDA holds the biopharmaceutical manufacturer responsible for the quality of raw materials, and therefore, the accuracy of data generated by outside suppliers or contractors becomes a critical issue. In a certification relationship, the raw material supplier becomes, in essence, an extension of the sponsor's manufacturing operation.

Introduction

Management of raw materials in a manufacturing operation is a complex problem in its own right, but even more so in the regulated environment of biopharmaceutical production. Process water, plus all of the compounds used in cell culture media or fermentation broth, purification resin, buffer ingredients, and formulation excipients are considered chemical raw materials in biopharmaceutical manufacturing. The manufacturer of the biopharmaceutical, referred to as the "sponsor" in this paper, has the ultimate responsibility for the delivery of the biopharmaceutical product. Thus, there are three parties interested in risk management of raw materials: the sponsor, the supplier, and the FDA.

Critical raw material (CRM) management, is a subject for risk management, because of the final product value and manufacturing cost. Biopharmaceuticals are high-value products with significant development costs. Manufacturing losses or the inability to manufacture are costly. Industry-wide manufacturing space is rare and costly, and available capacity must be kept operational.

This paper will focus on CRMs in general, with specific examples drawn from one particular group of critical raw materials — purification resins used in chromatography. Process development for the purification phase of a biopharmaceutical process is quite thorough since the purification problems can be very complex. When the purification process is developed, it is almost always developed with a resin from a single supplier. Alternative suppliers are available in many cases, but it is very costly to develop two purification processes when only one will go to commercial scale. For economic reasons, purification resins often become sole-sourced CRMs.

The best strategy for risk management starts with cGMP awareness that leads to a robust manufacturing process (Fig. 1, page 54). We will look at five areas needed to manage the supply chain of a CRM including: production planning, forecasting and master planning, inventory policy, and site operations. The fifth area is the thorough audit and certification of critical raw material suppliers. Of the five areas, the first four can be managed independently by the supplier and sponsor within their respective organizations. The fifth area, certification, requires collaboration between the sponsor and supplier, and therefore will be discussed in more detail.

The FDA holds the biopharmaceutical manufacturer ultimately responsible for the quality of the raw materials used

Robert M. Kennedy, Ph.D., *is Department Director, Separation Sciences for Amersham Biosciences, Inc., New Jersey; bob.kennedy@am.amershambiosciences.com.*

in the production process. However, if a sponsor has established confidence in a supplier's ability to provide acceptable products, certification and associated test data may provide acceptable documentation to establish material quality.

As stated in the Preamble for Quality Systems Regulations, 21 CFR: 820, "… certification may play a role in evaluating suppliers." However, the document goes on to caution sponsors against relying solely on certification by third parties as evidence that suppliers have the capability to provide quality products or services.

There can be several reasons for a sponsor to institute a supplier certification program. Among these reasons can be the development of a "just in time" inventory program, a cost control program, or an overall quality improvement program. Others have discussed the value of forming formal relationships with suppliers as a means of cost control, and as an integral part of a quality improvement program.[1,2,3]

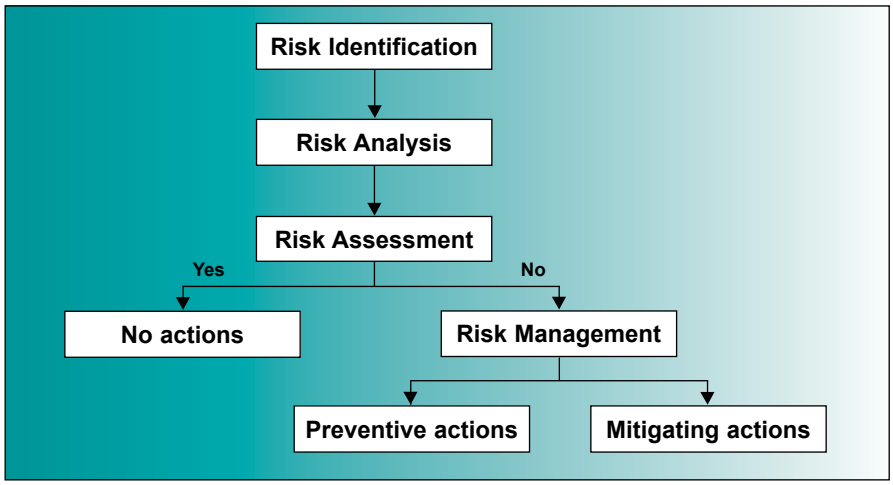


Figure 1. A risk management logic tree is shown. If there is no observation of risk at the level of risk assessment, no further action is required. If there is exposure to risk or hazard, then risk management plans are implemented to mitigate the effect of the risk and prevent its occurrence in the future.

