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UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION
Vienna International Centre, P.O. Box 300, 1400 Vienna, Austria
Tel: (+43-1) 26026-0 · www.unido.org · unido@unido.org

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Assuring quality of biopharmaceuticals: A prerequisite to start business and stay in business

Otto Doblhoff-Dier, Rudolf Bliem
Consultant

Regulations are necessary to ensure consumers protection and safety by providing an efficacious, pure, safe and qualitative pharmaceutical product. On the other hand the word "quality assurance" has acquired a threatening ring for many emerging economies and companies . Many organizations see regulations concerning product quality as concealed protective measures benefiting only the developed economies and established companies. This is mainly due to the widespread opinion that ensuring and improving quality in all sectors of industry is normally associated with enormous costs, thus excluding newcomers with limited resources. This seems particularly true for the area of biopharmaceuticals. In this paper the necessity of stringent regulations to improve and ensure quality of a pharmaceutical products derived from biotechnology will be outlined in order to improve the understanding of quality issues. Good Manufacturing Practice (GMP) concepts are reviewed and practical measures presented. GMP thus applied developes into a business asset, not merely a regulatory hurdle.

Regulations: Protectionism or Protection

An ever increasing number of national and international regulations have been and are currently being implemented all around the globe. These regulations are not only valid for the countries in which they were issued, but in the case of foreign companies trying to gain access to these markets, also for these companies, irrespective of their location and the economic status of the country. This is particularly true for the pharmaceutical industry and within this industry for the manufacturing of biopharmaceuticals. Why are regulators so concerned about this special sector of industry and are regulations hampering industrial development? The tight regulations in pharmaceutical industry have become necessary for a number of reasons:

adulteration and misbranding
wide distribution
the production of new drugs with increasingly complex production technology
potency of (bio)pharmaceuticals
stability of (bio)pharmaceuticals
political concern over possible environmental impacts of biopharmaceutical processes (especially those using recombinant DNA technology) and products

These points have to be considered carefully to understand the necessity of stringent regulations concerning the quality of biopharmaceuticals. Most of these points will also apply to both traditional pharmaceuticals (and indeed to many other goods) and biopharmaceuticals.

Adulteration: Adulteration is defined by the statutes of FDA's cGMP guidelines (Current Good Manufacturing Practices) as they were put forth under the Federal Food, Drug, and Cosmetic Act :

> A drug of device shall be deemed to be adulterated if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing or holding do not conform to or

> are not operated or administered on conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

The risk of the endangering consumers health by changing the products quality advertedly or inadvertedly is the foremost concern of all regulating authorities. Therefore any change to the process has to be proven to yield identical product (Kennedy 1995). In the case of modifications to the product characteristics, the resulting new product has to be fully evaluated.

Wide distribution: Due to international commerce an incredible variety of goods is being shipped for use or consumption throughout all of the world. The consumer purchasing one particular product may be located anywhere from within close proximity of the production site to another country thousands of miles away, with a different language, culture, environment and economic status. Products are increasingly manufactured not by diverse manufacturers, but by specialized production sites, in some cases providing supplies to cover large portions of world wide demand. In the event of defective product quality, a great number of individuals could be affected.

Complex production technology: Biopharmaceuticals are in most cases produced at moderate temperatures and pressures, using biocompatible chemicals, thus enhancing process safety for the operator and environment. But due to the complexity of the metabolic pathways and regulation of living organisms, process parameters have to be carefully adjusted and controlled to ensure batch to batch reproducibility. Small variations in these parameters can lead to modifications in the product. However not only the complexity of biosynthesis in the bioreactor has to be taken into account, but also the complex steps in downstream processing, to remove hazardous impurities from the product. Media used for bioprocessing in many cases provide good growth conditions for contaminating organisms, making aseptic and hygienic processing very important. The validation of the necessary equipment and processes have become an art in itself and has been the focus of many publications.

Potency: In many cases the potency of traditional biopharmaceuticals has been overestimated by the public. But in the last few years a number of drugs (e.g. immune modulators, substances with hormone-like action, neuro-active substances etc.) have been produced as biopharmaceuticals, that rival or even surpass traditional chemistry-derived drugs. Special care has to be taken to ensure quality in respect to dosing of such potent drugs. Another concern is the carry over of such drugs into subsequent processes in multifunctional bioprocessing plants. This is especially the case, if the subsequent product is less potent and has to be administered in comparatively high doses (see also equipment validation).

