

Biopharmaceutical Quality Assurance

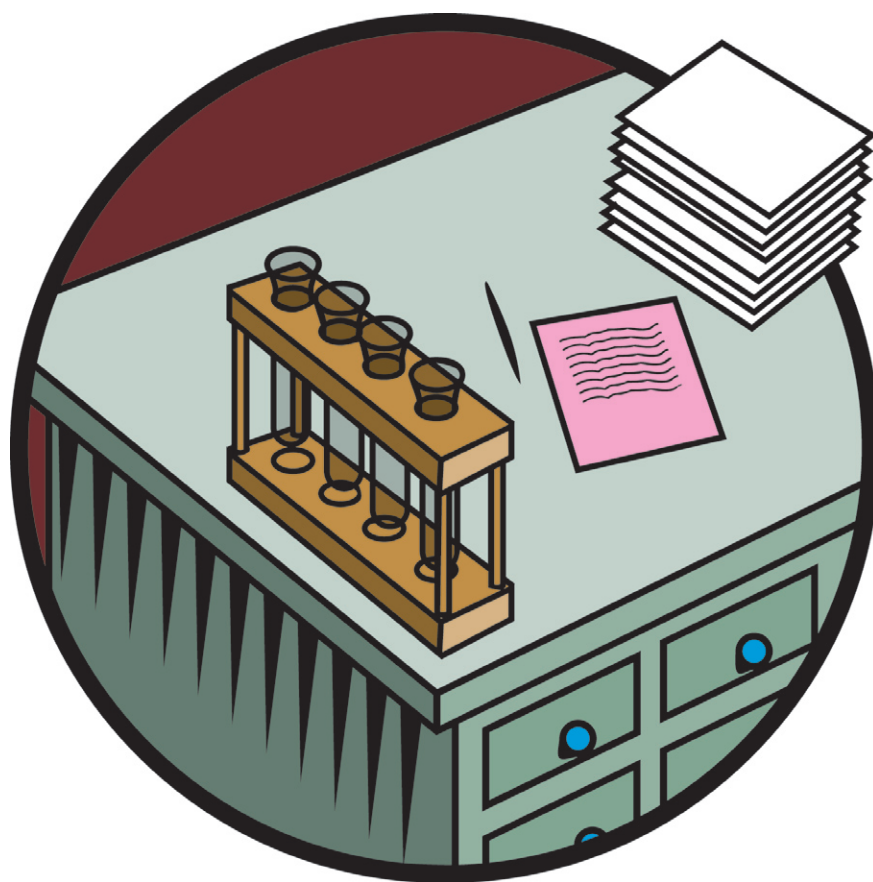
An Overview for Companies That Outsource

by Paul Stockbridge

The basic concepts and reasons for quality assurance (QA) in biotechnology are, of course, the same as for the manufacture of any other medicinal product or device: to assure the safety of the patient. So, what's different about biotechnology?

The variety of products is vast — from well characterized proteins in production for the past couple of decades, to cell based products, genetically modified oncolytic viruses, viral gene vectors — and many more, with new innovations almost daily. Although their variety is vast, all are incredibly complex, potentially difficult to define by analysis alone (with the exception of certain well characterized proteins), and highly potent. Additionally, “things” potentially can grow in the process stream releasing unknown metabolites, or on the product itself causing molecular abnormalities that you didn't even know were possible, let alone how to test for.

Furthermore, most of these products cannot be terminally sterilized, some cannot be filter sterilized without dramatic loss of potency, and some cannot be sterilized by any method whatsoever (because they are live cells) and thus require full aseptic manufacture from cell bank to dosage form. If that isn't enough, many of them require storage below -20°C (often -80°C or below) and can be critically affected by freeze-thaw



events, giving new meaning to the term “cold chain” and placing further stresses on packaging and labeling technologies.

