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REVIEW ARTICLE

# Managing Unexpected Events in the Manufacturing of Biologic Medicines

**Gustavo Grampp · Sundar Ramanan**



**Abstract** The manufacturing of biologic medicines (biologics) requires robust process and facility design, rigorous regulatory compliance, and a well-trained workforce. Because of the complex attributes of biologics and their sensitivity to production and handling conditions, manufacturing of these medicines also requires a high-reliability manufacturing organization. As required by regulators, such an organization must monitor the state-of-control for the manufacturing process. A high-reliability organization also invests in an experienced and fully engaged technical support staff and fosters a management culture that rewards in-depth analysis of unexpected results, robust risk assessments, and timely and effective implementation of mitigation measures. Such a combination of infrastructure, technology, human capital, management, and a science-based operations culture does not occur without a strong organizational and financial commitment. These attributes of a high-reliability biologics manufacturer are difficult to achieve and may be differentiating factors as the supply of biologics diversifies in future years.

## 1 Introduction

Modern biologic medicines (biologics) have become increasingly important for treating grievous illness in the past 20 years. Healthcare providers who prescribe and administer biologics may recognize the differences in the complexity of biologics compared with chemically synthesized pharmaceuticals (small molecules); however, there has been relatively little awareness of the intricacies of the manufacturing process for biologics.

The healthcare community's awareness of biologics manufacturing is derived from supply and quality issues that have occasionally impacted these medicines. However, the recent shortages of injectable small molecule drugs [1–4] are almost always related to manufacturing and quality issues and have illustrated the importance of manufacturing reliability. Of note, the US Food and Drug Administration (FDA) recently published an article in which they discuss the critical relationship between quality compliance and reliability of product supply and suggest that the incentives to underinvest in manufacturing could be changed if manufacturers were recognized and rewarded for commitment to quality [5]. Biologics are almost entirely injectables, but with typically more complex and sensitive active ingredients compared with small molecules. Thus, the criticality of high-reliability manufacturing for biologics should be readily apparent.

Biopharmaceutical companies—companies that produce medical drugs using biotechnology—have developed the applied science, engineering expertise, state-of-the-art equipment, and specialized practices to permit reliable, large-scale manufacturing of high-quality biologics. Robust process and facility design as well as a high level of regulatory compliance are prerequisites for pharmaceutical manufacturing. Because of the structural complexity of biologics and their sensitivity to processing conditions, successful biologics manufacturers have fostered a culture of continuous monitoring, investigation, and improvement, characteristics that are shared with those of other high-reliability organizations (HROs, Fig. 1). The technical, managerial, and cultural attributes characteristic of a

G. Grampp (✉)
Amgen Inc., 4000 Nelson Road, Longmont, CO 80503, USA
e-mail: ginog@amgen.com

S. Ramanan
Amgen Inc., Thousand Oaks, CA, USA

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number of high-risk fields of endeavor were studied and described by Weick and Sutcliffe in *Managing the Unexpected* [6]. Weick and Sutcliffe evaluated operations in a variety of HROs to identify common threads that permit these organizations to operate successfully in an inherently risky environment. 'Managing the Unexpected' refers to operational challenges under circumstances where unexpected events could progress to catastrophic failure, if not managed properly. HROs exhibit similar characteristics (Fig. 2) and are able to detect and rapidly investigate signs of potential failure, build infrastructure and processes that are resilient, and create teams that can make the best informed decisions. Weick and Sutcliffe did not evaluate the biopharmaceutical industry, but many of the lessons from their research can be applied to the manufacturing of biologics (Fig. 2).

Given the significant number of worldwide drug shortages and attendant policy discussions focused on mitigation, it is important for healthcare providers to understand how the complexities of manufacturing relate to ensuring a consistent supply of safe, high-quality biologics. These complexities manifest in risks throughout the life cycle of a biologic and are therefore relevant to a broad range of products. Here we discuss features that distinguish biologics from chemically based drugs as well as elements of process design, qualification, and control that embody high-reliability manufacturing. The case studies presented here rely heavily on Amgen's experience, and we have included examples of case studies from other manufacturers where sufficient details have been published.

## 2 Biologics are Sensitive to Manufacturing Processes

Biologics and small molecules have a number of key distinguishing features that inform a discussion of manufacturing reliability (Table 1). The manufacture of a biologic typically involves a series of biological and biochemical processing steps, followed by fill and finish of the sterile drug product (Fig. 3a). While the fill and finish steps for a biologic are similar to those needed for sterile injectables, the biological synthesis and purification steps used to manufacture the biologic "drug substance" are quite different from the manufacture of an active pharmaceutical ingredient. Biologic product quality is heavily dependent on drug substance manufacturing conditions, but fill and


**Fig. 1** HROs, analyzed by the authors of *Managing the Unexpected* [6], share similar challenges and objectives to the biopharmaceutical manufacturing industry