Stability: Biopharmaceuticals are in many cases less stable than chemically derived products. Therefore packaging, storage, transport and distribution are important issues to be dealt with in respect to product quality. Regulatory authorities have undertaken considerable efforts to ensure proper validation of product stability of biopharmaceuticals.

Environmental impact: Safety aspects have always been an issue and much discussed in the area of biotechnological production. Pathogenic species, toxins and allergens were considered to be the main risks associated with the use of biological agents. In classical biotechnology only some special cases, such as the production of vaccines with live pathogens, were considered to be hazardous, as most of the biological agents used in industrial biotechnology had a long history of safe use .

The introduction of genetic engineering has caused much anxiety and the fear of biological agents with unknown pathogenic or other detrimental traits being unwittingly created and released into the environment. These fears have resulted in the implementation of various regulations (e.g. by OECD, NIH, EC) concerning the application, containment and deliberate release of genetically modified organisms(NIH 1986),(OECD 1986),(EC 1990),(EC 1990; EC 1990). Specialized scientific publications such as the book on "Safety in industrial microbiology and Biotechnology" edited by Collins and Beale (Collins and Beale 1990), have recently become available. We are experiencing a new wave of biosafety awareness, and for this reason this chapter is dealing with a "new" aspect of bioprocess engineering although many technological solutions may be more than ten to twenty years old. In many cases gene technology has opened the way for safer products (e.g. vaccines), but as certain dangers could not be excluded, no major change in public opinion seems to be imminent. This is also true for the population in developing countries. At the same time developing nations perceive a big chance to benfit from these technologies, both in agriculture and in the biopharmaceutical industry, with the isolation, characterization and medical application of bioactive substances from e.g. indigenous plants. In all countries there now is a widely accepted concept for the safe handling of biological agents for contained use, that is based upon

-- biological containment (gene construct)
-- Physical containment
-- safe working techniques

Genetic engineers are striving to create different constructs, in order to limit proliferation of biological agents to the defined process areas (e.g. by introducing so called suicide genes). Bioprocess engineering is now called upon to design new low emission equipment or test existing equipment for worker and environmental protection.

If microorganisms are pathogenic to a certain species (e.g. human pathogens), risk assessment is relatively easy. Routes of infection and transmission are mostly well known and therefore safety measures can be tailored to the specific needs. The term environmental risk is a lot more difficult to define and to evaluate, as the scenarios become increasingly hypothetical. On the other hand environmental risk assessment has become one of the central issues for the acceptability of industrial biotechnology using recombinant organisms. The scenario for environmental risks of non-pathogens has been well defined and analyzed by Winkler and Parke (Winkler and Parke 1992) as being dependent on

escape, numbers and routes
survival of transport and arrival in a suitable niche
survival, adaptation and multiplication leading to competitive growth in the niche
survival of famine periods and/or transport to other niches
spread to and growth in many niches
disturbing one or more equilibria
transfer of r-DNA to indigenous strains, causing their increased multiplication

Although none of the non-pathogen rDNA production strains have shown any adverse effects in the environment, public concern has created a demand for low emission production methods to minimize residual risks. This approach seems to be controversial, but at least for the next few years bioprocessing will have to work with these higher containment levels.

Is this development legitimate? Are regulations hampering business efforts?

Quality management concepts

The quality systems have to meet the approval of regulatory agencies such as the US Food and Drug Administration (FDA) or the European Agency for the Evaluation of Medicinal Products (EMEA/CPMP), especially if the products are to be marketed in these countries. As mentioned above, companies from developing nations wishing to export their products to these countries will have to abide to their regulations. But even in the case of production for the own national markets, it is advisable to create a quality management system, that will comply to FDA standards, profiting at the same time from FDA's long experience in making drugs safe and at the same time being prepared for future market expansion into North American and European countries. A number of excellent reviews and books have been published on the different regulating bodies as mentioned above. By far the most frequently cited agency is the FDA, due to the fact, that all products sold in the US have to gain FDA approval and have to meet its quality standards. (For a review of typical FDA policies and philosphies see (Bozzo 1996)).

