QUALITY

1. Introduction

The objective of chemical manufacturing is to provide products that perform to expectation. The manufacturing unit is responsible for producing these products. The quality assurance (QA) and quality control (QC) units are designated to assure the product not only meets its stated specification, but also performs up to customer expectation. The activities typically performed by the QC laboratory ensure through testing that a product conforms to specification. The QA unit operates in support of the lab activities to assure the correctness of the results and the consistency of the product. The relationship between QA and QC and with production is shown in Fig. 1. A review of several quality improvement techniques applicable to the manufacture of chemical products is given herein. Several quality system standards used by chemical manufacturing organizations are also discussed.

The twentieth century has often been called the Century of Productivity; the twenty-first century may well be the Century of Quality (1). A discussion of how the chemical industry is organized to develop and manufacture quality products is available (2).

2. Quality Control

Within the chemical industry, QC is the systematic monitoring of product conformance to specification through testing (3). The reliability of laboratory testing is essential to operation of the production unit. Therefore, proper sampling and the accuracy and precision of measurements are important. This relatively narrow focus of QC differs from the broader responsibility of QA whose role usually involves monitoring all activities that impact product quality as well as service quality, and includes QC activities (see Fig. 1).

The principle role of QC is operation of the testing lab and the reporting of test results. Quality control usually inspects raw material quality prior to use in production. Testing of in-process material is conducted either by QC or production. Where production performs the in-process testing, there is usually oversight of this activity by either QC or QA. Quality Control performs finished product testing to confirm the quality of the product is adequate. Thus QC confirms whether a material has been manufactured in conformance with specification. Sometimes QC also assists the production unit in salvaging nonconforming in-process or finished product through reprocessing or rework.

As noted, the purpose of the QC laboratory is to monitor product quality through sampling and analysis. This sometimes results in an adversarial relationship with the production unit. Thus, the lab must balance competing risks that arise from a lack of accuracy or precision in lab testing. One consequence, called α-risk, is the risk of rejecting a product that in fact meets specification. The competing risk, known as β-risk, is that of erroneously releasing off-standard material that might lead to customer complaints. When QC reports to the site or facility manager these risks are generally well balanced. However, when QC reports directly to production, there is often a tendency to accept more

β-risk for the sake of greater production output by which production performance is evaluated and thus rewarded. Therefore, operation of the QC laboratory, as it relates to the accuracy of their test results, is extremely important to the harmony of the plant, the profitability of the company, and the satisfaction of the customer.

2.1. Sampling Plan. The first step to assuring accuracy, ie, the conformity of the measured value to the true or expected value (4), is to obtain a representative sample. Sampling is usually the responsibility of either production or QC. Since it is the responsibility of the QC unit to ensure that the sample represents all of the material under evaluation, a written sampling plan approved by QC should be followed.

A thorough sampling plan should describe when the sample is to be taken and how many samples are required. It also specifies from what location within the equipment, such as the manway, discharge valve, or recirculation loop to take the sample. The plan also describes how to take the sample, such as after flushing a specified amount or after flushing for a specified time. The plan should also indicate what sampling equipment and sample container should be used, as well as the types of tests to be performed and the acceptance criteria for these results.

The number of samples to be taken can be of importance. One sample often suffices where it can be shown that the material in question is homogeneous for the parameter(s) to be tested, such is the case of pure gases or bulk solvents. If the material is not homogeneous, then statistical sampling should be considered. Samples may need to be taken from various points within the material if the material stratifies.

Samples can be analyzed individually or may be combined into a homogeneous composite sample and then analyzed. In either case, only a portion of the sample is customarily used for a given test. Therefore, this test material must be representative of the entire lot. Where this may not be the case, as for particle size measurement of powders, it may be important to extract representative test quantities from the bulk sample. For powders this is best done using a spinning riffler; for liquids, it should be carried out only after thorough mixing (see MIXING AND BLENDING; POWDERS, HANDLING, BULK POWDERS; SIZE MEASUREMENT OF PARTICLES).

2.2. Calibration. Calibration of lab instruments is critical to the accuracy of test results. Calibration, the use of an accepted standard to adjust an instrument or measurement standard so as to improve the accuracy of the instrument or measurement, is an essential requirement of both the U.S. Food and Drug Administration (FDA), Good Manufacturing Practice (GMP) (5), and the ISO 9001 standard (6).

A calibration schedule appropriate for each instrument must be established. The frequency should ideally be based on experience. However, until sufficient experience is gained, the schedule is typically based on customary practices or the instrument manufacturers' recommendations. The calibration frequency can then be adjusted as experience is accumulated. If the instrument is often out of calibration, a more frequent schedule should be used; if in calibration, the interval can be extended.

For conformance to GMP or ISO 9001 requirements, instrument calibration must be documented including identification of the instrument and the calibration standard. The standard must be traceable to a recognized standard such as

those from the National Institute of Science and Technology (NIST). Calibration documentation also includes the method of calibration and a record of the calibration results.

2.3. Replicate Analyses. Confidence in the test result is improved by reducing the measurement variability. This variability in repeat analyses is known as precision. One method to improve the precision of the measurement is to perform complete replicate analyses of the same sample beginning with the sample preparation (7). This is appropriate when the sample is known to be representative of the material sampled. When this is not the case, multiple samples should be taken for analysis.

The average value of the replicate results is reported as the test result. The standard deviation, which reflects the variability in the measurement, should also be calculated. A large standard deviation relative to the average measurement is indicative of the need for an action plan to improve the precision of the measurement. This can be accomplished through increasing the number of replicate measurements or more appropriately eliminating the source of the variation, such as the imprecision of an instrument or poor temperature control of the sample during the measurement.

2.4. Statistical Control. Statistical quality control (SQC) is the application of statistical techniques to analytical data. Statistical process control (SPC) is the real-time application of statistics to manage process or equipment performance. Applied to QC lab instrumentation or methods, SQC can demonstrate the stability and precision of the measurement technique and shows the stability of the overall measurement process. Without such evidence of measurement stability, ie, statistical control, the reliability of the lab data is unknown and can lead the production unit to challenge the validity of adverse test results. Also, without control, measurement bias cannot be determined and the results derived from different labs cannot be compared (8).

Statistical control of an analysis or instrument is demonstrated best by SQC of a standard sample analysis. The preferred approach to demonstrate statistical control is to use a reference sample of the subject material that has been carefully analyzed or, alternatively, to use a purchased reference standard. Either material must be stored so that it remains unchanged, eg, sealed in ampoules or septum capped bottles. Periodically, a sample can then be reanalyzed by the technique used for routine analysis. These results are plotted in a control chart. Any change in the stability of the test in question results in a lack of randomness of the measurement and becomes apparent as a trend or shift. A change in measurement precision is indicated by an increase in the distance measurements are from the average line (9).