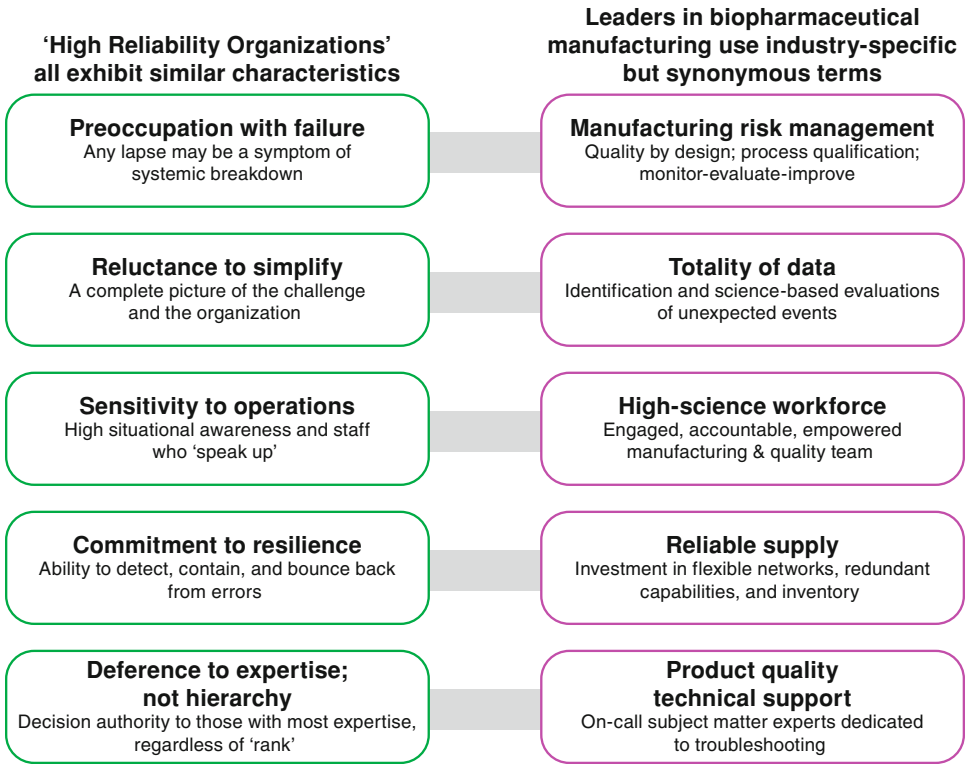
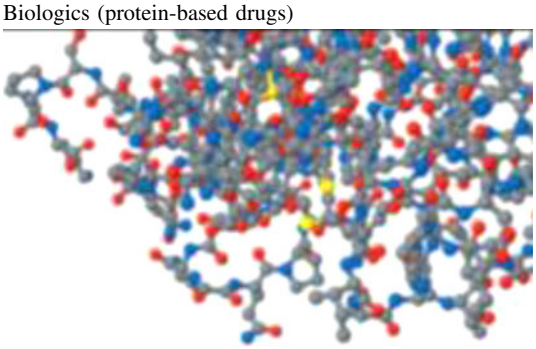



**Fig. 2** Characteristics of HROs [6] are also shared by the biopharmaceutical manufacturing industry

**Table 1** Characteristics of small molecules versus biologics

| | Small molecules (chemically based drugs) | Biologics (protein-based drugs) |
|---|---|---|
| |  |  |
| Size | Small [28] | Large [28] |
| Structure | Simple and well defined [29] | Complex with many options for post-translational modification [30] |
| Manufacturing | Predictable chemical process [28] | Each manufactured in a unique living cell line [28] |
| | Identical copy can be made [28]: generic drug | Similar but not identical copy can be made: biosimilar |
| Characterization | Easy to fully characterize [31] | Difficult to fully characterize because of a mixture of related molecules [28] |
| Stability | Relatively stable [28] | Sensitive to storage and handling conditions [28] |
| Immunogenicity | Low potential [28] | High potential [28] |

finish steps can also pose higher risks for biologics because of their greater sensitivity to temperature, shear, and light exposure.

The manufacture of small molecules from well-defined starting materials and their purification from a discrete set of reaction by-products are understood from the first principles of chemistry and physics (Fig. 3b). However, the synthesis and purification of biologics typically involve complex source materials and several biological and biochemical processing steps that cannot be fully characterized from first principles of biology and chemistry (Fig. 3c). Thus, it is not straightforward for process