Three basic terms are very often used in quality management:

Good Manufacturing Practice (GMP)

Quality Control (QC)

Quality assurance (QA)

To date there is still no internationally agreed upon definition of what these terms compromise, how they relate to on another (GMP, especially QC and QA) and how they are to be implemented in practice. However existing national (e.g. FDA, MCA) and international definitions (EC, WHO, ISO) suffice to establish Quality Management Systems, which, overall meet the spirit of the regulations world-wide, and if implemented with proper care, awareness for quality issues and effort, will satisfy most inspection authorities.

Good Manufacturing Practice

As Good Manufacturing Practice (GMP) regulations were originally developed to cover preparation of the final dosage form of pharmaceutical products, much confusion exists as to how GMP applies to biopharmaceutical production (Fitzpatrick, Ma' Ayan et al. 1990).

In the countries where it applies, GMP compliance for the production of pharmaceuticals, cosmetics and foods is a legal requirement, not merely an optional standard. Enforcement is ensured through inspections by government investigators. Although enforcement is practiced in most countries, it is given the most attention by the FDA, who investigate not only within the US, but also as outlined above foreign companies wanting to import into the US.

Good Manufacturing Practice Regulations, or guidelines, are aimed at assuring quality of the product, by assuring the quality of the process. Therefore, quality control by product testing is only part of the overall assurance concept. In practice GMP begins with process research and development (e.g. development reports, approval requirments, see further below), proceeds through validation, continues through manufacturing and controls, end-product testing and reaches into the distribution network of the product (Bliem). However, GMP only applies to the manufacture and control of pharmaceuticals; it does not apply to a companies finance and research departments, if there is no involvement with manufacturing. It applies to research only, if this department is to develop recombinant agents for

biotechnology products, or develops processes that are to be transferred to Manufacturing; here it concerns primarily the testing and systematic documentation of the strains, genes or processes.
The difficulties most often encountered applying GMP regulations involve their interpretation in terms of „nuts and bolts", i.e. reduction to practice. The difficulties are exacerbated on the one hand by the dynamics of regulatory and interpretational change,s on the other hand by the differences in GMP philosophies between countries worldwide. GMP guidelines state what is to be achieved, not how, although investigators have fairly clear concepts of the „how" through their investigational experience across the industry. This has led to a set of industry standards such as for clean room quality, Water systems, validation practices and other elements.

GMP regulations are but one element of the regulatory framework for the approval to market pharmaceuticals. Approval requirements and GMP regulations are interwoven. For example, the above cited requirement for the testing and documentation of genetic production agents at the research stage is not strictly a GMP requirement, but is required for product approval.
However; it is best assured by way of a quality management system, such as GMP or Good Laboratory Practice. Another area where GMP and approval are closely intertwined is in the changing of processes and equipment. Changes in the process, the product, methods of analysis, facilities or equipment may need registration with the approval authorities. This interwoven texture of GMP and approval requirements adds to the complex nature of GMP.

The GMP guidelines vary in their content structure between countries, however for the most part the content is very similar and compromises the following elements.
Organization and Personnel
Quality Assurance / Quality Control
Facilities and Equipment
Raw Materials, product containers
Production and process controls
Cleaning and Hygiene
Packaging and labeling
Storage and distribution
Laboratory testing
Documentation and document control
Inspections
Validation
This list, by and large, represents the structural categories that make up today's GMPs.

Compliance to GMP standards has to go hand in hand with process development aimed at product quality and productivity. Process improvement is very often seen as being incompatible with GMP compliance, as it requires process modification. If examined more closely compliance will always involve process improvement as the process is defined as the overall activities in relation to the product ont the one hand (e.g. documentation, control of starting materials, training, environmental monitoring etc.) (Bhatt 1996) and GMP regulations require 'state -of-the-art' production and control on the other hand.