Statistical quality control charts of variables are plots of measurement data, preferably the average result of replicate analyses versus time (Fig. 2). Time is often represented by the sequence of batches or analyses. The average of all the data points and the upper and lower control limits are drawn on the chart. The control limits are closely approximated by the sum of the grand average plus three times the standard deviation for the upper control limit (UCL) and minus three times the standard deviation for the lower control limit (LCL).

Several rules are applied to control charts to spot a lack of randomness. The most obvious is a point outside the control limits. Using control limits calculated

as described above, a point outside of the control limits due to random variation happens about three times in 1000 occurrences and thus is rare. A trend such as a run, where at least seven consecutive data points are either above or below the average line, or a trend of seven consecutive points either increasing or decreasing in value, also indicates an out of statistical control (nonrandom) situation (10). A lack of randomness is also apparent from a pattern in which there is a repeated sequence of points cycling between rising and falling, or when points tend to cluster around the center line (average) or near the control limits. Since out-of-control points due to normal variation are rare, it is more likely that the lack of randomness is due to a change affecting the measurement.

The value of control charts is to provide early warning to lab personnel of changes affecting the reliability of test results such as the drift of an instrument resulting from the deterioration of a chromatographic column, or the need for cleaning or servicing an instrument, as from the weakening of the light source in a liquid chromatography detector. Control charts can also point to variation in the test results owing to inconsistencies in analyst technique arising from insufficient training. The performance of lab equipment should always be monitored using control charts.

2.5. Laboratory Information Management System. The QC lab analyzes raw material, in-process, and finished product samples, adheres to calibration schedules, records data, and performs statistical analyses. These activities lend themselves to the application of software packages such as a laboratory information management system (LIMS). An inexpensive LIMS is within the reach of even small laboratories.

The LIMS software is essentially a database for tracking, reporting, and archiving lab data as well as scheduling and guiding lab activities. A comprehensive LIMS package is also used for graphical and statistical treatment of data for improved process control as well as for preparation of certificates of analysis (COA) for the customer (11).

Samples logged into LIMS are assigned a unique number, often represented with a bar code, printed on a label that is physically attached to the sample container. The sample testing protocol is contained within the LIMS and is based on the point in the process from which the sample was taken. This information and the identification of the type of sample, eg, finished product, enable the LIMS to schedule appropriate testing of the material.

Sample test data are either manually entered into the system or captured from analytical instruments connected to the LIMS. The system performs any necessary calculations and compares the result to the appropriate specification stored in the database. If the comparison indicates the material is in conformance, the system can automatically indicate the material is acceptable. Otherwise, the LIMS can alert lab supervision to the nonconforming sample status. When LIMS is interfaced with the inventory system, LIMS can change the status of the lot to “approved” or “quarantine” as appropriate.

When test data are already in the computer, tracking lab performance using statistical techniques can be done with little effort. By having this data archived, historical trends can be charted and past process capability can be readily compared to current capability. This can be useful in responding to chal-

lenges to test results (11). The availability of test data makes periodic comparison of process capability to specification limits easy.

Whereas issues of technician productivity, sample status, and scheduling of analyses are economically important, these take second place to the issue of measurement quality in the laboratory. The LIMS software enables activities such as calibration and preventive maintenance of instruments to be automatically scheduled. By recording the results of these activities in the LIMS, the data is readily available to monitor instrument performance with SQC techniques and confirms the measurement validity. Additionally, the calibration and preventive maintenance schedule of individual instruments can be adjusted to reflect their actual needs.

Another benefit of using LIMS is the ease of ensuring that tests are performed according to the most current procedure. Test methods can be incorporated into the system and printed either as a recipe or worksheet for the analyst, thus helping to assure the most current method is used and facilitates consistency between analysts.

Finally, the laboratory expends significant effort communicating results to both internal and external customers. Production, quality assurance, and purchasing all have various information needs ranging from the simple pass–fail decisions to statistical summaries of the data and reports of supplier product quality. Customers expect to receive lot analyses in the form of a COA and often also want their own product-specific information on the document as well. This information can automatically be applied to the COA if the LIMS is so configured. Oftentimes, a quality-conscious customer will want, periodically, information about the product they purchase in the form of process capability or control charts. Using LIMS, these charts can be provided on demand.

3. Quality Assurance

Responsibilities of the quality assurance unit are generally to support the proper operation of the company-wide quality system (12). The support activities of QA often include employee training, quality system documentation, method validation and method transfer, audit, and customer complaints.

Whereas QC is responsible for monitoring production, the responsibility of QA encompasses the entire product cycle from product development to customer satisfaction (see Fig. 1). The QA activities vary from auditing raw material suppliers to evaluating in-process sampling plans, the equipment calibration and preventive maintenance program, and the implementation of statistical process control. Quality assurance may also assess the production and packaging operations and labeling procedures, as well as warehousing and shipping functions. This quality oversight activity plays a large role in assuring procedures, equipment, personnel and materials are suitable to prevent nonconforming product from ever reaching the customer.

Quality assurance must remain independent of manufacturing so that problems can be reported freely to upper management without fear of retribution. QA should have oversight responsibility for QC to minimize the influence production has on product disposition recommendations made by QC. The company

should have an organizational chart showing this reporting structure to demonstrate the independence of both quality units that would conform to the requirements of both the GMP and ISO 9001 quality systems.

3.1. Employee Training. Quality assurance will often provide training related to quality topics to employees. For companies manufacturing pharmaceuticals or chemicals used for pharmaceutical manufacturing, such training would be in GMP compliance, which is mandatory (13). If a company is pursuing ISO 9001 certification, employee training would cover relevant requirements of the ISO standard (14). In many organizations, employees are trained in improvement techniques such as statistical process control, tools of quality, and the requirements of the quality system under which the products are being manufactured. The extent of QA involvement ranges from assisting in the development of the curriculum to providing trainers and facilitating implementation. Employee training results in a better educated workforce that can perform more productively while achieving higher quality output.

3.2. Quality System Documentation. Quality system documentation is divided into two levels. Higher level documentation is typically called a quality manual, which is the description of how the company's quality system is to operate (15,16). This manual addresses how the company plans to comply with quality related requirements such as those falling under quality system standards such as GMP or ISO 9001.

The quality manual should be organized to facilitate referral to the appropriate clause or section of the quality system standard. The quality manual should briefly set the requirement since the manual generally expresses policies and should refer to other documentation, such as Standard Operating Procedures (SOP) for more detail. The manual should be under document control, ie, each page is uniquely identified as to date or revision number and the name or department of the preparer. It is common practice to offer customers a copy of the quality manual upon request, ie, the manual should not be treated as proprietary.