I nearly forgot to mention that many of the producing organisms (and for live products, the products themselves) are genetically modified and come under requirements for containment, giving another dimension to their manufacture and

distribution. In addition, if you are a qualified person (QP) involved in the manufacture of investigational biotechnology products, you may be releasing them for first-in-man trials. (A QP, under UK regulations based on European Union directives, is a quality assurance professional for medicines who ensures that every batch released to the market complies with its

specification and has been made according to GMPs.) The bottom line is that QA in the manufacture of biotechnology products is one of the most interesting, challenging, and exciting in the industry.

I aim here to give a flavor of the challenges facing the implementation of CGMP quality systems in biotech manufacture, to highlight the thought processes required, and suggest ways of approaching the subject when seeking a contract manufacturer.

REGULATIONS, RULES, AND GUIDANCE

There are, of course, many sources of regulations, rules, and guidance regarding the manufacture of biotech products. It is beyond the scope of this article to review them in depth. Apart from the fact that such a review would fill a very large book, not all the guidelines are applicable to every type of product, and for some types of novel product there are no regulatory guidelines that adequately cover the required operations. That is a particular challenge for novel investigational medicinal products (IMPs). The most important and widely used references are listed in the “Widely Used Guidances” box.

So, what are the challenges, and how do we approach the implementation of quality assurance in practice? I believe the challenges and their solutions reside in people, premises, equipment, products and processes, procedures, and product release.

PEOPLE

There is no more important element in the manufacturing of pharmaceuticals than the people involved, and that includes all staff at all levels and in all functions. So what’s different about biotechnology? All staff involved in the manufacture, testing, QA, release, warehousing, logistics, and materials management must be aware of the special nature of these products and the materials used to manufacture them. Staff members

QA BEFORE YOU OUTSOURCE: TEN QUESTIONS TO ASK A CMO

- 1: Licensing.** Does the provider need a license for the proposed work, and if so, does it have one already?
- 2: Inspections.** Is the provider regularly inspected by a regulatory agency or certified body?
- 3: Adequate Facilities.** Are the provider’s facilities designed and constructed to meet relevant regulatory, health, and safety requirements?
- 4: Current Facilities.** Will your process fit into the provider’s existing facilities?
- 5: Subcontracting.** Can the provider meet all your process needs, or will parts of the process need to be further outsourced? If the latter, can your provider both provide and control such activities to the standards you require?
- 6: Staffing.** Does the provider have an adequate number of appropriately qualified, trained, and experienced employees?
- 7: QA/QC.** Does the provider have an independent quality unit, and can it release products to the clinic or market if required?
- 8: Compatibility.** Does the provider handle materials that are incompatible with your process or that are highly sensitizing?
- 9: Transparency.** Is the provider “transparent” in its operations, communicating with its clients such that the obligations in all technical/quality and commercial agreements will be met or exceeded?
- 10: Management.** Is there an effective project management system in place to ensure that your work is performed to required standards, timelines, and cost?

have to ensure that the products are correctly manufactured and are not adversely affected. Those directly involved in manufacturing operations must be well educated to understand the products they are manufacturing and equally well trained in the manufacturing operations — not just how and what to do, but also why it is being done that way.

Biological manufacturing processes are usually very complex operations with multiple stages. At each stage it is possible to contaminate the product, whether with microbial and/or particulate contaminants. People directly involved usually have to wear cleanroom clothing and follow cleanroom practices throughout the whole manufacturing process. It is therefore essential that staff members are capable of gowning satisfactorily and maintain scrupulous attention to detail not only in what they do, but the way in which they do it.

There is no getting away from it — the gowning and rigorous attention to procedures and operating conditions can be unpleasant for manufacturing staff.

It is essential that they fully understand the whys to maintain the right attitude toward what they are doing — especially at 2:00 AM on a cold, wet, February day.

PREMISES

All premises used for the manufacture and testing of biotechnology products must be constructed, validated, cleaned, classified, and maintained to ensure that products are adequately protected from the environment and thus from all forms of contamination — both microbial and chemical. Because many products and process streams are highly potent, contain (or actually are) genetically modified or highly potent organisms, the premises must also protect people and the environment from the product itself — seemingly conflicting requirements. Ensuring such protections requires careful design of cleanroom pressures and air flows, material flows (raw, product, and waste), people flows, and also the use of special biological safety cabinets or isolator technology.