Forecasting

Limited production capacity at the supplier's facility can cause interruptions in the supply of CRMs, and reserving additional supplier capacity can be expensive. Therefore, forecasting the need for CRMs becomes a critical function for the sponsor's production planning group.

Forecasting is a complex issue, part art and part science. There are several types of forecasts, and there can be several areas of shared responsibility for each type of forecasting. Management will typically define three levels of forecasting which are based on the timeline for specific projects. Long-range forecasting usually pertains to five-year plans for equipment acquisition and plant expansion. Medium-range forecasts typically look out two years, and are intended to account for seasonal variations in product demand and raw materials with long lead times. Short-term forecasts run in the 6-month to 18-month time frame, and are used to develop master plans and procure raw materials.

Production planning, which is usually part of operations or manufacturing, must share forecasting responsibility with the marketing group. Marketing ultimately decides the product requirements for both the clinic and the market. Production planning will then plan the raw material needs for each product, and determine the production schedule. Marketing will have a sense of the general business climate (i.e., is our business growing or not?), plus knowledge of the plans for promotions and product introductions. Both production planning and marketing will be able to contribute a historical perspective for product demand including data for statistical analysis of trends. However, marketing activities, such as promotions and product launches, can significantly alter a forecast that was based on trends or historical data.

Over- and under-estimation of raw materials is a subject that needs serious evaluation. Forecast deviations must be examined, and trends must be recognized. Of course, some deviations can be very difficult to predict such as those due to changes in consumer preference or competitor activity. While forecast deviations can be anticipated and promotional plans can be changed, additional actions are required. Failure to reschedule manufacturing can result in excess inventory or an out-of-stock situation. Failure to plan for promotional activity can also result in an out-of-stock situation, which will result in customer frustration plus competitor opportunities. On the other hand, excess stock impacts capital spending.

Master Plan

A second tool for managing the supply of CRMs is a production master plan. Management must decide how far into the future the plan should extend and how frequently the plan should be revised. Once these criteria are set, the master plan will set the minimum inventory level for each material, and customer satisfaction should be used as the measure for acceptable inventory level.

A common measurement is needed to relate production requirements, like doses or packages, to the amount of facility utilization and labor needed to make the raw materials. The demand forecast should also be in units common to production, such as units/time, and not revenue. In the master plan, the production requirements are spread over the planning period, which helps to identify capacity problems, as well as other areas of concern in the plant.

Inventory turnovers can also be estimated from the master plan. Higher turnovers equal a more efficient use of capital. The plan should include regular analysis to measure how the plan compares to reality. This information can then be used by manufacturing and marketing to plan inventory levels.

Table 1. Site Operations Management can contribute to the efficiency and safety of the manufacturing operation. Use of the site operations group to help manage the supply chain is an efficient use of resources.

Emergency Planning	Training
Crisis Management Committee	Evacuation
Incident Group	Fire exercises
Evacuation Plans	Incident group
Collaboration with Authorities	HSE
Preventive Maintenance	Contractor program
Disaster Recovery Plan	New hire program

Obviously, production management must involve upper management in the approval process of the master plan since it ultimately involves the scheduling of work, the consumption of materials, and the generation of inventory.

Inventory Policy

Inventory policy is another tool that can be used in the management of CRM supply. A balance must be achieved between inventory investment and the achievement of customer satisfaction. Too little material on the shelves will cause out-of-stock situations and frustrated customers, while too much material uses capital that could be spent on other projects. There are three primary principles that are commonly used to formulate raw material inventory policy: safety stock, anticipation stock, and economic order quantity. Safety stock is a quantity that is intended to take care of fluctuation in demand or manufacturing lead times. Anticipation stock supports promotional activity in either plant expansions or shutdowns, and is material that will go into inventory as close to the intended use date as possible. Economic order quantity is an amount that can be purchased at a lower cost due to efficiencies it offers the supplier.