The lower level of quality system documentation is the detail of how the work processes referred to in the manual are to be performed. The QA unit is often the organization responsible for issuing this set of procedures designed to implement the policy set forth in the quality manual to assure conformance to the appropriate standards or to company policy. The procedures, often called SOP, quality operating procedures (QOP), or standard practice instructions (SPI) should include such topics as customer complaints, audit protocols, stability testing, preparation of COA, test method validation, specification review and approval, etc.

Well-written procedures should begin with a purpose and scope. The procedure section usually follows, describing the work process that should be clearly and concisely written. The procedure should include copies of all forms used to record evidence of conformance to the procedure as well as a process flow diagram for illustration.

3.3. Test Methods. Test methods also have a significant impact on the accuracy and precision of the laboratory results. Preferred methods are those that are accepted in the chemical industry such as those from the American Society of Testing Materials (ASTM), Association of Official Analytical Chemists

(AOAC), or from compendia such as the *United States Pharmacopoeia* (USP) or the *Food Chemical Codex* (FCC) (17). The use of such methods eliminates the need to demonstrate the suitability of the test methods to make the measurement or for validation of the test method developed in the company against a standard method such as found in the above mentioned compendia.

Method validation is the demonstration, with a high degree of assurance, that the test method consistently performs as expected. Validation of test methods is especially important when the intended method differs from a compendial or other standard reference method and yet is expected to provide equivalent or perhaps better test results. When the compendial or standard reference method is to be used unchanged, no validation is necessary. Thus a primary benefit of using such methods as written is avoiding the need to do method validation.

An analytical method validation study should include demonstration of the test methods' accuracy, precision, specificity, limits of detection and quantitation, linearity, range, and interferences. Additionally, peak resolution, peak tailing, and analyte recovery are important for some methods, especially in the case of chromatographic methods (18,19).

For methods used to measure relatively small quantities, limit of quantitation and limit of detection must be determined as well as the limit of linearity. The limit of quantitation is defined as the level at which the measurement is quantitatively meaningful; the limit of detection is the level at which the measurement is larger than the uncertainty; and the limit of linearity is the upper level of the measurement reliability (20). These limits are determined by plotting concentration versus response.

Interferences in the method can reduce its selectivity and thus the reliability of the measurement. Therefore it is important to evaluate the method for interferences and to utilize techniques to reduce their impact as well as to make them known to the analyst (21).

The analytical research and development (R&D) unit is often responsible for the preparation and validation of test methods. The R&D lab is not faced with the same pressures for rapid analysis as the QC unit, where pending results often hold up production. In addition, R&D often assigns personnel to specific instruments or techniques, whereas QC generally requires technicians to perform varied analyses. This leads to an expertise on the part of analytical chemists and technicians which is difficult to duplicate in QC. These discrepancies in the operation of analytical R&D and the QC lab lead can lead to the development of test methods that are unsuitable for QC operations. Therefore R&D should be sensitized to develop test methods that are rugged enough to withstand the different environment within which the QC lab operates and yet still provide valid results.

3.4. Method Transfer. Method transfer involves the implementation of a method developed at another laboratory. Typically, the method is prepared in an analytical R&D department and then transferred to quality control at the plant. Method transfer demonstrates that the test method, as run at the plant, provides results equivalent to that reported in R&D. A validated method containing documentation eases the transfer process by providing the recipient lab with detailed method instructions and reference to the accuracy and precision, limits of detection, quantitation, and linearity that should be achieved.

Preferably the transferring lab provides a sample that has already been analyzed, with the certainty of the results being known (22). This can either be a reference sample or a sample spiked to simulate the analyte. An alternative approach is to compare the test results with those made using a technique of known accuracy. Measurements of the sample are made at the extremes of the method as well as the midpoint. The cause of any observed bias, the statistical difference between the known sample value and the measured value, should be determined and eliminated (23). When properly transferred, the method allows for statistical comparison of the results between the labs to confirm the success of the transfer.

3.5. Quality Audit. Another important responsibility of quality assurance is the quality audit function. Using the quality audit as a tool, QA can monitor the operation of the manufacturing facility; a toll, ie, contract manufacturer; or raw material supplier to assure that written procedures are in place and that there is documentation to indicate the procedures are being followed. Properly executed audits allow QA to spot potential weakness in the quality system that could allow errors to occur. Once identified, these weaknesses can then be corrected before they result in nonconformance.

An audit must be exercised with great care lest it become a policing function. To optimize the effectiveness of the audit, proper techniques include the following (24):

1. Initiation: The audit host should be given ample notice of the impending visit.
2. Plan: Clearly identify to both the auditor and host the audit standard, such as GMP or ISO 9001, the audit scope, the schedule, duration, etc.
3. Implementation: Carefully collect factual information to document all observations while objectivity is maintained and avoid casting blame.
4. Wrap-up: The audit host should be informed of any negative findings immediately and the audit results presented to senior management representatives, along with any positive observations, at an exit meeting.
5. Reporting: A written audit report should be available in a timely fashion, typically within two to four weeks.
6. Conclusion: An appropriate period of time, typically 4–6 weeks, should be allowed for receipt of the corrective action plan from the audit host.

Quality Assurance should audit at least the most important suppliers. This type of review often results in the exchange of ideas for improvement to quality systems of both the supplier and the customer. Sometimes such an audit also identifies a supplier with a serious quality system deficiency.

3.6. Customer Complaints. A failure in the company's quality system often shows up in the form of a complaint from the customer. These reports of nonconformances, whether for product or service deficiencies, are typically received by the sales or customer service organization and then channeled to QA. Quality assurance is often responsible for tracking the progress and coordinating investigation of the complaint. Once completed, it is QA who reviews the report of the investigation and proposed corrective and/or preventive action for

thoroughness and efficacy. Quality assurance can then either pass the information along to the sales or customer service organization to present to the customer or QA can contact the customer directly, as directed by company policy.

4. Quality Systems

Besides internal quality audits of the company production facilities, there are also audits conducted by external authorities for conformance to established quality systems. The two chief standards affecting the chemical industry are the FDA Current GMP regulation and the International Organization for Standardization ISO 9000 series. A quality system performance-related standard is the Malcolm Baldrige National Quality Award (MBNQA).

4.1. Good Manufacturing Practice. The GMPs were issued by the FDA in 1978 to provide minimum quality standards in the production of pharmaceuticals, which is applicable to the finished dosage form as well as their ingredients. The standard has been updated periodically. In 1979, these requirements, described in 21 CFR parts 210 and 211 (13), became legal requirements for the manufacture of drug products. Since that time, the FDA has issued numerous guidance documents that elucidate their expectations for GMP compliance.