Some products consist of inactivated (or killed) organisms.

WIDELY USED GUIDANCES FOR BIOTECHNOLOGY MANUFACTURE

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) quality guidelines (especially *Quality of Biotechnology Products Q5A-D*) www.ich.org/cache/compo/363-272-1.html

Eudralex: The Rules Governing Medicinal Products in the European Union (<http://ec.europa.eu/enterprise/pharmaceuticals/eudralex>), especially the following:

- Volume 3, *Medicinal Products for Human Use: Guidelines*
- Volume 4, *Good Manufacturing Practice, Medicines for Human and Veterinary Use* (with special emphasis on Annex 1, Manufacture of Sterile Medicinal Products, and Annex 2, Manufacture of Biological Medicinal Products for Human Use)
- Part II, *Basic Requirements for Active Substances Used as Starting Materials* (with particular emphasis on Chapter 18, specific guidance for APIs manufactured by fermentation or cell culture)

US FDA *Code of Federal Regulations*, Title 21, Parts 210, 211, and especially 600 (www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=600&showFR=1)

EU and national pharmacopoeias for specific products and general analytical testing requirements

The related premises, people, and material flows must ensure that it is impossible for such products to be contaminated with the producing organism after the validated inactivation stage. All premises where the product might be exposed have to be designed for rigorous cleaning procedures, including disinfectants capable of inactivating both environmental contaminants and the product itself. If the product is itself a live organism, the premises must be able to withstand fumigation with vaporized hydrogen peroxide or equivalent. This is particularly important with viral products because it is very difficult to test for their absence by traditional swabbing methods. Multiproduct facilities add another complex layer to all the above, but success is achievable.

EQUIPMENT

As with all pharmaceutical manufacture, equipment used must be validated, maintained, and calibrated to ensure its fitness for purpose and operational reliability. Although the subject of validation is well outside the scope of this article (there are journals and even institutes dedicated to the subject), it is worthwhile to point out some differences with biotech equipment, which has its own special complexities.

Most biotech processes start with the cultivation of live organisms. This involves equipment as diverse as Petri dishes, roller bottles, cell factories, and complex fermentation systems involving computer controlled stainless steel bioreactors or increasingly, disposable bioreactors with equally complex control systems. Not only is it essential to validate a system's ability to operate within defined process operating parameters, but it's also essential to ensure that it presents a barrier to the ingress of adventitious organisms (and escape of the producing organism into the environment). That requires an intricate validation process involving temperature mapping of the

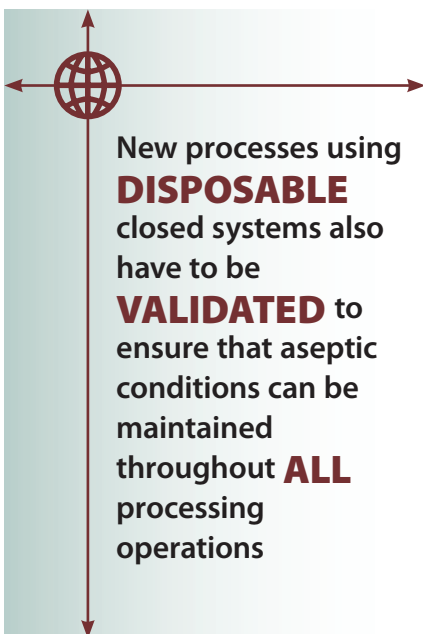
sterilization process together with the use of media holds to demonstrate that sterilization techniques are effective — both of which have to be done regularly. Cleaning validation is an equally complex subject. You cannot rely on normal product analysis because the product may not be in its final form at this stage. Even if it is, it will be swamped with media and constituents from the producing organism. Using the normal 1/1,000 dose in the daily dose of the next compound isn't a realistic option here, so limits must be set and justified.