Site Operations

Another tool for supply chain risk management is the use of a site operations group for emergency planning and training – two items that are essential for the smooth and safe operation of a manufacturing site, plus the prevention of production interruptions (Table 1). Organizationally, production planning is usually part of operations. It is important to note that operations is also responsible for the recovery plan in the event of an interruption in manufacturing.

Overall, the best risk analysis model starts with an internal audit of the production facility, as well as an understanding of the likelihood and impact of an interruption to any part of the process. Process interruptions are then graded on two scales, which show the likelihood and impact of the event. Finally, contingency plans are based on the likelihood and seriousness of the event. Table 2 (page 56) shows a grading system for such a contingency plan, as well as a contingency plan matrix.

If a serious event were to occur, the disaster recovery plan would be implemented. A hypothetical disaster readiness plan is shown in Figure 2. Site operations are included in this discussion because of their crucial role in maintaining CRM output. A key part of a disaster readiness plan would be a list of preventive actions that reduce the risk of an interruption in production. If there is an interruption, the site operations group then has a plan to minimize the consequences. By building some redundancy into production, site operations can move a process to another location, plus have operators that are trained to handle several processes at different sites.

Certification

The decision to certify a supplier is a serious one for both the sponsor and supplier, and one that will require an open relationship between the parties. Initial discussion typically involves how and why a raw material is used in manufacturing, and how it meets the specifications of the manufacturing process. If the candidate biopharmaceutical is moving forward in the clinic, then discussions are needed on increasing the supply of the raw materials that will be required. The sponsor often has concerns that these increased requirements will result in unanticipated changes in raw material specifications, composition, or performance. As a result, it would be helpful for suppliers to share any concerns they have concerning an increase in their production level.

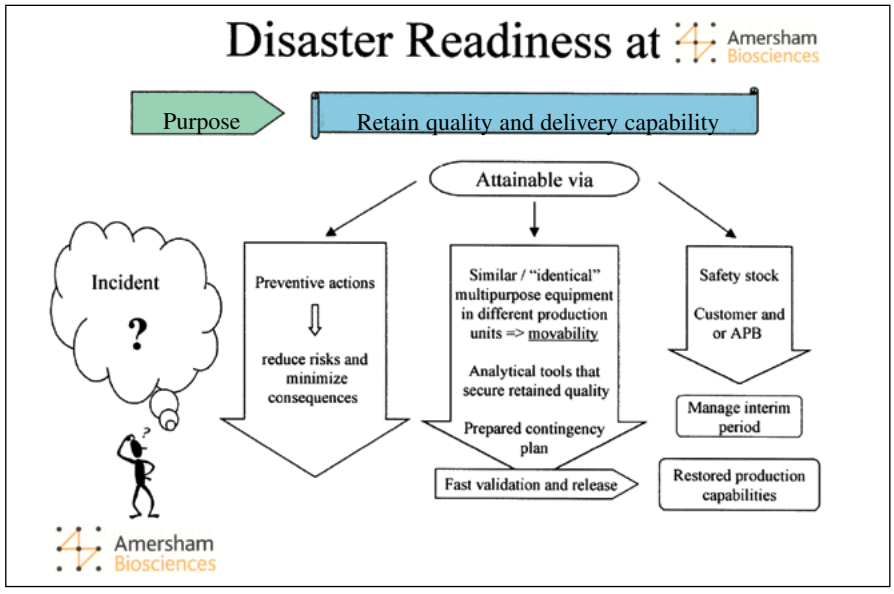


Figure 2. In the event of a disaster, a plan such as this would be implemented at a production site. Similar plans are in place in both sponsors' and suppliers' manufacturing facilities worldwide.

Likewise, sponsors should share project information including product priority, market projections, and anticipated demand for raw materials.

While it is true that certification can reduce redundant testing of raw materials, this reduction will not be realized immediately. A lengthy period of testing and verification is required before the sponsor can rely on the supplier's certificate of analysis (C of A) for acceptance of a raw material. A QC program established by the sponsor at the supplier's facility does not eliminate the sponsor's overall testing responsibility. However, a properly designed testing program can eliminate testing the sponsor must do, plus reduce CRM lead times.