The GMP regulation details certain requirements for the quality system, such as the need for an independent quality unit with defined responsibilities; ie, oversight of every department to assure conformance to GMP requirements. The GMP quality system specifies such activities as internal auditing to monitor GMP conformance, employee training, complaint investigation, failure analysis, and verification of proper manufacture and testing by Quality Control through review of applicable records prior to release of the batch.

The GMP regulations also ensure the quality of pharmaceuticals by requiring suitable manufacturing equipment, air and water quality, sanitation, insect and rodent control, and housekeeping.

There are GMP guidelines for the manufacture of active pharmaceutical ingredients (API) and the inactive pharmaceutical ingredients (excipients). The API and especially excipients are typically manufactured by chemical companies. The International Conference on Harmonisation (ICH) has been active in issuing guidelines applicable to API manufacture whereas the International Pharmaceutical Excipients Council (IPEC) has issued several guidelines for various aspects of excipient GMP compliance.

In 2001, the FDA adopted ICH guideline Q7A (25) to describe GMP quality system requirements suitable for the manufacture of active pharmaceutical ingredients. While enforcement of manufacturing requirements for API is governed under the GMP requirements found in 21 CFR Parts 210 and 211 (13), FDA inspection of API manufacturing facilities follows the Q7A guideline.

In 1994, IPEC, a trade association comprised of excipient manufacturers and users, issued GMP quality system guidelines for the manufacture of bulk pharmaceutical excipients (26). This GMP guideline was developed using the ISO 9001 format and thus was revised in 2001 to conform to the ISO 9001:2000 format. USP has added the excipient GMP guideline as a general chapter (27) and producers of excipient ingredients should conform to these

GMP requirements. Again FDA enforcement of GMP requirements, even for excipients, is governed by 21 CFR Parts 210 and 211.

The FDA periodically sends inspectors to audit the manufacturer of the prescription or over-the-counter drug as well as the API. However, manufacturers of bulk pharmaceutical excipients will generally only see an FDA inspector if the site has never been assessed by FDA or if the FDA has reason to be concerned about conformance to GMP at the site.

Whereas conformance to GMP requirements ensures that the product meets pharmaceutical quality standards, it does not ensure conformance to customer requirements particularly for service. Also the GMP quality system places an emphasis on consistent pharmaceutical ingredient quality and does not encourage continuous quality improvement.

4.2. ISO 9001. The ISO 9001 standard was first issued in 1987, and then updated in 1994 and again in 2000. The ISO 9001:2000 standard describes the quality system requirements for the manufacture of a product beginning with design and development in R&D through to commercial production and after-sale service and technical support.

The ISO 9001 (6) is organized into sections beginning with Quality System Management, which describes the requirements for the operation of the quality system including documentation of the plan for quality, its implementation, maintenance, and improvement. This is followed by the section Management Responsibility, which establishes requirements for top management commitment to the ISO standard, customer focus of the company, issuance of a quality policy, quality planning activities, administration of the quality system, and management review of the quality system performance. The next section, titled Resource Management, focuses on the adequate provision of resources, personnel requirements, facilities and the work environment. This is followed by the Product Realization section that deals with such quality system topics as process planning, customer process issues, product development, purchasing, production and service activities, and instrumentation. The final section, Measurement, Analysis, and Improvement, includes such measurement and monitoring issues as customer satisfaction, internal audit, and in-process and finished product control. Also included in this last section is the handling of nonconforming product, analysis of data and improvement of the product and quality system.

Conformance to ISO 9001 is verified by third-party audit for which the company to be certified pays the certifying company a fee. Continued conformance is assured through periodic reaudit by the certifying company. The ISO 9001 is not a product quality standard since conformance by the manufacturer to ISO 9001 ensures that their customer will receive product in conformance to mutually agreed-upon specifications. Other agreed-upon requirements such as packaging and labeling and service provisions are also to be met. The benefit of ISO 9001 certification to the manufacturer is the confidence such certification provides to their customers that the company has met the minimum requirements for this internationally recognized quality system.

The chemical industry led other U.S. companies in the early 1990s in achieving conformance to ISO 9000 primarily because of the importance of international trade to chemical companies. The ISO 9001 certification was once thought to be necessary for access to the European market (28). The emphasis

on registration and recertification continues at a fast pace, as certification continues to be considered an important supplier selection criterion by U.S. chemical companies.

4.3. Malcolm Baldrige National Quality Award. The most stringent and comprehensive quality system criterion is described in the MBNQA. The award was created by an act of U.S. Congress in 1987 and has been given annually since 1988. The award program is managed by NIST and administered by the American Society for Quality (ASQ). The award is a competition for the annual honors given to the highest scoring companies that exceed a minimum score. A maximum of two awards each are given in the categories of large manufacturing and small manufacturing company. There are also separate categories for other organizations such as service companies. Selection is based on a written application that describes how the company meets the award requirements. A site visit by a MBNQA audit team seeks to verify the applicant's claim in fulfilling the award criteria.

The winning quality system has three principal features: (*1*) integration with business strategy; (*2*) active organizational learning processes tying together all corporate requirements and responsibilities, eg, customer, employee, supplier, productivity; and (*3*) multidimensional results that contribute to overall business improvement and competitiveness (29). Winners of the award in the large company category have included chemical and allied industry companies and their customers, including Eastman Chemical, Motorola, Xerox, and Millikan Company. Companies having exemplary quality systems have shown benefits such as "better employee relations, higher productivity, greater customer satisfaction, increased market share, and improved quality" (30).

4.4. Selection of a Quality System Standard. Conformance to GMP is mandatory for most chemical companies supplying the pharmaceutical industry; conformance to ISO 9001 can be an important first step toward achieving a world-class quality system and ultimately the Malcolm Baldrige Award. There are many differences between the ISO 9001 standards and criteria for the Malcolm Baldrige Award. The most important of these is their purpose. The ISO standard is meant to demonstrate conformance to customer requirements. The Malcolm Baldrige criteria are intended to show that a company is capable of "delivery of ever-improving value to customers; and systematic improvement of company operational performance" (31). This leads to a difference in executive commitment. Winning the Baldrige Award requires significant top management involvement. Conformance to ISO 9001 can often be led by a level of management other than top management.

5. Quality Improvement

The chemical and allied products industry was stated to be the largest U.S. exporting sector since the mid-1980s (32). Quality improvement has evolved as companies struggle to maintain this position. The United States has lost some competitive edge in many other technological areas, sometimes even when it was the low cost producer. This loss has been attributed in part to the quality of goods and services not meeting competitor's performance.