Downstream processing equipment is equally complicated. It frequently involves equipment for the following:

- extracting compounds from the organism using various lysis equipment or high pressure homogenizers
- centrifugation to clarify process streams (and occasionally to purify products such as viruses using differential centrifugation)
- large-scale chromatography systems (which are sometimes extremely large — 2m diameter columns and 2m high HPLC columns) for product purification, together with their feed, control, and detection systems.

All of those have to be validated, not only for their operational performance, but also for sterilization procedures because process streams have to remain essentially free from microbial contamination. In addition to the reasons mentioned in the introduction, sterilization is necessary to ensure that filters used for final product sterile filtration do not exceed their validated retention capabilities.

Live cell, microbial, and viral products intended for injection have to be produced by aseptic processes. That can be achieved using open processing under appropriate conditions. However, new processes using disposable closed systems are under development. Those also have to be validated to ensure that aseptic



conditions can be maintained throughout all processing operations, and that may involve validation of everything from the gamma irradiation of the assemblies, to media hold simulations of the process.

Biotech product filling is another interesting area. Although it is perfectly possible to use conventional open filling techniques, the need to contain some products requires using biocontainment cabinets, which limits the volumes that can be filled. Biotech product filtration can also cause problems. Many products, particularly those of high molecular weight, can exhibit considerable losses or be structurally damaged during filtration; they may also be unstable in liquid form. Such factors have to be taken into consideration when planning fill process validation.

Using isolator technology for filling products is becoming more common. But this in itself poses new challenges for process validation due to the need to sterilize everything that enters the isolator. All plastics used in the process stream have to be examined to determine what compounds can be extracted by the process stream that flows through them (and which could potentially end up in the product). And I haven't even touched on the final packaging and labeling, which may have to be performed with frozen products and withstand routine storage at temperatures of -80°C .

PRODUCTS AND PROCESSES

The complexity of products and the relative lack of specificity in the related analytical methods have led many regulatory authorities to consider that these products are not only characterized by analytical means, but also by the process (and facility) used to produce them. (Don't forget it's not only the desired product that needs testing, you also have to test for the absence of complex metabolites, host-cell DNA, proteins, and adventitious organisms.)

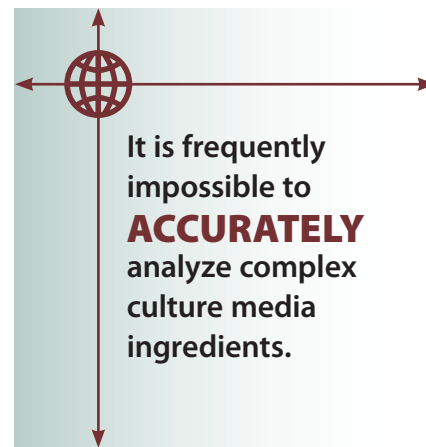
What biotech processes have in common is that they are almost always complex and have a higher level of inherent variability than those used for most synthetic small molecules. No matter what process is used, it is important to ensure that both the process stream and product are adequately protected from the environment, and that usually involves the equipment and premises discussed above. As a result, it is essential to identify realistic, proven, acceptable ranges for all critical parts of the production process — and there may be many — and to put a system in place to ensure that they are reliably achieved in practice. That usually results in large and complex batch manufacturing records that, if not kept simple and to the point (while containing all the information and key data), can be extremely difficult to follow, complete, and review, which highlights the need for effective training.

PROCEDURES

All manufacturing and testing activities must be described in approved procedures and analytical methods. Key quality system procedures must include training, validation, change control, deviations, vendor assurance, and product release. Although all pharmaceutical manufacturing must include these procedures, along with many others, there are special considerations for biotech manufacturing.

Training: I have already discussed this in the "People" section, but it is worth reiterating how important training is for biotech production processes. It's not just the "whats" but also the "whys" that are important. There must also be special emphasis placed on training in at least the basics of microbiology for all who come into contact with process or product so that they can really understand the potential impact their activities can have on the end results and patients.

