

FROM GENE TO CLINICAL PRODUCT: AN OVERVIEW OF GMP REQUIREMENTS ASSOCIATED TO THE DEVELOPMENT OF NEW BIOTHERAPEUTICS, IN A MULTIPROCESS/MULTIPRODUCT FACILITY

Jean-François POLLET

Henogen sa, University of Brussels, Belgium

Alex BOLLEN

Henogen sa / Applied Genetics, University of Brussels, Belgium

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1. Introduction

To continue the development of new potential biopharmaceutical products that have passed with success through the earlier stages of the Research and Development programme, there is a necessity to entrust the following development (process development, scaling up, manufacturing of clinical batches for pre-clinical and clinical studies) to integrated bioengineering companies in full compliance with Good Laboratory Practices (GLP) and current Good Manufacturing Practices (cGMP) requirements [see also – *The Regulation of genetically modified Food*].

Medicinal products for human and veterinary use, in development or with Marketing Authorisation, must be manufactured, formulated, packaged, controlled and distributed so as to ensure that they are fit for their intended use and that they do not place patients at risk due to inadequate safety, quality or efficacy.

To achieve these objectives, a system of Quality Assurance (QA) incorporating concepts of GMP and Quality Control (QC) must be designed and implemented.

A system of Manufacturing Authorisation is also required by the pharmaceutical industry: it ensures that all medicinal products are manufactured only by authorised manufacturers, whose activities and compliance with contemporary requirements are regularly inspected by National Competent Authorities.

Directives for national implementation and other regulatory requirements such as the *Title 21 Code of Federal regulations* from the Food and Drug Administration (FDA), the *European Directive 91/356/EEC* and the *European GMP guide*, the *International Conference on Harmonisation (ICH)* and *World Health Organization (WHO) guidelines*, give an international framework for current good manufacturing practice requirements (see web links at the end).

2. Basic requirements for a State-of-the-Art Biopharmaceutical Development Facility

2.1. The quality management concepts and the current Good Manufacturing Practice (cGMP)

For the pharmaceutical companies to meet their regulatory requirements and the legitimate expectations of patients for quality, safety and efficacy, a high level of suitable quality assurance system has to be ensured.

In many branches of industry, quality management have been developed according to CEN/ISO standards. The pharmaceutical industry is not governed by these standards seeing that the manufacture of medicinal product has for many years taken place in accordance with guidelines for Good Manufacturing Practice and also because these companies are deluged with a rising number of specific directives, guidelines and other legal requirements that must be respected. Nevertheless, input can be taken from these CEN/ISO regulations. High standards of quality assurance must be maintained in the development, manufacture and control of medicinal products.

The principal objectives of a quality management are to understand specific requirements on organization, process, procedures and resources, and to develop systematic actions necessary to ensure sufficient confidence that a product will satisfy to the quality standards appropriate to their intended use.

A pharmaceutical quality system is the responsibility of senior management and has to include the active participation and commitment of personnel from different relevant departments and these at all levels within the company. As key personnel, the managers of quality assurance, production and quality control have to be taken into account. The heads of these departments must be independent from each other.

In a pharmaceutical company, the basic concepts of QA, cGMP and QC are interrelated aspects of quality management. Their relationships and their importance to the production and control of medicinal products are described here.

2.1.1 Quality Assurance [QA]

QA is a wide-ranging concept covering all matters, which individually or collectively influence the quality of a product. It is the totality of the organised arrangements, which ensure that the drug is of the right quality for its intended use. QA therefore incorporates cGMP and QC concepts plus other factors such as compliance with Good Laboratory Practice for pre-clinical development and process/manufacturing developments, Good Clinical Practice (GCP) for clinical trials, and product design or customer-oriented services.

A Quality Assurance system appropriate for the manufacture of substances for therapeutic use must be able to cover various aspects, ranging from managerial duties to self-inspections (Table 1).