5.1. Early Activities. Historically, quality was entrusted to the artisan, who was solely responsible for the products made. Thus financial success often rested on the quality of their product. The industrial revolution replaced this system with one in which product quality was the result of the combined efforts of a group of factory workers. Quality was ensured through the combination of worker skills and monitoring of worker activities by a production supervisor.

The adoption of the Taylor System in the late nineteenth century changed the lines of responsibility for product quality (33). This management philosophy was based on using incentives, such as pay based on output, to motivate worker productivity. However, as the workforce became better educated and labor unions gained strength, it became difficult to motivate workers doing simple, repetitive tasks (34).

The Taylor System, successful in the United States until the end of World War II, resulted in a dramatic increase in productivity. The transfer of responsibility for product quality from production to the QC laboratory allowed production to emphasize productivity; while relying on quality control to keep nonconforming products from reaching the customer. In the years following World War II, the race for productivity allowed quality to became secondary (35).

In this period, leading executives in Japan were convinced by W. Edwards Deming, who lectured on statistical methods, and Joseph M. Juran, who taught the principles of managing for quality, that Japanese economic recovery from World War II could best be achieved through the manufacture of quality products (36,37). During the 1970s, Japanese quality improvement became apparent as Japanese manufacturing costs dropped dramatically while the quality and reliability of their manufactured products increased. This change was demonstrated in such Japanese products as radios, televisions, and videocassette recorders. However, it was Japanese automotive quality that caught the undivided attention of U.S. industry (38). As a consequence, to meet future threats, the U.S. chemical industry began to respond with improvement initiatives of its own.

5.2. Quality in Japan. Japanese economic prowess was attributed variously to such quality improvement activities as Quality Circles, SPC, Just-in-Time delivery (JIT), and Zero Defects (ZD). However, the real key to success lies in the application of numerous quality improvement tools as part of a management philosophy called Kaizen, which means continuous improvement (39).

During the 1970s and 1980s, U.S. companies tried to adopt Japanese improvement techniques, but not their philosophy of continuous improvement. Thus Quality Circles, ie, problem-solving groups of production workers, was the first Japanese improvement initiative used by U.S. companies (40,41). When this approach as applied by U.S. companies failed to achieve results similar to those in Japan, it was replaced by other Japanese techniques, such as SPC (42), JIT (43), and ZD. The use of these differing approaches has been summarized (44).

The quality management tool at the opening of the twenty-first century is Six-Sigma. This approach to company-wide quality improvement is discussed in detail below. Its' important difference with earlier U.S. quality management efforts such as the adoption of Japanese quality ideas piecemeal, or of Total Quality Management is that Six-Sigma emphasizes rigorous employee training and deployment of these highly trained individuals as a resource to improvement

teams. These teams are tasked with completing well-defined improvement projects that lead to measurable quality improvement and dollar savings.

5.3. Quality Techniques. *Statistical Process Control.* A properly running production process is characterized by random variation of the process parameters for a series of lots or measurements. The SPC is a statistical technique used to monitor such variation in a process. If the variation is not random, action is taken to locate and eliminate the cause of the lack of randomness, returning the process or measurement to a state of statistical control, ie, of exhibiting only random variation.

This technique was developed at Western Electric in the 1920s and was widely used in U.S. plants during World War II, helping to ensure the reliability and performance of military supplies. Once the war ended, SPC lost favor in the United States emphasis on productivity. However, in the face of rising Japanese product quality, SPC was reintroduced in the 1980s. In the chemical industry the use of SPC continues to grow in popularity as a key element of an ongoing continuous improvement effort.

Just-In-Time. Just-in-Time closely followed the reintroduction of SPC into the American workplace. The application of JIT in the United States was limited to an emphasis on keeping component inventories low to reduce the cost of inventory (45). However, the Japanese used JIT primarily to force management attention on quality problems and only secondarily to reduce inventory cost.

Prior to implementation of JIT, defective parts found on the production line would be discarded and a replacement taken from inventory, in order to keep the lines running. With JIT in place there is insufficient inventory to replace defective parts, which often leads to a shutdown of the assembly process. The Japanese use this impact of poor quality to heighten awareness of nonconforming material and to ensure that management identified and corrected the causes of the defective part. United States industry, however, saw the disadvantageous tradeoff between interrupting production to improve quality and the economic savings from reduced inventory. Thus in the United States, JIT was merely a tool to keep inventories low, even if it meant requiring the supplier to maintain inventories nearby at the suppliers cost.

Quality Function Deployment. Sometimes referred to as the House of Quality, Quality Function Deployment (QFD) is a technique for translating the voice of the customer into design requirements (46). This is a systematic approach identifying customer expectations and relating their expectations to product properties. The usage of QFD in the chemical industry appears to be growing. The QFD results in chemical specifications optimized to assure the material is suitable for its intended use and performs to customer expectations.

Zero Defects. Whereas ZDs was often interpreted to be a quality goal, its full meaning, as applied in Japan, was to encourage continuous quality improvement (47). In the United States, when ZD was treated only as a slogan, it too failed to have the desired impact on product quality.

5.4. Quality Management. *Total Quality Management.* Total Quality Management (TQM) was the term used to describe the overarching quality management effort to use the philosophy of continuous improvement to achieve the goal of world class quality. This corporate culture was to establish a favorable

climate for companywide quality improvement activities using the improvement techniques discussed here.

Companies following a TQM philosophy placed heavy emphasis on employee training for quality improvement. Top management monitored improvement through well-designed metrics. Those organizations using TQM had a comprehensive employee recognition and reward program to celebrate success. Successful implementation of TQM resulted in higher customer satisfaction, employee involvement and motivation, and financial success.

In the chemical industry, TQM evolved from a corporate-run program to a decentralized one (48). Responsibility for implementation was turned over to local sites so that often the roll of a small corporate staff was to provide resources and guidance to facilitate improvement activities led by local staff.

While there were successes with TQM, implementation depended upon altering the corporate culture to fit the TQM model, thus making TQM difficult to replicate across companies. Also management lost interest in TQM when there were insufficient financial metrics to show the benefit of quality improvement on company profitability.

Six-Sigma. As of the late 1990s the term ZD was no longer heard. One U.S. manufacturing company, however, successfully changed its culture using this approach. However they made one key adjustment to ZD. Motorola set measurable improvement goals, based upon the concept of process capability, with the objective of establishing virtually error-free (ZD) processes. When their initial goal of three sigma, or approximately three defects per 1000 was achieved in 1987, Motorola developed "Six-Sigma Quality" as their quality improvement program (49). All work processes were to be improved on a continuous basis with the 1992 goal to reduce defects to the six-sigma level, which corresponds to 3.4 defects/million. Motorola top management fixed their sights on this aggressive goal, provided employees with the resources to accomplish it, and then closely monitored progress. Their quest was successful, leading to world class quality, the winning of the MBNQA, and, most importantly, resulting in the economic revival of the company.