Validation is essentially a very simple concept that has



unfortunately gained a mystique of its own. Basically, validation consists of the following:

- saying what you are going to do (validation master plan)
- documenting what you actually need (user requirement)
- agreement from all parties that your design is suitable for its intended purpose (design qualification)
- verifying that you have received what you ordered (receipt verification)
- checking that you have connected it correctly (installation qualification)
- showing that each individual piece of equipment works as expected when you turn it on (operational qualification) and
- demonstrating that the whole system or facility works as required when it is connected together and everything is turned on and that its operating characteristics can be traced back to the fundamental user requirements (performance qualification).

Although the basic concept is simple, validation is exceptionally complex in practice for a biotech production system — and don't forget that it all has to be properly documented.

Process validation is similar to that used in the manufacture of many other pharmaceuticals — except that there may be many more complex stages and critical parameters to identify, control, and monitor.

Change Control: Even a very small change in the equipment or

A CONTRACTUAL PERSPECTIVE: HOW TO ENSURE QUALITY?

In February 2006, in a BPI article titled "The Critical Role of Bioprocessing Contracts: Defining Your Rights, Obligations, and Liabilities," British author Simon Portman offered the following advice regarding how liability should be handled in outsourcing contracts.

"Both customers and process developers can incur significant liabilities if anything goes wrong with their arrangements, and they will want contractual protection. For example developers want to ensure that supplied products conform to agreed specifications and are accompanied by all relevant information relating to toxicity, safe-handling, and use. They also want their customers to supply all necessary advice, assistance, and cooperation while projects are under way. Conversely, customers want warranties that processes will meet agreed-on standards regarding manufacturing efficacy and efficiency and can be used in the future with no breach of legal or regulatory requirements.

"As I mentioned, processes can end up making customers a lot of money. Such sums are likely to far outstrip those initially paid to have those processes developed. The flip side is that if a process is defective in any way or noncompliant with any relevant regulations, product manufacture could be held up while things are put right, and a customer's liability in terms of lost revenue could be extensive. Even more worrying, a defective process could make defective product that might harm patients, who would then look to the customer for compensation. Any such defect is ultimately the fault of the process developer, and the customer will therefore want to be indemnified by the developer against such loss. Under such an indemnity, a developer would be obliged to stand in the place of the customer and foot the bill for any damages or

compensation that the customer might have to pay as a result of any such liability.

"In such circumstances, developers want to avoid being liable for an entire amount. They may argue that because customers derive the most benefit from commercialization of their products, those customers should bear most of the risks. In any case, large pharmaceutical companies are better placed in terms of resources to meet such liabilities and will most probably have insurance to cover them.

"Developers are therefore well advised to seek to limit their contractual liabilities in two ways. First, they can exclude liabilities for indirect or consequential losses such as losses of business or of profit. Such an exclusion precludes a customer from claiming that a defective process has denied it millions of dollars from product commercialization and expecting its process developer to be responsible for the whole amount. Second, a developer can cap its overall liability under contract at a fixed amount. Ideally, that amount should not exceed sums due to that developer under contract, although its customer might argue that such a limit is unreasonably low given the nature of the potential liability. In some countries, courts of law can set aside clauses in contracts that cap liability at unreasonably low levels. Certainly, a liability limit shouldn't exceed a process developer's insurance coverage. Both parties should agree to a compromise limit somewhere between the two."

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process used for biological manufacture can potentially cause a major difference in the product outcome. Therefore, it is critically important to fully assess the potential impact of any proposed change before it is implemented and assess the outcomes afterward. A minor change to one step of the process can directly affect further processing stages — so a change in a fermentation parameter for example, must be assessed for potential and actual impact on recovery and downstream processing operations.

Don't forget the regulatory submissions either. Make sure that proposed changes fall within the boundaries of the "design space" submitted for the product or that appropriate license variations have been accepted before making the change — or you might find the QP refusing to release the product.