Pitfalls to avoid

Although the *technical intricacies in interpreting regulations* is the primary difficulty in developing and maintaining a GMP system, the second and third are *project, staff and resource* management.
The latter is often overlooked in the beginning of a GMP development program, and the assumption that GMP development is something, that is secondary to the manufacturing development, becomes both a resource and management obstacle. Management should be advised, that manufacturing development must proceed hand in hand with GMP development, that GMP staff must have full management backing, or management and regulatory mistakes may result in very expensive and time-consuming exercises in correction programs, involving facility and process retro-engineering.
Quite frequently facilities are not approved because they are not yet in GMP compliance. This could be because the facility has design flaws, because the procedures are not yet in place, validation was not complete or any other number of reasons. All due to the fact, that the GMP development project was not planned and managed to coincide with the product approval process. The price is generally at least 6 months postponement, if the mistake can be corrected in that time. 6 months in terms of losses can amount to tens of millions of dollars.
Moving a biopharmaceutical from research to the market is a tedious and expensive procedure. Typical estimates range from 150 to 250 million US dollars. During this phase unnecessary costs can be avoided, if problems most commonly encountered in validation and registration of the product can be avoided. In an excellent series of papers James Akers et al. summarized many of these issues (Akers, McEntire et al. 1994), (Akers, McEntire et al. 1994). These include

Failure to consult with the regulating authorities at an early stage
Inadequate Product definition
Unrealistic expectations regarding market potentials, costs, time-lines etc.
Development of labscale process that can not be transferred to production scale (see also: Keeping it simple)
Neglected cGMP issues such as raw material quality, inadequate pilot facilities for the production of clinical trial material, inadequate hygienic and aseptic equipment design, insufficient in-process controls, poor documentation during process development, insufficient cleaning validation (see also potency of drugs) in multi-use pilot plants
Inadequate documentation of cell line history
Insufficient purification methods derived from lab procedures incompatible with scale-up and necessary sanitization procedures
Inadequate analytical procedures such as undefined reference material, non-validatable bioassays, inadequate assay validation (e.g. assay controls and ruggedness), setting product specifications (especially regarding impurities) at the assay limit
Limited resources for technology transfer (i.e. validation of procedures during process development) causing insufficient information of QC, production and validation personnel

Making quality assurance feasible

By avoiding the pitfalls described above validation and quality assurance become less daunting a task to perform. In this section of the paper a number of very basic

principles and examples are outlined, with no intent to give an exhaustive list, a task that would surely fill a series of monographs.

Keeping it simple

One of the ways to reduce the cost for quality assurance measures is to keep the production process simple. This seems like a trivial statement, but in real life works out to be a real challenge. Data from research and development departments are in many cases not as accessible as data from production. Decisions on the final production scheme are very often based on laboratory developments with very little emphasis on simplicity and scaleability. Time invested to rethink and reengineer the most problematic process steps, can turn out to be a major asset for installation, validation and ongoing quality assurance measures.

Setting priorities - risk assessment

To develop a feasible validation plan, it is of utmost importance to perform a hazard analysis in order to identify critical points in the process. A number of methods such as HAZOP (Hazard and Operability Study) (Kletz 1992), FMEA (Failure Modes and Effects Analysis) Critical Points Analysis, Life Cycle Assessment etc. can be used to aid the systematic exploration of the process and to implement actions to deal with hazardous consequences. These hazards include not only health hazards to the operator and environmental effects, but also all aspects of product safety and quality. In any case all activities will have to involve major issues such as conceptual and detailed design; fabrication and construction; calibration; installation qualification; operational qualification; performance qualification; process validation

The Standard Operating Procedure (SOP)

After identifying key procedures standard operating procedures have to be provided. This formal written system of documents describe in detail all tasks that have to be performed to ensure a certain goal, such as performance of analytical procedures, product safety, organizational matters etc. In addition Standard Operating Procedures have to contain specifications, to define the circumstances under which the procedure is deemed successful.
SOPs are just one element in an array of necessary procedures such as Master Production Procedures, Batch Production records, Analytical Procedures etc.

Records and Document Control

One of the fundamentals of all quality assurance concepts is meticulously kept records of all activities. Activities that have not been recorded are worthless, in respect to regulatory compliance as inspecting authorities consider them 'not performed' unless recorded. Organizing documentation structure and maintenance is therefore one of the most important tasks in setting up a QA system and the basis of any validation. Documentation has to be adequate to ensure the tracebility of the production history of every batch, including all associated issues such as raw materials, cleaning procedures, packaging, labeling and distribution.