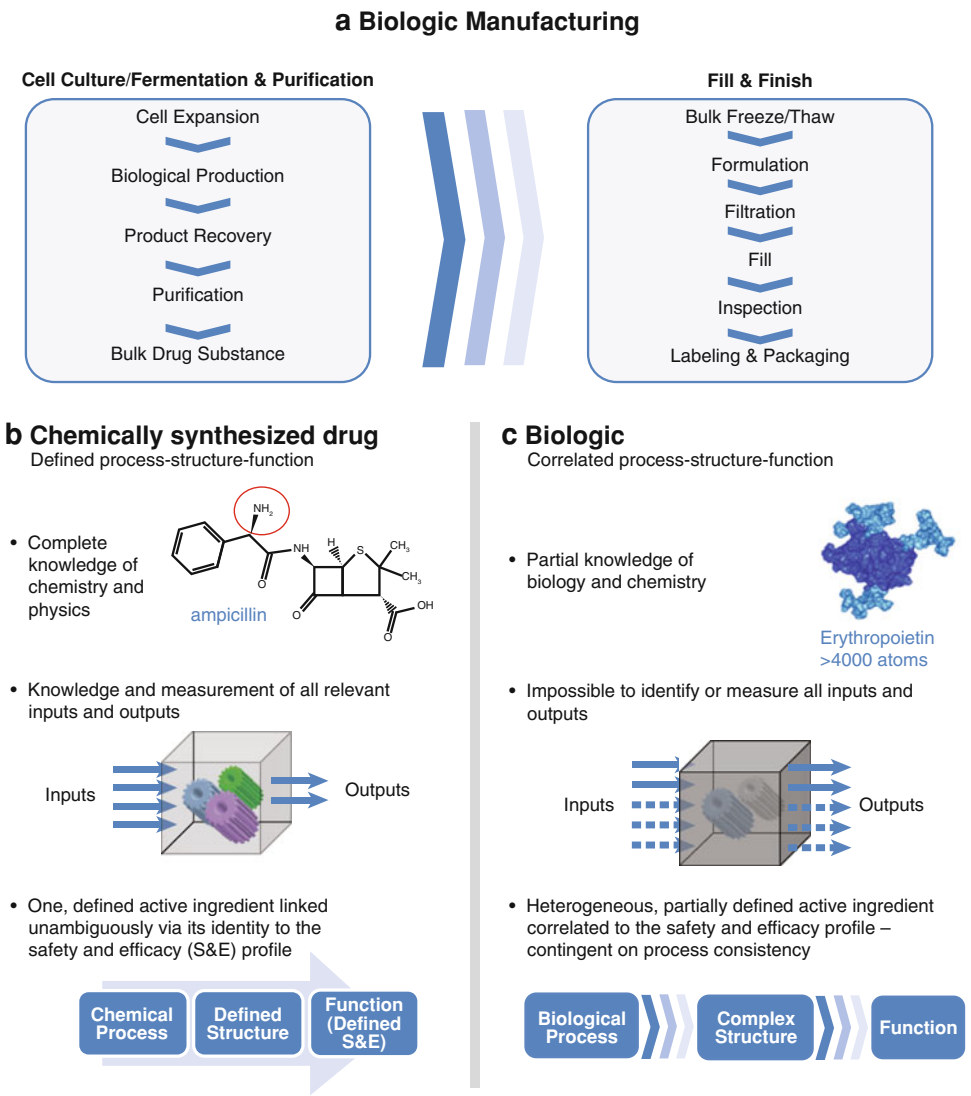



**Fig. 3** **a** Biologics manufacturing processes typically involve several critical steps, starting from cell expansion from a unique manufacturing cell bank, proceeding through the biological production phase of the process using live cells (the "upstream" process), and then through a series of recovery steps and purification formulation steps to produce the active ingredient (drug substance). The final product is formulated and filled in a sterile injectables facility. The identity, quality, and purity of biologics can be sensitive to any of the steps in this chain. **b** For the manufacture of a small molecule active pharmaceutical ingredient, the relationship between the chemical process and the resulting active ingredient is well understood, and unexpected outcomes are relatively rare. Furthermore, routine quality tests can verify the structure of the active ingredient in any given batch and provide a high level of assurance that the product's function (safety and efficacy profile) will be exactly as established for the product. **c** For a biologic product produced using biotechnology processes, the relationship between the process parameters and the structure is only partially determined. Unexpected outcomes are always within the realm of possibility when process inputs (raw materials, procedures, and controls) shift slightly away from their historical ranges. It is not possible to model, measure, or characterize all process inputs or structural attributes. Furthermore, routine quality tests cannot unambiguously confirm that a biologic's structure remains within historical ranges. Shifts in a structure may go undetected, and these have unknown impact on the product's function (safety and efficacy profile)

scientists to understand how manufacturing conditions might impact the quality of biologics. For example, changes in the quality of the raw materials, temperature, or pH may modify the product's purity or potency in an unexpected manner, modifications that cannot be reliably predicted by protein scientists and engineers.

The distinction between biologics and small molecules is further compounded by the differing capabilities of quality control tests used to determine their identity, quality, and purity. For chemically synthesized active ingredients, these attributes can be established with a small set of analytical tests. Because of the structural complexities of biologics, many of their attributes cannot be comprehensively measured with routine tests, which may not be able to detect atypical product variants or impurities that might unexpectedly appear in a product batch. Product quality cannot

be confirmed through routine testing, but instead must be inferred from the totality of manufacturing data. Thus, well-characterized and robust processes are needed to ensure that biologics are manufactured reproducibly.

The sensitivity of biologics to processing conditions and the difficulty in anticipating or measuring the relationships between inputs (raw materials, procedures, and controls) and product quality can be illustrated by four case studies, described below. The first two concern unexpected impacts of subtle changes in cell culture conditions, and the second two concern unexpected interactions of biologics with their primary containers.

## 2.1 Case Study 1: Changes in Cell Culture Aeration Conditions Can Affect Product Carbohydrate Structure

While seeking to improve the yields of a recombinant human erythropoietin (rHuEPO, epoetin alfa) at Amgen in 1991, process conditions were adjusted to increase the oxygen supply and to improve the removal of $CO_2$ from the cell culture medium (Fig. 4). The test batches had improved yield with consistent product quality as determined by routine quality control tests. However, routine tests are not sufficient to characterize epoetin alfa, which contains protein modifications that include complex mixtures of carbohydrates attached to the erythropoietin protein backbone [7]. Sophisticated mapping techniques were utilized to compare the identities and quantities of the carbohydrates on epoetin alfa before and after the process change (pre-change versus post-change). An increase in the level of a modified sialic acid, *N*-glycolylneuraminic acid (NGNA), was detected in the post-change epoetin alfa.