The Motorola achievement attracted the attention of corporate executives and beginning in the mid-1990s other companies such as General Electric, Honeywell, DuPont, and Polaroid all launched Six-Sigma programs. Their long-term goal "is to integrate and standardize companywide system improvements at every level in order to raise the overall "sigma" performance" (50).

Six-Sigma differs from TQM and other quality programs in that Six-Sigma focuses on the establishment of teams, sponsored by management, to achieve measurable improvement, ie, quantifiable as a consequence of cost reduction or cost improvement. Management advertises the savings internally as a means to motivate further improvement efforts and often externally to satisfy the investment community.

Six-Sigma companies provide resources to the improvement teams through the training of selected individuals in the concepts of Six-Sigma. These individuals receive intensive training in statistical and problem solving methodology and then are assigned to assist improvement teams. As they gain experience they progress to the level of Black Belt.

Six-Sigma improvement teams follow a well-defined improvement roadmap using a model referred to as DMAIC which is a modification of the model first proposed by W. Edwards Deming known as PDCA, an acronym for Plan-Do-Check-Act (51). Under PDCA, the "Plan" step involves clearly identifying the problem or the gap, gathering data to identify the cause and possible solutions and developing a means to test the solution. The "Do" step follows, where the planned solution is tested prior to full implementation. Next is the "Check" stage where the affect of the tested solution is verified and concludes with the final step, "Act", where if successful, the improvement is made permanent.

The Six-Sigma DMAIC improvement process expands on the Deming PDCA cycle as follows. The process begins with "Define" where the improvement team defines the problem and establishes the improvement goal. This is followed by the "Measure" step where measurements are made to quantify the problem and to set a baseline against which improvements will be measured. Then comes the "Analyze" phase where the data is evaluated to identify the primary root cause or causes that impede improvement of the process. The "Improve" step is when possible preventive measures to eliminate the root cause are identified, tested and their improvement results compared against the baseline from the "Measure" phase. The effort ends with the "Control" step where the improvement is made permanent by implementing performance measures.

Six-Sigma teams use many of the quality and statistical methods known collectively as the Tools of Quality. The Tools of Quality have long been used as a set of problem solving tools by the quality professional. Six Sigma teams often use the flow chart and cause and effect diagram in the "Define" phase and the control chart, histogram, check sheet, and scatter or correlation diagram in the "Measure" and "Analyze" steps. The Pareto chart is a tool used in the "Improve" step and the control chart or SPC is often implemented in the "Control" phase. These seven of the tools of quality have been summarized in Quality Progress magazine over several issues in 1990.

The first tool is the flow chart, used to help understand the organizational flow of a procedure or process (52). A flow chart should be constructed with the full participation of the people who do the work. Its principal benefit is to enable teams, such as problem-solving or Six-Sigma, to reach a common vision of the work flow. Its use enables the improvement effort to begin with this common understanding. Figure 3 contains an example for manufacture of a polymeric material.

The second tool is the cause and effect diagram (53), illustrated by Fig. 4. This type of diagram is used by teams to relate an effect to its potential causes. Diagram construction often begins with the four main branches Machines, Employees, Method and Materials. These diagrams resemble the skeleton of a fish and thus are sometimes called fishbone diagrams. All possible primary causes and their associated subordinate causes and their next-level associated causes should be shown. When the lowest level causes are identified, the team can use the chart to evaluate the interactions and rank the most likely origin of an effect. Once this is accomplished, other Tools of Quality can be used for the collection of data to confirm the cause leading to the effect in question.

The third tool is the control chart (see Fig. 2) (54). This type of chart is used to display how a measurement such as purity, or a control parameter such as

temperature, varies sequentially. The sequential parameter is often expressed in batch or process order or in time sequence. The technique is used to identify a situation where a variable measurement or series of consecutive measurements differs more than normal variation would predict. This situation is described as being out of statistical control or just out of control. Corrective action might be to adjust the equipment to regain control such as through process adjustment, or through preventive action resulting from the determination of the root cause for being out of control followed by fixing the underlying problem. The latter might lead to identifying the cause, eg, as a change in raw material, deficient training of the chemical operator, or flaws in the manufacturing process.

The histogram is the fourth Tool of Quality (55). These charts, such as that shown in Fig. 5, illustrate the variability of data as a frequency distribution. Typically, the range of variability is broken down into ~10 intervals. The total number of measurements in each interval is represented as the height of a bar graph. The resulting pattern shows the spread of the variable and whether it is normally distributed. If the graph is bell-shaped, ie, symmetrical with its peak in the center of the data range, then the data has a normal distribution. If the curve has a different appearance, its shape can often suggest possible causes for the quality problem. For instance, a histogram of the measurement of particle size can show that a lot of powder is the result of mixing lots of differing particle to achieve the desired average particle size. In this case, a bimodal distribution is expected whereas the histogram of particle size measurements for a single lot would be expected to display a normal distribution of measured values.

The check sheet, tool number five, is a simple technique for recording data (56). A check sheet can be used to present the data as a histogram when the tabulation is converted into a frequency distribution or can be converted to a run chart when the data is plotted sequentially. The advantage of using a check sheet for data collection is the ability to rapidly accumulate and analyze data for trends. A check sheet for causes of off-standard polymer production is shown in Fig. 6.

The Pareto chart, tool number six, is a special type of histogram (57), where the frequency data is grouped in order of decreasing occurrence or other measures of importance rather than in sequential or numerical order. The chart, an example of which is shown in Fig. 7, illustrates the causes in decreasing order of importance. It clearly shows the most important item and thus enables the improvement effort to be focused where it can have the most impact making Pareto charts an effective management communication tool.

Pareto charts often illustrate the principle that 80% of the effect is the result of 20% of the causes (58). Thus these charts are valuable in prioritizing improvement activities. Identifying and correcting the 20% often results in an 80% improvement in the measured effect.

The seventh tool is the scatter or correlation diagram also known as an XY plot (59). This plot of one variable vs. another variable is most useful in confirming interrelationships. Thus, scatter diagrams can verify the relationships such as shown in the cause and effect diagram.

Proper application of one or more of the tools of quality by the Six-Sigma team usually lead to the elimination of the causes effecting the quality or cost of the item and thus lead to improvement of the process under investigation.

6. Economic Aspects

The chemical industry uses quality as a strategic tool for financial success. One measure of quality is the degree of product variation from lot to lot. In the chemical industry, it is often difficult to provide product specifications comprehensive enough to ensure product performance in all customer applications (60). However, the manufacture of product having a minimum of lot-to-lot variability allows the customer to use the product without modifying the formulation or process to accommodate such variation.