Deviations: I have covered deviations in a previous article (1). The complexity of biotech

production processes can originate many of them if great care is not exercised in the manufacturing activities. And establishing their root causes and preventive actions can be an extremely interesting exercise.

Vendor assurance is another area of complexity for biotech. The raw materials used for biomanufacture can be very complex and not easy to define analytically. It is frequently impossible to accurately analyze complex culture media ingredients relying on the use of near infrared spectra and comparison against spectra libraries. Although it is desirable to use non-animal-derived materials, that may not always be possible, particularly for complex culture media. Where animal-derived materials have to be used, it is essential to ensure that they are sourced from countries certified free from transmissible spongiform encephalopathy (TSE) — and that they really are from those countries. Vendor auditors need specialized

knowledge of biotech regulations and requirements as well as finely honed auditing skills (and frequently a willingness to travel to interesting locations).

PRODUCT RELEASE

And what of the QP? Does any single QP possess sufficient knowledge and experience to cope with the complexities of biotech manufacture and the sometimes specialized fill, finish, packaging, labeling technologies, techniques, and requirements to perform his/her professional responsibilities? Although there are such rare individuals, a process often involves several QPs. Many authorities consider the manufacture of formulated bulk biotech drug substances as "partial manufacture" requiring QP release in its own right. Annex 16 of the EU rules and guidance must be followed when multiple QPs are involved in releasing a product. This guidance states that QPs can rely on the decision or

signature of other QPs as long as a quality agreement is in place between them detailing the requirements and responsibilities of each QP.

MANUFACTURE OF BIOTECH INVESTIGATIONAL PRODUCTS

Investment in the development of new biotech products is rapidly accelerating, leading to a great number of innovative solutions and proposed investigational products. Investigational medicinal product (IMP) production can pose new and very real challenges to GMP. Although the quality systems described here are equally applicable for IMP manufacture, the authorities consider quality assurance even more important here. Because the intrinsic safety of (novel) materials is in some cases totally unknown (particularly for first-in-man trials), the GMP systems used in their manufacture have to be rigorous to ensure that their extrinsic safety is not

compromised, which could compound patient safety issues.

Although compliance with certain aspects of CGMP is a given for IMP manufacture — for example the facilities and equipment must be validated and suitable to protect the product — it is highly unlikely that a manufacturing process will be totally developed. It will progress toward validation only during the manufacture of material for Phase 3 clinical trials. The process will possibly change from one batch to the next as knowledge is gained. Although it is entirely appropriate to raise deviations for departures from approved procedures or failure of validated equipment, this will not work in practice for departures from compliance with the batch manufacturing records. These were written with the best knowledge available at the time, but in practice the process may not quite go that way, and unplanned interventions may be required to keep a product

on track. It is frequently impossible to determine root causes and preventive actions, particularly for the initial manufacture of early phase materials. What is important is that the releasing QP has all production information available to assess potential impact on the safety and quality of the IMP and to ensure that its manufacture is still within the (probably very vague) descriptions in clinical trial authorization submissions. Similarly, the analytical methods used at this stage may be novel, or they may not have been optimized for the particular molecule under manufacture. As such, it may be impossible to set definitive specifications until much more has been learned about the process and analytical methods involved. It is, however, essential that the assays used have a sound scientific rationale to support them and that there is an ongoing dialogue between the company and regulatory reviewers assigned to its product by the competent bodies involved in authorizing the clinical trials.

The innovation, development, and manufacture of biotech medicinal products is a rapidly developing area of pharmaceutical manufacture and special approaches to the quality systems used for their manufacture are required to ensure the safety and quality of this class of products. I hope that this very brief article, although not a definitive guide, will have at least given a flavor of some complexities involved in assuring the quality of biotechnology products, one of the most challenging, interesting, and exciting fields in the industry.

REFERENCE

1 Stockbridge P. Deviations and Failure Investigation. *GMP Review* 6(2) 2007: 4–7.



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