Although sialic acid is critical to the bioavailability and potency of erythropoietin [8], NGNA is not normally made by human cells and is found only at trace levels in human glycoproteins [9]. Therefore, the increased level of NGNA was an unexpected and undesirable change in the test batches. After thorough investigation of this unexpected event, it was determined that reducing the level of dissolved carbon dioxide in the cell culture medium had

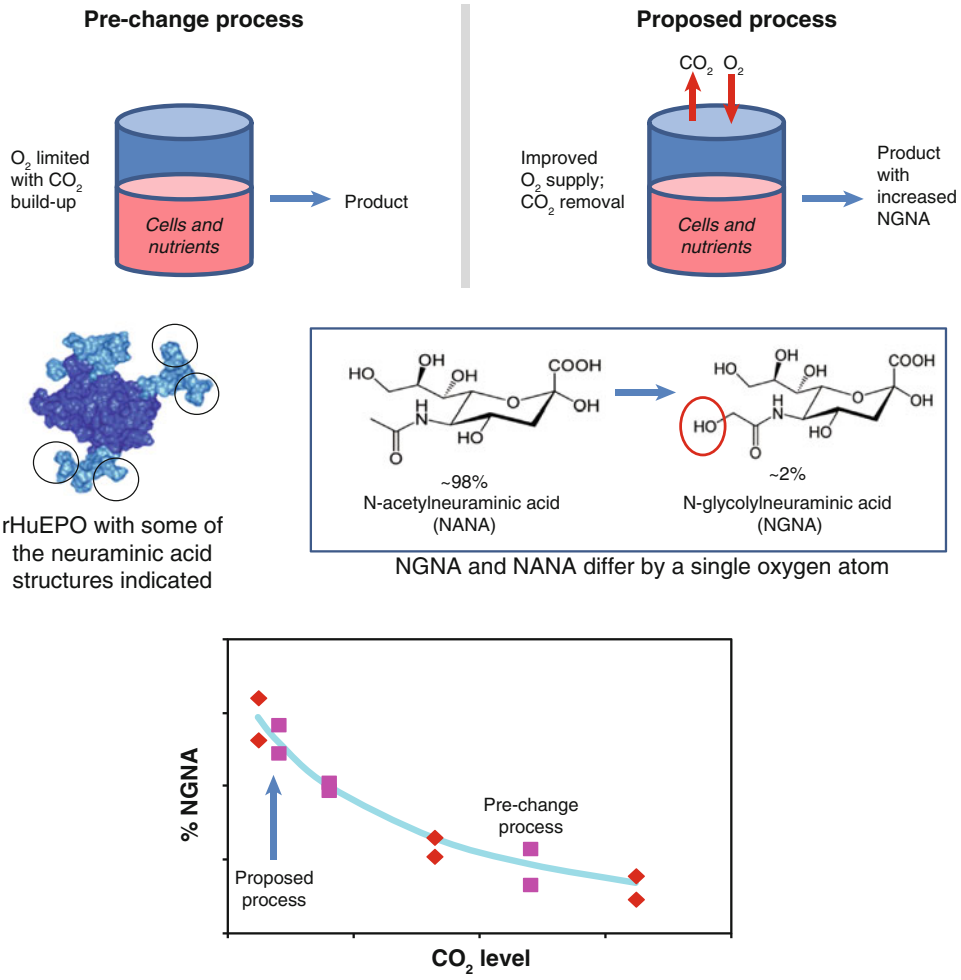



**Fig. 4** A minor change was proposed for the biological production step of recombinant human erythropoietin (rHuEPO), improving oxygen supply and $CO_2$ removal. The resulting product was comparable to the pre-change product with the exception of a slight increase in the level of NGNA. NGNA is a variant of *N*-acetylneuraminic acid (NANA), an important active component of the carbohydrate side chains of rHuEPO. NGNA and NANA differ by only a single oxygen atom, but this difference could potentially be recognized by the human immune system. Subsequent controlled experiments showed that the reduced $CO_2$ was responsible for shifting the cell physiology towards a higher level of NGNA. The process was modified to improve oxygen supply while restoring $CO_2$ to original levels so that NGNA would remain within historical trends

promoted an increase in the level of NGNA. Although there were no known safety issues associated with NGNA in recombinant therapeutic proteins, increased levels could potentially be immunogenic in humans [10]. Therefore, the process was reengineered to restore the original levels of carbon dioxide and maintain NGNA within the range of the pre-change process.

### 2.2 Case Study 2: Changes in Raw Materials Can Alter the Product Charge Profile

An unexpected shift in product profile occurred after the transfer of a manufacturing process for a monoclonal antibody from one facility to another. The scale of production was not altered; therefore, there were no changes in the size of equipment or associated processes, and there were no changes to critical operating conditions, which, if changed, potentially present additional evaluations with respect to quality. Nevertheless, test batches from the new facility exhibited a shift in the product profile with an increase in the level of the predominant product species and a decrease in the level of a minor, more positively charged product variant (Fig. 5). These changes were due to a decrease in the levels of an amino acid, amidated proline (aP), at the C-terminus of the protein sequence—the negatively charged glycine at the C-terminus of a protein can be converted by cellular enzymes to uncharged aP [11], making the protein more positively charged. While the shift in product profile was within the historical experience for the product and was presumed to have no relevance to safety or efficacy, it was nonetheless unexpected. Therefore, an in-depth root cause analysis was performed. The investigation started with any known minor differences in procedures or operating conditions in the new facility, even if they were considered unlikely to impact product quality. Once these factors were ruled out, the focus narrowed to potential differences in raw material batches.