Validation

Validation is the action of proving that any material, process, procedure, activity, equipment or mechanism used, can, will and does achieve the desired and intended

results. That means that sufficient scientifically and technically sound data have to be provided to prove that specifications are met, or in other words, the demonstration that what was supposed or intended to happen did in fact happen.

Validating biopharmaceutical production - process steps

Validating a biopharmaceutical process involves steps ranging from design and construction to production. Complete validation of a process can extend from planning an equipment item to ist routine inspection within production. The whole cycle of installing and operating a production plant can be split into different tasks:

Design qualification (DQ) including user requirement specifications and detailed functional specifications used for engineering design and procurement

Installation Qualification (IQ)

Operational qualification (OQ) verifying that subsystems perform as intended with model process materials (e.g. water)

Performance qualification (PQ) of equipment and process (latter refered to as process qualification of process validation) run with active materials. Once the process has been fully established three or more batches have to be produced with all parameters recorded and documented.

Process change control has to be established to ensure that product quality is maintained or optimized after changes have been made to the process.

Facilities

Over the years a number of regulatory requirements for biotechnological plants have been developed, including e.g. requirements for containment measures as well as for equipment systems such as HVAC (Heating, Ventilation, Air Conditioning) systems, water, steam and sterilization systems, material-, equipment-, product- and waste flow, personnel flow and personnel control (Hill and Beatrice 1989), (Hill and Beatrice 1989). This is one of the more complex areas of regulatory compliance, as the requirements are rarely laid down in actual engineering terms. Instead these are subject to interpretation by the authorities, so that the requirements must be based on knowledge of current policies, expectations and issues of the individual regulatory authorities. In other words, one must be fluent in the 'language and philosophy' of the individual authorities in order to translate the regulatory guidelines into engineering details for facilities and equipment. Although this is true for all areas of GMP regulation and compliance, it often presents particular difficulties with changes of facilities and major equipment. Two reasons are dominant: one is that major equipment and facilities are infrequently changed or built, so that individual companies, large or small, rarely have the resource to develop and maintain the necessary in-house know-how on current engineering compliance; the other reason is that the interpretations are subject to state-of-the-art technology, and both technology as well as regulatory requirements are constantly in state of improvement.

Improving facilities to comply with international standars can prove to be very expensive. For companies in developing nations with limited financial funds, it is of utmost importance to set priorities (e.g. improving air quality and wall/floor surfaces in the downstream area first, as processes are normally as well contained as in the fermentation area). In many cases, some problems in facility design can be dealt with by implementing adequate organizational measures and additional safety precautions. By setting clear priorities, the necessary long-term changes in facility

design can be done step by step, without overstressing existing budgets.

Equipment

To ensure the safety of the product, manufacturers must show that fermentation was run under aseptic conditions. The art of aseptic design has rapidly developed during the last years. The importance of hygienic design on the other hand is sometimes underestimated. Surface finish, dead legs, alignment of piping and many other criteria are important to maintain a high standard cleanability and to avoid the build up of contaminating materials. The necessary technology was basically developed by the food industry and was then adopted for bioprocess engineering. Reproducibility of cleaning procedures can be optimized by automatic Cleaning-In-Place (CIP) systems, without the need to dismantle the equipment. As some confusion has been created by the diverting use of certain terms such aseptic, sterile, cleanability the European Hygienic Equipment Design Group (EHEDG) (EHEDG 1992)] has established a number of definitions as outlined below:

Soil	Any undesired matter including product residues, whether or not containing undesired microorganisms
Cleanability	Suitability to be freed from soil
In-place cleanability	Suitability to be cleaned without dismantling
Destruction of microorganisms	Irreversible physical or chemical damage to microorganisms to prevent them from surviving and multiplying
Sterilization	Removal of destruction of microorganisms, including all relevant bacterial spores
Steam/hot water sterilization	Sterilization by saturated steam or water at 120oC for 30 minutes
Hygienic Equipment Class I	Equipment that can be cleaned in-place and freed from relevant microorganisms without dismantling
Hygienic Equipment Class II	Equipment that is cleanable after dismantling and that can be freed from relevant microorganisms by steam sterilization or pasteurization after reassembly
Aseptic equipment	Hygienic equipment that is, in addition impermeable to micro-organisms

The design and construction of hygienic equipment class I is based upon some very basic and simple rules , but the problems arising in real world applications may not be underestimated. In many cases (e.g. centrifuges) *optimal* hygienic design is difficult to achieve without performance loss.