Quality professionals use the term quality cost when discussing waste in a company. Quality cost includes any form of waste associated either with an activity that is unnecessary or an effort that must be corrected. There is internal waste in the form of rework, scrap, failure investigation, downgrading, etc. External waste includes customer complaints, including returned product, price concessions, and complaint investigation. Appraisal costs are those used to ascertain conformance to specification during the manufacturing cycle. Chemical companies have come to recognize the costs associated with wasteful efforts and attempt to identify and eliminate waste. The savings accrued have a dramatic impact on profitability.

Companies with a strong quality control and quality assurance emphasis attempt to redefine the corporate culture to reflect quality improvement and customer satisfaction. It has been estimated that U.S. companies spend from 20 to 40% of their sales dollars on various forms of waste (61,62). Quality-related expenses for quality plant laboratories and corporate staff associated with control and improvement activities run $\sim$1–3% of sales (63). Thus, these control and improvement efforts have the potential to provide a return of $10 for every $1 invested.

The impact of quality improvement activities on companies is reflected in the financial achievements that result from Six-Sigma activities. The impact from Six Sigma on Motorola during the period from 1987 to 1997 was reported as a

> Fivefold growth in sales, with profits climbing nearly 20%/year.
>
> Cumulative savings based on Six-Sigma efforts pegged at $14 billion.
>
> Motorola stock price gains compounded to an annual rate of 21.3% (64).

The benefits of quality improvement through Six-Sigma are still being seen as reported in company Annual Reports. In 2003, Dow Chemical stated that ongoing Six-Sigma projects continue to reduce costs and measurably improve performance as demonstrated by their ability to upgrade the plastics manufacturing process without capital expenditures for an annual savings of $10 million (65). In 2004, DuPont completed its sixth year of Six-Sigma efforts and has announced it has become the way they work and is key to their execution going forward (66). In a recent article, Honeywell reported the impact of Six-Sigma activities as >$2 billion (67).

General Electric is probably the company whose Six-Sigma efforts have been most followed. Their efforts began in 1995 with training which continued

in 1996, a year in which GE invested $200 million in Six-Sigma but only generated a return of $170 million in savings (68). In 1997, the benefits of Six-Sigma began to become apparent with the company investing $380 million and accruing a return of $700 million in savings. In the next 5 years, it has been widely reported that GE saved several billion dollars through 2003, thus enhancing their competitive position.

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IBS Consulting in Quality LLC

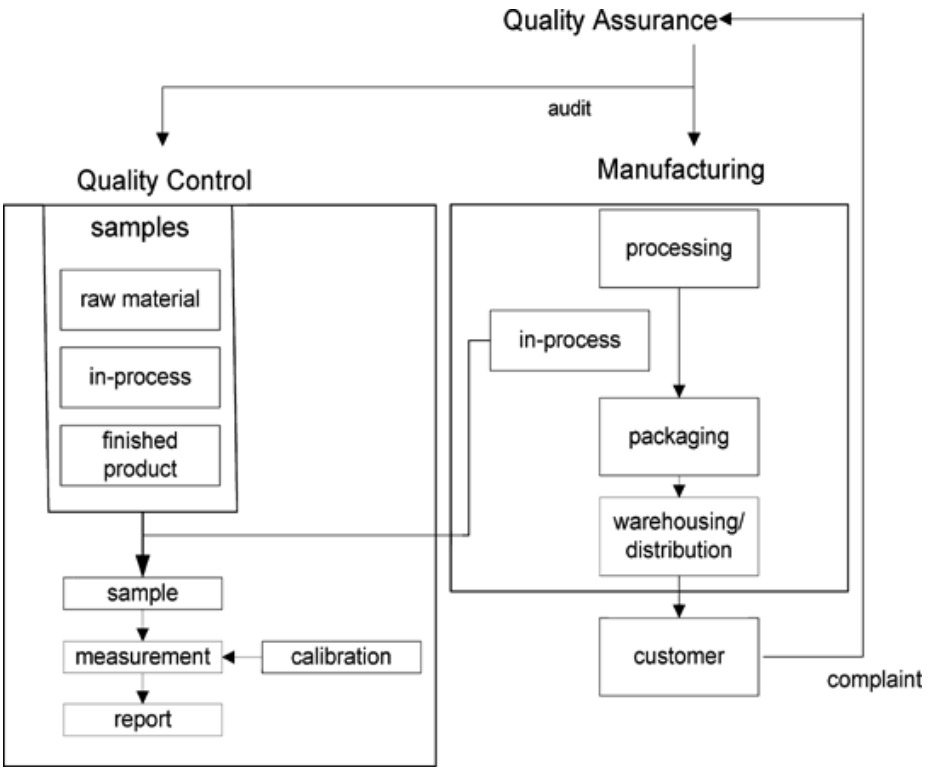

Fig. 1. Quality organization activities.

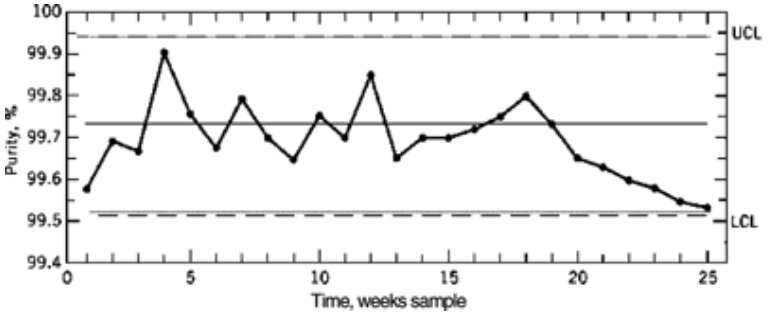

Fig. 2. An SPC control chart of the purity analysis of a reference standard, where (—) represents the average value and (- - -) UCL and LCL.