Laboratory experiments on raw material batches used in the new facility reproduced the unexpected results. It was discovered that one of the raw materials contained lower

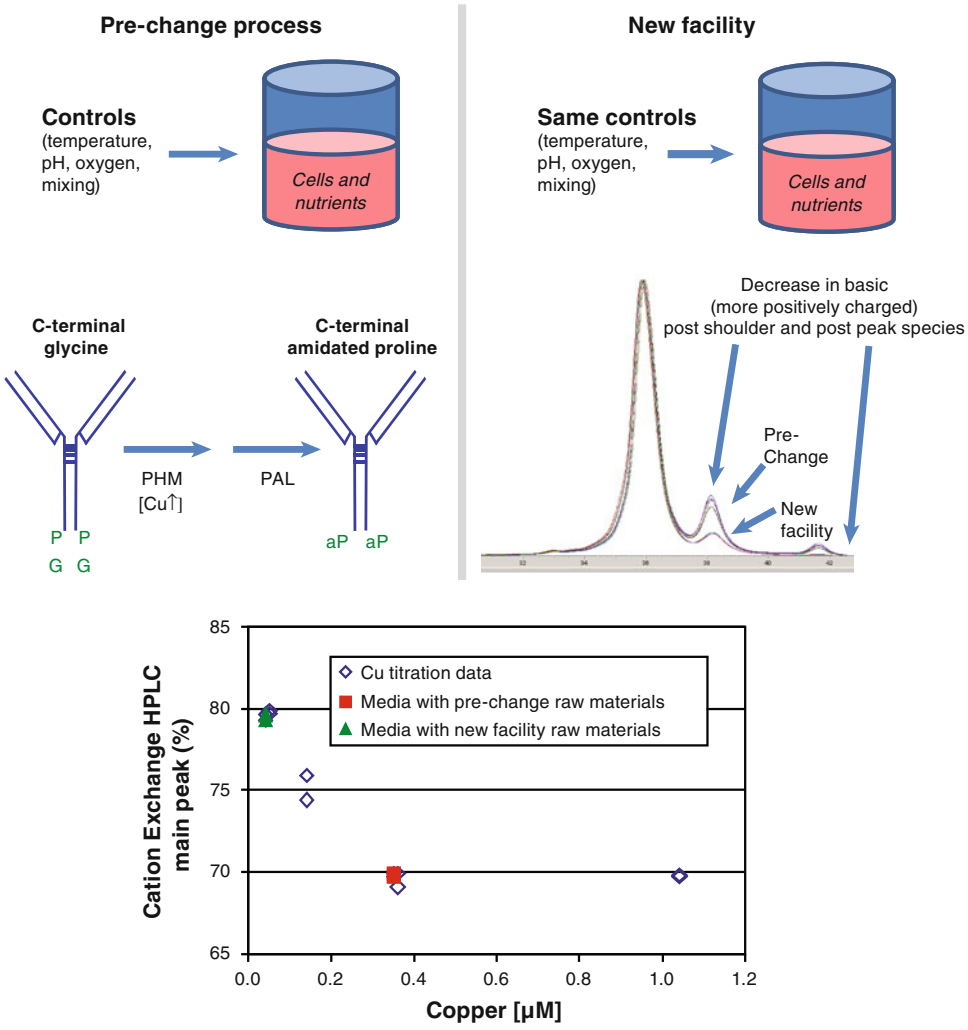



**Fig. 5** The manufacturing process for a monoclonal antibody was transferred to a new facility. The bioreactor step was at a similar scale, and critical control parameters were unchanged, but a shift in the charge profile of the product was observed. Further investigation showed that the product in the new facility had lower levels of a more positively charged variant terminating in aP and higher levels of the more negatively charged major species ending in glycine (PG). The conversion of the terminal glycine to amidated proline requires two enzymes, PHM and PAL. PHM has copper as a critical co-factor for its active site. Measurements of the raw material batches in the new facility showed that they had lower trace levels of copper, and controlled experiments confirmed that the charge profile of the monoclonal antibody was dependent on the level of copper in the process

trace levels of a copper-containing impurity than historical raw material batches. A literature search led to further experiments demonstrating that the lower levels of copper in the cell culture medium inhibited a copper-dependent cellular enzyme responsible for proline amidation. The potential impact of modified proline levels was evaluated by performing non-clinical and clinical pharmacology studies, and it was concluded that the product made in the new facility had the same potency and bioavailability as the pre-change product. On the basis of these findings, the raw material supply was ultimately harmonized to specify a more consistent level of copper impurities.

### 2.3 Case Study 3 and Case Study 4: Interactions of Drug Product Container with a Biologic Can Increase Immunogenicity

In recent years, two recombinant human erythropoietin products used to treat European patients with chronic renal insufficiency resulted in an unexpectedly high incidence of neutralizing antibodies against human erythropoietin. In some patients, these neutralizing antibodies progressed to a severe autoimmune syndrome known as pure red cell aplasia (PRCA). In PRCA, the immune system neutralizes the activity of any endogenous or therapeutic erythropoietins and renders patients transfusion-dependent for a period of time.