The supplier must view the raw material sale as only one phase of the sponsor relationship, and accept that it must involve its entire logistics train in the relationship and become a virtual arm of the production effort. The increased risk the supplier accepts with a larger inventory level and capacity reservation is more than offset by the efficiency gained in the management of these QC and inventory management programs, plus the increased ability to anticipate the sponsor's demand for the materials.

A certification program is composed of four components: an initial product testing phase, an audit phase, a provision for change control, and a testing and confirmation phase.

Prior to acceptance of a supplier's C of A, the raw material must be thoroughly evaluated. Several lots must be tested, preferably not just from the midpoint of the specification range, but also from the high and low ends. Test methods must be obtained and verified by the sponsor's quality group. Using these methods, results reported on the C of As must be verified for various lots. During this process, the supplier will need to explain the variation observed in the raw data, plus the rationale used to select the standards and calculation methods. Areas of improvement for QC procedures must also be discussed.

The sponsor should audit the supplier for compliance with ISO, GMP, or other accepted standards. The supplier must have an adequate quality system in place that is sufficiently documented, and this documentation must be available for the auditor's inspection and review. Follow-up is then essential to assure that progress is being made in the areas that the audit has identified for improvement.

Table 2. Grading system for performing a risk analysis on a production process and a risk analysis matrix showing the use of the grading levels.

Disaster Level	Likelihood	Impact
5: Worst	5: Common	5: Catastrophic
4: Very serious	4: Occasional	4: Major
3: Serious	3: Moderate	3: Significant
2: Less serious	2: Uncommon	2: Minor
1: Incident	1: Rare	1: Insignificant

Disaster level	Description of disaster level	Examples	Likelihood	Impact	Estimated full recovery time	Mechanism of control
5	Worst scenarios which include...	Plane crash war, earthquake	1	5	3 years	Choose a "safe" place for the production facilities
4	Very serious	Fire in tankyard or fire in several manuf. units	1	5	3 years	Detectors (flame,fume & solvent) & sprinkling (foam/ water/ inert gas)
3	Serious	Fire in one manuf. unit	1	4	3 years	Detectors (flame,fume & solvent) & sprinkling (foam/ water/ inert gas)
2	Less serious	Breakdown of critical equipment	3	2	<18 months	Spare parts, preventive maintenance
1	Incident	Handling error, critical personnel	4	1	<9 months	Calibration, education job rotation

Written change control procedures are one of the most important aspects of a supplier certification program. When the supplier makes a change in the production of a raw material, the sponsor must receive written notification of any changes in starting materials, processes, equipment, or manufacturing location. The supplier must also inform the sponsor of changes in the quality procedures, routines, and test methods being used. If change control procedures differentiate between minor and major changes, the rationale and differences must be explained to the sponsor. Finally, testing and verification should continue after supplier certification.

Conclusion

Since CRM supply interruption exposes the sponsor to financial loss, supply chain management of CRMs is an area of risk management. Forecasting demand for CRMs requires the joint effort of production planning and marketing groups.

A certification program requires a long-term relationship between the sponsor and supplier, where the supplier becomes an extension of the sponsor's manufacturing process.

Acknowledgements

The author wishes to thank Jorge Cerda, Guenter Jagschies, and Roger Nordberg in Uppsala, Sweden, and Charlie Mason, Lisa Gonzales, Sherri St. Clair, and Donna Testa in Piscatatway, NJ for helpful discussions.

REFERENCES

1. Dysart, J., et al. Supplier certification: A model program. PDA J. Pharm. Sci. Techol. 43:151-157. 1989.

2. Ram, K., et al. "Raw material and components: Enhancing quality, minimizing risks and reducing costs". Presented at Williamsburg BioProcessing Foundation Raw Materials Conference, St. Louis, MO. 1999.

3. Del Tito Jr., B. J., et al. Qualification of raw materials for clinical biopharmaceutical manufacturing. BioPharm 9 (November): 45-49. 1996.

4. Kennedy, R. M. and L. Gonzales. Minimizing risks from chromatography media: Management of raw materials in biopharmaceutical production. BioPharm 14 (May): 56-58. 2001.

5. Joyce, Martin H. So you want to be a preferred supplier: A pharmaceutical industry purchasing managers perspective. Contract Pharma. April/May:28- 37. 2001.