- Clearly defined managerial responsibilities
- Independence of QA from production and other departments
- Integration of GLP and cGMP rules into manufacturing design and execution
- Clear Standard Operating Procedures (SOPs) for production and control operations
- Correct manufacturing, supply and use of well-characterized raw materials and packaging items
- Effective control and validation steps for all stages of manufacture and packaging
- Set up of production files for each batch, to ensure complete traçability
- Strict processing and control of finished products, before release, using well-defined SOPs
- Release of finished products by a qualified person certifying compliance, in manufacture, control operations and regulatory aspects, to conditions and specifications put in place by the manufacturer, the national competent authorities and the regulations relevant for medical products
- Maintaining quality of the finished products, up to the end of the validity period, by taking appropriate step for storage, sending and handling
- Follow-up of any change, deviation and taking correction action

- Regular internal self-inspections and audits of all operational departments in the company to evaluate effectiveness and applicability of the Quality System and the compliance with GLP and cGMP

Table 1: Conditions for an efficient Quality Assurance System appropriate for the manufacture of pharmaceutical products

2.1.2 Current Good Manufacturing Practice for medicinal product [cGMP]

cGMP is an element of the Quality Assurance : it is a set of current, scientifically sound methods, requirements, practices or principles that are implemented and documented during product development and production to ensure consistent manufacture of safe, pure and potent medicinal products.

Good Manufacturing Practice is important for multiple reasons:

- Quality of pharmaceutical products cannot be determined by the user;
- Pharmaceuticals are prescribed by physicians who rely on data supplied by the manufacturer;
- GMP protects the validity and completeness of data on which further development and marketing authorisation decisions are made;
- Poor quality medicines are not only a health hazard, but a waste of money for both governments and individual consumers;
- GMP is designed to minimize risks that cannot be controlled by testing of final product (cross contamination, incorrect labels on containers, insufficient or too much active ingredient resulting in ineffective treatment or adverse effects, etc);
- GMP ensures a common language and requirements.

Good Manufacturing Practice is concerned as well to the production as to the quality control of medicinal products. The basic GMP requirements are shown in Table 2.

- Clear definition of all manufacture steps and systematic review according to acquired experience
- Evaluation by QA of manufacture process, feasibility, in the framework of quality and biosafety
- Validation of crucial manufacturing steps, including when significant modification are brought into the production process
- Instructional, clear and unambiguous instructions and procedures, specifically related to a given facility
- Adequate means to perform the production, i.e. skilled and trained personnel, appropriate space, validated equipment, sufficient services, approved and validated procedures and instructions, proper storage and transport infrastructure
- Continuous training of operators for optimal compliance to cGMP procedures and requirements
- In-process record of production parameters to ensure consistency with predefined instructions and specifications.
- Recording and interpretation of any significant deviation

- Full traçability to check whole historical background for every production batch
- QA interfacing between manufacture and clinical trial site
- Recovery system in place to recall any batch of defective product
- Complaints' analysis system, in place, and measures to prevent reoccurrence

Table 2: Basic cGMP requirements

2.1.3 Quality Control [QC]

Each pharmaceutical manufacturer must establish and maintain a Quality Control department, in total independence from production and other departments. The QC is the part of the Good Manufacturing Practices (GMP) related to the sampling, testing and acceptance/rejection of starting materials, packaging materials, intermediate and finished products. It must guarantee that the necessary and appropriate analyses are really carried out and that materials, components and products are not released for use until their quality has been judged sufficient relatively to defined specifications. The basic requirements of the QC are shown in Table 3.

- Availability of dedicated spaces, personnel and QA and QC approved procedures
- Sampling, control and analysis of raw materials, packaging articles, intermediate, bulk and finished products; storage and preservation of samples
- Quarantine and storage system for starting materials and products
- Inspecting, testing, environmental monitoring for GMP purposes, releasing or rejecting starting materials and products
- Accessing production area for in-process sampling and investigation
- Recording sampling operations, observations and measurements to guarantee conformity
- Traçability and interpretation of all significant change or deviation from specifications
- Standardized and validated tests methods
- Control of finished products; conformity to expected composition, purity, packaging and labelling
- Follow-up of product stability
- Collecting and preserving appropriate amounts of starting materials and products for possible future analysis

Table 3: Quality Control: Conditions for success

2.2. Design of building, facilities and equipment

Buildings, facilities and equipment used in the manufacture of biopharmaceutical products for clinical trials need flexibility for multi-product and multi-dosage form capability. They should be designed, located and constructed to facilitate operations as appropriate to the types and stages of manufacture, and to permit effective maintenance, decontamination, cleaning or sanitization in order to suppress risk of cross-

contamination. Of course, they must have full cGMP compliance to ensure acceptance by the regulatory authorities.