Case study 3 occurred between 1998 and 2003. An approved change in the drug product formulation for a marketed recombinant human erythropoietin, Eprex® (epoetin alfa), was correlated with a 10- to 20-fold increase in the incidence of PRCA in some patients receiving subcutaneous epoetin alfa [12]. The manufacturer, Janssen, performed a root cause investigation to evaluate the role of the drug substance manufacture, the formulation, the container, and product handling practices. The probable root cause was ultimately attributed to an interaction between epoetin alfa and the drug product container, among other potential hypotheses including multifactorial causation. Concurrent with investigating the root cause, Janssen had improved the container quality, and the incidence of PRCA returned to historical levels [12].

Case study 4 occurred in 2009. A clinical trial of the European Medicines Agency (EMA)-approved biosimilar HX575 (epoetin alfa) being studied for label expansion to the subcutaneous route of administration resulted in neutralizing antibodies in two of 174 patients treated with HX575, with one confirmed case of PRCA [13]. The manufacturer, Sandoz, evaluated product quality in the relevant batches and identified individual pre-filled syringes with elevated levels of aggregated protein. As aggregated protein was considered a likely contributor to immunogenicity, the root cause investigation focused on parameters that could result in variable aggregate levels. Shipping and handling as well as chemicals that had leached from the drug product container were evaluated; Sandoz ultimately traced the issue to the interaction of epoetin alfa with tungsten residuals from the drug product container [14]. The manufacturer of the syringes subsequently converted to low-tungsten components [14].

In both examples, neither routine quality control tests nor additional analytical testing required for regulatory approvals of the respective drug products was sufficient to detect the underlying product quality issues. Only after actively monitoring for and ultimately receiving unexpected safety signals could the companies embark on the exhaustive investigations that ultimately revealed the root causes and appropriate mitigations to improve product quality and safety.

### 2.4 Case Study Summary

In conclusion, three factors, namely (1) complex and sensitive molecular structures, (2) incomplete knowledge of process chemistry, and (3) inability to confirm all aspects of product quality with routine tests, leave a gap in quality assurance of biologic products that can best be filled by an HRO. An alert, experienced, and accountable team is essential to detecting the unexpected, and in many instances can detect, investigate, and mitigate product quality issues before the product is distributed to patients. Occasionally, the unexpected may manifest as a safety signal, and in such cases it is even more important for the manufacturer to be alert, dismiss the easy explanations, defer to experts, and strive for robust solutions to mitigate harm to patients or a disruption of supply of critical medicines.

## 3 Biologics Manufacturing Requires Robust Design, Rigorous Testing, Continuous Monitoring, and Risk Management

Manufacturers can use several approaches to mitigate risks inherent in biologics manufacturing. These include risk-based process design (also known as Quality by Design), rigorous process qualification studies, and ongoing quality risk management. Biologics manufacturers are expected to apply these approaches according to international regulatory guidelines; however, their appropriate application requires experience, discipline, and committed management support.

### 3.1 Quality by Design

Many product quality risks can be anticipated and mitigated at the process design stage. Using Quality by Design concepts, a biologics manufacturer should identify the

critical attributes of a product with potential impact on safety or efficacy, establish Quality Target Product Profiles (QTPPs), and then assess the process inputs most likely to impact these attributes. For example, given the association between protein aggregation and increased risk of immunogenicity [15, 16], QTPPs are typically selected to permit only trace levels of aggregation, and manufacturers carefully study the robustness of various process steps known to impact the formation and removal of aggregates.

### 3.2 Qualification Studies (Process Validation)

Process characterization studies are performed to select and confirm operating conditions (e.g., components of the cell growth medium, temperature, and pH) that provide for a robust and reproducible process. The final operating conditions should allow for any minor excursions that occur in a manufacturing environment and are selected to prevent process failure, even at the sacrifice of a potentially higher product yield.

Qualification of the manufacturing process, also referred to as process validation, is required as an element of Current Good Manufacturing Practice (cGMP), and typically consists of process characterization studies combined with at-scale consistency runs in the manufacturing facility. This data package is submitted to regulatory agencies to permit licensing of the new manufacturing process.

### 3.3 Quality Risk Management

Mitigation of quality risks does not end with licensure. Manufacturers are required to assess the ongoing risks to quality or supply in order to identify potential failures within their complex process and supply chain. They must also continuously monitor their process and product data for signals that could indicate a departure from the normal state of control. Continuous evaluation of monitoring data should also drive opportunities for process improvements. This cycle of monitoring, risk assessment, and continuous improvement is a critical element of quality risk management.

## 4 Biologics Manufacturing Requires Alert and Accountable Manufacturing Teams Partnered with Experienced and Accessible Technical Support

Even with a well-designed manufacturing process and with a comprehensive monitoring program in place, there remains a need for manufacturers to maintain teams in place that can detect, understand, and react to unexpected outcomes from the manufacturing floor, the quality control laboratories, and other sources.

### 4.1 Detecting Unexpected Outcomes

Biologics manufacturing occurs in a complex environment that must integrate data from multiple sources spanning a considerable length of time. The totality of data associated with a product batch ranges from equipment-maintenance and raw-materials-testing data that can predate the batch manufacture by months, to product-stability and customer-complaint data that are collected many months after a batch is manufactured. Data collected during the manufacturing process can include thousands of data points.