General Criteria for Hygienic Design

Product surfaces resistant to product, cleaning, full range of operating pressures and temperatures

Product contact surfaces free from crevices.

Product contact surfaces roughness 0.5 µm or better.

Product contact surfaces either easily accessible for manual cleaning and visual inspection or validated CIP

Avoid condensate on external surfaces of the equipment
Insulation sealed with stainless steel cladding, preferably fully welded
Equipment must be self draining
Dead legs must be avoided.
Dead legs that can not be avoided have to be positioned correctly to ensure SIP or CIP.
Equipment and supports either sealed to the building with no gaps or pockets or adequate clearance to allow for inspection and cleaning.

The validation of cleaning procedures has been focused upon by many publications. Especially in multi-purpose plants the potential carry-over into subsequent products is of major concern. Validation has to ensure, that the cleaning procedures are adapted to the equipment and the type of contamination. The hygienic design of fermentation equipment is crucial for cleaning procedures to be successful. In order to assess in-place cleanability, methods have been developed for food-processing equipment (EHEDG 1992),(Lelieveld 1985), to test the removability of model contaminants. Validation methods for the cleaning of fermentation equipment and have been reported. (Vranch 1991),(Chisti and Moo Young 1994).

As outlined in the introduction, the carry over of drugs into subsequent processes in multifunctional bioprocessing plants has to be carefully considered. This is especially the case if the subsequent product is less potent and has to be administered in comparatively high doses. The question is how to determine the maximum allowable carry-over residue concentration. Calculation can be performed by taking into account factors, such as product toxicity or maximum tolerable dose, the maximum dosage of product taken per day, number of dosage units per batch, quantity per batch, surface area in common between products (Fourman and Mullen 1993).

Companies with low financial resources may find it difficult to obtain the necessary funds for expensive up-to-date equipment with optimal hygienic and aseptic design. In many cases, by using common sense and carefully identifying critical parts, the overall performance of equipment in respect to cleanability and sterilizabilty can be dramatically improved with comparatively small changes of existing equipment. These changes (e.g. reduction of dead legs) can very often be done in the companies own shop, thus reducing costs and at the same time improving the knowledge and understanding of local engineers. This building of expertise is of great importance for decisions on subsequent investments, negotiations with equipment manufacturers and operation of equipment.

Downstream:

Purification processes must be validated to prove that they are capable of removing impurities to an acceptable level. Special consideration has been given to the capacity of the downstream procedure to remove:

components originating from the host cell (e.g. protein, DNA)
impurities caused by media components or substances used during downstream processing (nutrients, buffer components, stabilizers, chromatography media etc.)
potential external contaminations by adventitious agents (e.g. viruses of mycoplasme in cell cultures, bacterial contaminants), which should not be present throughout the process, but could contaminate the culture by accident

Biopharmaceuticals produced from animal cells have been scrutinized for the possibility of transmission of viruses to patients. Manufacturers have to validate their purification systems to demonstrate inactivation and/or removal of viruses, nucleic acids, mycoplasma and scrapie-like agents (Sito 1993). These validations are

extremely costly as they are time consuming and need expertise for the handling of adventitious agents and analytical procedures. Each step of the purification procedure has to be spiked with model contaminants to evaluate the inactivation or removal capacity of the step if the contaminant will not be present in the process (e.g. viruses). These spiking tests will be performed on a model scale and sound scale-up strategies have to be used to guarantee equivalent contaminant clearance on the production scale. A number of approved techniques for virus inactivation/removal have been developed, such as virus inactivation by pH extremes, heat, radiation, chromatography, filtration (Grun, White et al. 1992). But procedures have to be validated for the specific product and process on hand, case by case.
As with fermentation equipment cleaning of downstream equipment is of great importance. As chromatography media very often not steam sterilizable, adequate sanitation procedures have to be developed and validated. (Adner and Sofer 1994). Sanitation procedures and normal operation are important factors when evaluating chromatography resin reusability and maximum number of cycles. General criteria such as small ion capacity, total protein capacity, flow versus pressure, particle size distribution, microbial and endotoxin analysis, total organic carbon removed by extreme cleaning solutions, chemical challenge (subjecting the resin to the harshest chemical solution used in the process) (Seely, Wight et al. 1994). Other parameters, such as capacity and selectivity, efficiency can be used in technique specific tests.