In principle, dedicated facilities should be used for: receipt, sampling and quarantine of incoming materials; separated storages for rejected materials and released materials; staff changing and showering; technical rooms accessible from outside the manufacturing areas: for replacement of HEPA filters or lighting, for maintenance and cleaning of HVAC, Water systems or other pipework; logistic facilities: weighing, media preparation, storage of cleaned/sterile materials, assembly and washing; manufacturing : upstream and downstream processing, aseptic processing; control and laboratory operations; clinical trial-compliant packaging and labelling; quarantine of final product before release, and product dispatch.

Normally, QC laboratories should be separated from production areas, but in-process controls may be carried out within the production area, provided they do not adversely affect the production.

The manufacturing of pharmaceutical products should be carried out in clean areas to which entry must be through airlocks for personnel and/or for equipment and materials. The environmental standards of particulate and microbial contamination of these premises must be adapted to the product and the production step, bearing in mind the level of contamination of the starting materials and the risk to the finished product.

These environmental cleanliness levels and their appropriate operations are summarized in Table 4.

- Grade D (class 100000, M 6.5 or ISO 8) for preparation of non-sterile solutions and components, media and buffer storage, tablet manufacture, or non-sensitive product packaging
- Grade C (class 10000, M 5.5 or ISO 7) for seed/cell bank manipulations and culture in bioreactor (plus local grade B or A laminar flow over critical open steps), downstream operations, preparation of solution to be filtered, or oral/inhalation manufacture
- Grade B (class 1000/100, M 3.5 or ISO 5) with localized Grade A (class 100, M 3.5 or ISO 5) for aseptic process, lyophilizer load/offload steps and filling of sterile products
(References for standards of air quality: European GMP guidelines, US Federal Standard 209E or standards ISO 14644 and 14698)

Table 4: Clean room classification and examples of appropriate operations

Airflow patterns are a critical factor: the Heating, Ventilation and Air Conditioning (HVAC) system should include control of air pressure, air velocity, temperature, inert particles, micro-organisms and humidity, as appropriate to the different production steps. If air is recirculated to manufacturing areas, appropriate measures should be taken to control risks of contamination.

All utilities used in the process (e.g. gases, compressed air, steam, etc) should be qualified and monitored to ensure that specifications are respected and corrective action is taken when limits are exceeded. Pipework systems, vent filters and valves should be designed for effective cleaning and sterilisation.

Purified water, water for injection (WFI) and, where appropriate, other water pipes should be controlled and sanitised according to procedures detailing physical/chemical and microbiological quality specifications, planning and description of controls, action limits and measures to be taken.

A monitoring control station should be installed to permit the continuous monitoring of environmental sensors and critical equipment sensors, the comparison of their status with the normal operating conditions, and the immediate reporting of abnormal situations combined with alarms notification to designated personnel.

The production equipment must be designed and constructed so that it does not present any hazard to the products. Surfaces of equipment that contact starting materials, intermediate or finished products must not be reactive and must not alter the quality of these products. The production equipment must only be used within its qualified operating range. After each use in a batch production, the equipment must be cleaned, checked, stored and, if appropriate, sanitized or sterilized before any new production campaign, to prevent build-up and carry-over of contaminants. “Cleaning in place” and “sterilization in place” systems must be encouraged for major equipment (e.g. bioreactors, storage containers) and permanently installed processing lines. Critical equipment such as measuring devices, balances, recording, production and test equipment must be checked, maintained and calibrated according to written SOPs that detail specifications, calibration criteria, defined intervals and appropriate methods, instructions to maintain adequate records and the measure to be taken in case of deviation. Equipment with defective status must be clearly labelled and/or removed from manufacturing and QC areas.

2.3. Organisation and management of documentation for pharmaceutical development and cGMP

Adequate and comprehensive documentation constitutes an essential part of the quality assurance system and cGMP requirements. All steps concerning the development, manufacture, control and application of medicinal products have to be documented clearly and carefully. The documentation system helps to ensure that each of these steps are correctly executed, effectively monitored and therefore, under control. It also facilitates the making-up of dossiers required for the application of a Marketing Authorization of medical products by having appropriate documentation readily available.