Manufacturers should be prepared to identify and respond to signals of potential problems, including deviations from procedure or excursions from normal data trends. An HRO is sensitive to these signals, and can reliably triage them according to their potential impact on product quality without bringing the manufacturing enterprise to a standstill. It is critical that staff are trained to be alert to the unexpected so that they can document and report observations in a timely manner. Management should encourage and reward science-based evaluations of unexpected results, and strike the appropriate balance between meeting supply, scheduling, and cost targets while encouraging appropriate escalation and in-depth investigation of potentially serious issues.

### 4.2 Understanding and Reacting to Unexpected Outcomes

When an unexpected event is identified for further investigation, it is often necessary to engage experienced technical support staff of scientists, engineers, and product quality experts. An HRO will ensure that technical support staff are familiar with the product's history, the current manufacturing environment, and with any analogous situations that may have been encountered within the company and among industry peers. They should be empowered to lead a scientific investigation that includes the manufacturing floor, in-house laboratories, suppliers, and external consultants and forensic services, as needed. Management support of the investigation plan is critical for a thorough and open-minded investigation, while limiting the line of questioning to those topics most relevant to understanding the root cause and corrective actions for the unexpected event. Once a root cause is identified, management should identify and implement appropriate corrective and preventative measures to ensure consistent product supply and quality.

Three case studies illustrate the means by which manufacturing organizations detect, evaluate, and react to unexpected outcomes.

### 4.3 Case Study 5: Identification of a Tungsten Residual

Some years ago it was noted that a small, but statistically significant, number of final product units of a marketed Amgen biologic were being rejected during the visual inspection step conducted prior to batch release. Specifically, a few product syringes from certain product lots were rejected because of a cloudy appearance. The frequency of rejection exceeded normal trends for the facility, so further investigation was warranted.

After eliminating the possibility of equipment or procedural issues, the investigation focused on forensic analyses of particles in the turbid syringes. A tungsten residual associated with the particles was detected, and its source was traced to the tungsten pins typically used in the syringe manufacturing processes. The phenomenon was reproduced through controlled tungsten spiking experiments in formulated product. The investigation culminated in a collaborative evaluation with the syringe supplier, and the implementation of new controls to reduce and control the residual tungsten levels in syringe lots. Very little had been previously published about this phenomenon; therefore, the findings were published to make regulators and industry peers aware of the unexpected sensitivity of protein to tungsten [17]. In addition, the potential impact of tungsten on other Amgen biologics was evaluated. While no other products exhibited the same level of sensitivity to tungsten, the quality of syringes for those products was also improved as a precautionary measure.

### 4.4 Case Study 6: Impurity in Raw Material

An impurity that was tracked in the stability program for a marketed Amgen pegylated protein product was observed to increase to higher-than-expected levels after several months of storage. While the product was still within approved specifications for purity, this observation required additional investigation to determine the impact on the expected shelf life of the product and to determine the root cause and any potential impact on other batches. After additional testing confirmed the observation, a technical team performed rigorous analytical characterization of the product batch and identified a previously uncharacterized product variant, which was traced to an impurity in the mPEG aldehyde raw material [18]. The team worked with the mPEG-acetal aldehyde supplier to identify the source of the impurity and to implement preventative measures in the raw material manufacturing and quality assurance. The investigation was managed without disrupting the supply of commercial product, and the scientific findings were published so that regulators and industry peers could be made aware of the previously unknown risk to the quality of pegylated products [18].

### 4.5 Case Study 7: Contamination in Cell Growth Medium

Because mammalian cell culture processes can involve a month or more of cell cultivation in rich growth media, they are very susceptible to microbial contamination. Owing to modern facility design and control, such contaminations are very rare, but when they do occur, they are typically easy to detect through a number of indicators including direct impact on the culture performance and microbiological testing. If detected early, contamination can be contained to minimize impact on product supply. However, this detection and investigation paradigm can fail if the microorganism grows slowly, does not impact the culture performance, and is not detected with typical microbiology tests.

In 2011, manufacturing staff at Genentech encountered just such an organism, *Leptospira* sp., in the early culture steps of a production batch [19]. The *Leptospira* was detected only because the process monitoring program included a microscopic examination of the production cells. Although the microorganism was detected microscopically, it could not be cultured in traditional agar medium. The company engaged experts to look past the simple explanations for the unexpected contamination. The organism was eventually identified using DNA sequencing techniques, and the company devised more sensitive tests to permit earlier detection in case of future events. Indeed, when a second contamination event was detected a few months later, the company was able to investigate the root cause. Although the ultimate source of the organism was not discovered, the investigators learned that it could breach the sterile filtration barrier used to prepare the growth medium. Genentech shared its findings with industry and regulators so that appropriate measures could be implemented and supply disruptions prevented [19].

These case studies illustrate how manufacturing organizations must be sensitive to failure, push the investigation beyond the simple explanations, engage and defer to experts, and take steps to ensure a more resilient operation. These attributes are critical to ensuring a consistent supply of high-quality biologic medicines.