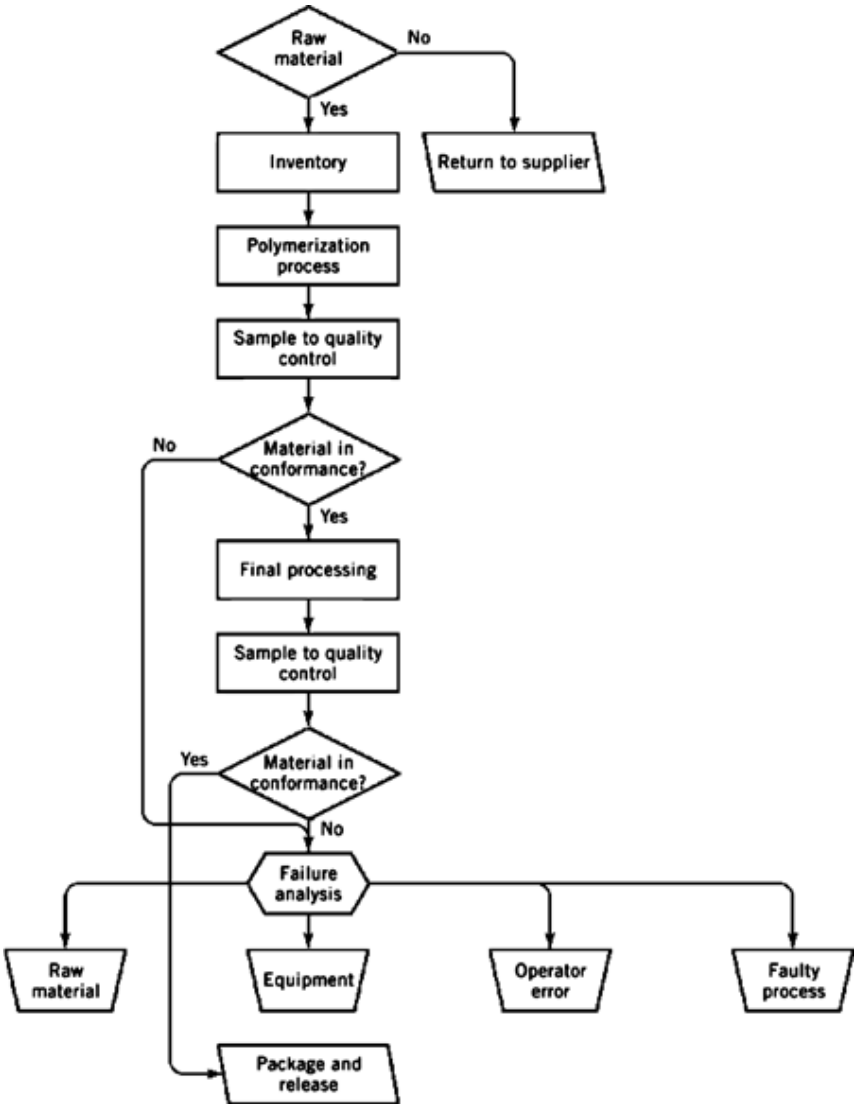

Fig. 3. Flow chart of polymer quality control.

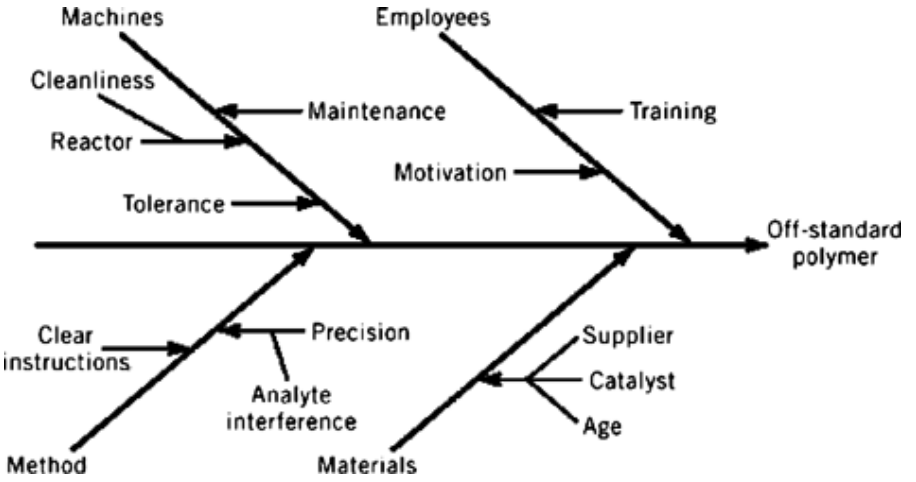

Fig. 4. Cause and effect diagram of off-standard polymer production.

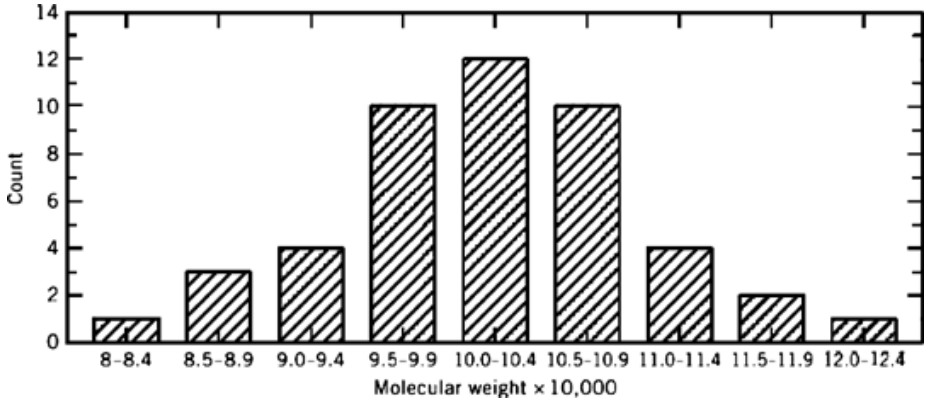

Fig. 5. Histogram of polymer molecular weight distribution.

Attribute	Occurrence
color	XXXX
moisture	XXXXXXXXXX
pH	XX
viscosity	XXXXXXXX
particle size	X
monomer	XXX
solvent	X

Fig. 6. Check sheet for causes of off-standard polymer production.

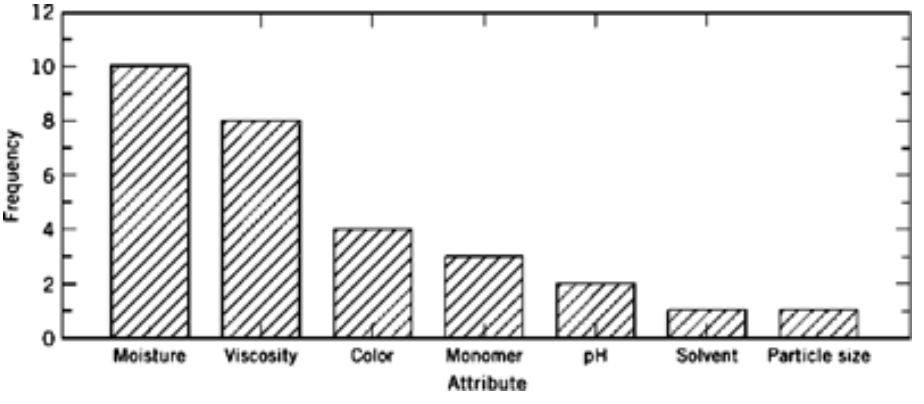

Fig. 7. Pareto analysis of causes of off-standard polymer production.