The quality assurance system incorporating GMP firstly requires a Quality Manual and/or a Site Master File, with a complete description of design, objectives and performances of this system. The basic elements of these documents are the following: description of the company and organisation of its quality management; organizational structure of facilities and relational outline of departments and services; organization

chart with tasks and responsibilities; list of personnel plus signatures and curricula vitae of key personnel; ground-plan of buildings, departments and rooms; general layout, design and finishes of the site; description of manufacturing and control activities per room; block drawing of rooms according pharmaceutical cleanliness classification (A,B,C,D); complete routing of manufacturing processes through departments and services, including flows of personnel, raw materials, auxiliary products (water, media, sera,...), intermediate/bulk products, finished products, packaging materials, QC sampling, reusable materials, cleaned/sterilized materials, waste, quarantine and storage; validation, cleaning and maintenance programmes of premises and equipment; organisation of environmental monitoring; complete description of water (purified water, pure steam, WFI), process gas and HVAC systems; and description of production documentation system.

The other documents recommended for the production under GMP can be divided in five categories: *Manufacturing Formulae, Specifications, Procedures, Instructions and Records*.

2.3.1. Manufacturing formulae and specifications.

Manufacturing formulae and specifications state all the raw materials and packaging materials to be used, provide a description of the pharmaceutical form, dosage and batch size of the product, and describe in detail the requirements to which materials or products have to conform. Specifications should be established for starting and packaging materials, intermediates or bulk products where necessary, and for finished products. These specifications include a description of the materials/products with a reference to a pharmacopoeial or other specific monograph, the identity of the approved suppliers and/or producers if appropriate, the qualitative and quantitative requirements with acceptance criteria, a description of sampling and testing methods to carry out before the release of the materials/products, the conditions and the maximum period of storage plus any special handling precautions where necessary.

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Web links for keeping abreast of cGMP and other regulatory developments:

- ICH : <http://www.ich.org>
- EMEA : <http://www.emea.eu.int>
- EUDRA : <http://www.eudraportal.eudra.org>
- FDA : <http://www.fda.gov>
- MCA : <http://www.mca.gov.uk>
- WHO: <http://www.who.int>

Biographical sketches

Alex BOLLEN was born in January 10th 1940 in Etterbeek, Belgium. He is a general Manager of Henogen sa, a spin-off of the University of Brussels and Associate Professor (ULB) and Director of the Applied Genetics Department (ULB). He has a PhD in Chemistry from the University of Brussels (ULB, 1968). He spent two years as post-doc in the USA to train in molecular genetics and in biochemistry. He then engaged in basic research for more than 15 years at the ULB and became Professor in 1985. From then on, he founded and directed the Applied Genetics Department (ULB), which for 20 years closely collaborated with major national and international pharmaceutical companies in the developing field of biotechnology applied to human health. As a scientist, he has been primarily active in the field of new therapeutics and new vaccines derived from DNA recombinant technology and was recently awarded the Sabin prize for vaccine research. He is author of many scientific papers and inventor of several patents. He now serves as CEO of Henogen, a spin off Biotech Company.

Jean-François POLLET was born in August 12th 1964 in Mouscron, Belgium. He is a Quality Assurance and Regulatory Affairs Manager of Henogen sa, and a Biopharmaceutical company, spin-off of the University of Brussels. He has a MSc and a PhD in Biological Sciences from the Universities of Louvain (UCL) and Brussels (ULB). As a research scientist, he has been working in ULB for more than 10 years undertaken missions in basic and applied research. He has gained extensive experience in genetics, immunology, biochemistry and molecular biology. He has developed with success several projects of research in the development of live multivalent recombinant vaccines, in pharmacogenetics, and in the study of the Cystic Fibrosis. Since 2000, he is responsible of the Quality Assurance and

Regulatory Affairs department of Henogen, a spin-off biotech company active in the discovery, manufacturing and clinical development of investigational biopharmaceuticals for human health. He has a large expertise in GLP, cGMP and GCP requirements.

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