## 5 Publically Available Information About High-Reliability Biologics Manufacturers

The initial licensure and ongoing approval to distribute pharmaceuticals, including biologics, are subject to regulatory oversight of the manufacturing facilities and processes. This oversight can provide important signals regarding a manufacturer's readiness for reliable operations. The licensure process for a biologic includes a pre-approval inspection by the regulatory agency, whereby

inspectors with expertise in manufacturing visit the manufacturing facility and the laboratories used to test the product. This step also requires manufacturers to assure regulators that appropriate "quality systems" are in place to consistently manufacture high-quality pharmaceutical products [20]. Licensure to manufacture is granted after the agency deems minimum requirements are met. Subsequent to the licensure, the manufacturer is expected to ensure that quality systems can maintain the original standards and to enhance them as necessary to stay current with evolving regulatory expectations. These standards are commonly referred to as cGMP and Current Good Documentation Practice (cGDP). The regulatory agents periodically visit the facility (e.g., once every 2 years) to evaluate whether or not the facility is meeting current standards.

A key distinguishing factor between high-reliability manufacturers and others is the effectiveness of their quality systems, which are largely invisible to patients and healthcare providers. Regulatory agencies do not publically laud manufacturers with excellent quality systems, although the FDA is now considering a mechanism to do so [5]. Unfortunately, patients and healthcare providers usually gain insight into the relative capabilities of biologics manufacturers via drug recalls and shortages driven either by regulatory actions or by voluntary recognition of a manufacturing problem. Companies may issue press releases regarding measures that result in product recalls, delays in facility commissioning, or delays in product approvals related to manufacturing issues. Other public sources of information about manufacturing reliability may not be as visible, but the FDA does publish information about significant observations and warnings resulting from periodic compliance inspections. An awareness of these publications can supplement healthcare providers' awareness of manufacturing reliability. These undesirable actions fall into three categories of increasing severity.

### 5.1 FDA Form 483

FDA Form 483 notifies a company of objectionable conditions or practices discovered after an inspection that may violate the Food, Drug, and Cosmetic Act and related acts. The conditions or practices would indicate that a drug or device has been or may become adulterated or rendered injurious to health [21].

Companies are responsible to take corrective action to address the objectionable conditions. Some examples of observations in Form 483 include inadequate investigations, inadequate validation, inadequate procedures to perform operations, inadequate change control system, inadequate or lack of quality management oversight and/or quality systems, not following written procedure, and concerns with data integrity [22].

### 5.2 Warning Letter and Untitled Letter

The FDA sends a company a Warning Letter when it finds that the company has significantly violated FDA regulations. The Warning Letter identifies the violation and provides directions and a time frame for the company to inform the FDA of its corrective actions [23, 24]. A Warning Letter is one of the FDA's principal means of achieving prompt voluntary compliance with cGMP. Examples of typical language in the warning letter include the following: "failure to identify root cause," "failure of the licensed manufacturer to promptly notify the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research (CBER), of errors and accidents in the manufacture of products that may affect the safety, purity, or potency of any product…," "failure to notify the FDA prior to implementing manufacturing changes," and "failure to follow written procedures" [25].

The FDA may issue an Untitled Letter, which cites violations that do not meet the threshold for issuance of a Warning Letter. An Untitled Letter differs from a Warning Letter in that it does not include a warning statement that failure to take prompt correction may result in enforcement action, it does not evoke a mandated district follow-up, and it requests (rather than requires) a written response from the company within a reasonable amount of time [23].

### 5.3 Consent Decree

Upon repeated cGMP violations, the FDA may impose a legal agreement with the company to force them to make specific changes; this agreement, the Consent Decree, is enforced by the federal courts. Usually, Consent Decrees include fines, reimbursements to the government for inspection costs, due dates for specific actions, and penalties for noncompliance. An example of language from a Consent Decree is as follows: "Because this company continued to violate current good manufacturing practice regulations and falsify information on drug applications, the FDA took these actions in an effort to protect consumers" [26].

These escalating compliance enforcement mechanisms are visible via the Gold Sheet and other publically available sources. The absence of recent citations for serious Form 483 observations, Warning Letters, or other enforcement actions does not prove that a manufacturer is successfully managing the unexpected but may be useful supportive information. It should be noted that even manufacturers with the best quality systems can encounter occasional issues during the inspection; however, the frequency of violations and the severity of such violations are discerning indicators of regulatory compliance.

### 5.4 License Revocation or Suspension

Willful noncompliance or a current history of repeated or continuous violations may result in the revocation or suspension of a license according to Section 351(a) of the Public Health Service Act PHS Act. Revocation results in the cancellation of a license and withdrawal of marketing authorization either by the FDA or at the request of the manufacturer. Suspension may be an initial or intermediate step in the revocation process and provides for the immediate withdrawal of marketing authorization when grounds for revocation exist and there is a danger to health [27].

## 6 Conclusions

Because of their complexity and the difficulties in fully characterizing their manufacturing processes, biologics are inherently more vulnerable than small molecules to unexpected changes in their quality. Risks can be partially mitigated with disciplined process design and qualification studies, informed by quality risk management concepts. However, these measures cannot account for all sources of variability potentially associated with dozens of raw materials, hundreds of operating parameters, and dozens of manufacturing steps. Therefore, HROs invest in continuous monitoring, learning, and improvement to ensure the resilience of their operations. In the context of worldwide drug shortages and their impact on healthcare, providers may gain awareness of the capabilities and commitment of biologics manufacturers through publications, public information about regulatory observations and actions, and through other evidence about the reliability of supply.

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