Quality consideration for (bio)pharmaceuticals - product testing

Critical criteria for biologics are:
safety
potency
consistency
purity
efficacy
Final product safety testing must include (Schiff, Moore et al. 1992):
general safety or abnormal toxicity
sterility
pyrogens
mycoplasma contaminating DNA
viral contaminants (under certain circumstances)
Due to the diverse composition of biotechnological products (e.g. Proteins, polypeptides, polysaccharides etc.) different approaches to stability studies are often necessary. For biopharmaceuticals consisting of proteins or polypeptides such as cytokines, erythropoeitins, plasminogen activators, blood plasma factors, growth hormones, insulin, monoclonal antibodies and certain types of vaccines there is a major thrust towards international harmonization of testing procedures, such as storage test conditions, study durations and frequency of testing, release and expiration specifications. The methods used for purity and molecular characterization must be validated to prove they allow the accurate detection of changes during storage, including subtle changes that reflect the degradation and loss of biological activity (potency) of a product (e.g. oxidation, deamidation, aggregation, fragmentation) (Haase 1995), (Federici 1994).

Analytical Procedures

Analytical procedures have to be tested for accuracy, precision, sensitivity and other

statistical parametersand for the ruggedness of the method. Validation will have to include the evaluation of matrix effects. Analytical procedures used to evaluate the quality of the final product have highest priority for full and comprehensive validation.

Automated Systems

As with all other systems used for the production of pharmaceuticals, automation equipment has to fully documented and validated. Hardware and software have to be tested for proper performance. As is the case for other system components, installation- operational and performance qualification have to be performed. Test data have to be documented and evaluated. Systems have to perform within specified limit (performance test) and have to cope with certain events, such as erroneous operator inputs, sensor failure etc. (stress test). Software should be reviewed, with the rule of thumb being priority given to software that has only distribution (such as custom process control sequences or algorithms)

Turning the burden into an asset

What are the benefits to be gained out of a stringent QA/QC and validation programs. If handled with care such a program can help a company to establish an efficient , logical quality managment system covering all activities (e.g. management, research, QC laboratories etc.). This will not only help the company to achieve fast approval for new processes , but will also create awareness throughout the company to quality issues, thus boosting performance. Also the definition of clear and measurable objectives helps to streamline activities, this being applicable to both fully developed companies as a to emerging businesses (Wright 1996).
An important part of a total quality management system is the quality control and quality assurance of all laboratory operations, including so diverse activities such as upstream (e.g. cell banking, strain improvement, inoculum preparation etc.) or analytics. By following a stringent control program, laboratory operations can be streamlined. If, for example, analytical equipment is qualified following the classical qualification stages (design qualification, installation qualification, operational qualification, performance qualification) expensive calibrations runs may be reduced to the necessary amount. By setting method-specific system suitability criteria (SSC)as part of PQ, the performance of the equipment's critical components can be monitored. This enables early detection of trends towards unacceptable performance, helping to reduce equipment downtime (Freeman, Leng et al. 1995).
For companies from developing nations with limited financial resources, the clear benefit of implementing stringent QA/QC and validation programs, will be the intensive evaluation of the processes and the identification of critical points. In many cases, major improvements of product quality and safety can be achieved with modest investment into facilities and equipment, mainly by adapting organizational structure and Standard Operating Procedures to eliminate or reduce hazards. Improved consistency of product quality improvement and will reduce the amount of rejected batches boosting productivity. If handled with common sense and by identifying priorities, QA/QC programs and validation efforts will pay off, even with limited resources, in the short term and will build the foundation for the expansion in multinational markets in the long term.

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