Good Quality Practice (GQP) in Pharmaceutical Manufacturing: A Handbook

Authored By

Jordi Botet

Glez. Tablas 17
Barcelona
Spain
Dedication

This book is dedicated to the love and support of my parents, who unfortunately will not have the possibility of seeing it.

And to Pol on behalf of my whole family.
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As a regulator, scientist, and expert in pharmaceutical quality, I am always searching for the best and most practical tools and reference material available in order to ensure pharmaceutical drug quality. A challenge lies in keeping up with technological advances and frequent updates to the information available. In today’s world technical information is so easy to obtain with a few strokes of our fingertips. However, actually understanding and managing the information has become a global challenge. In this age of information overload, it is difficult to determine what of this vast information is actually required and how much understanding on the part of the pharmaceutical personnel is needed to be utilized in practice.

What regulators, consultants, and industry all need is a sensible book that describes GMP topics and international guidance in a simple manner, that both the layman and the expert could understand and put to practical use. Such a book would ultimately benefit the global quality culture.

This handbook responds to the needs previously articulated. It introduces the world of pharmaceuticals in a manner that a layman would understand, but that an expert would also appreciate. It describes GMP topics in a straightforward manner, providing clarity to frequently discussed topics related to pharmaceutical quality and follows international guidance requirements of “knowledge management,” and “continual improvement.”

I met the author in Estonia, at an International Pharmaceutical Quality Training Conference he was attending, where I was an instructor. From the questions he asked and comments he made it was evident he had extensive world-wide knowledge of Pharmaceutical GMPs. Whereas books in general may not be as popular as they used to be when I was obtaining my education, this handbook will be. It has a world-wide perspective and achieves its goal to provide a clear GMP understanding in Good Quality Practices in Pharmaceutical Manufacturing.

_Diana Amador-Toro_
Parsippany
New Jersey
USA
PREFACE

Because of my work as a GMP-consultant I often travel and this allows me to meet people from different countries all around the world. As a result I have come to understand how varied human cultures are but also, curiously enough, how the concerns of the technicians from the pharmaceutical industry are shared.

Thanks to modern technologies, the personnel of the pharmaceutical industry can easily obtain all the necessary information. GMP regulations and associated guidance documents are readily accessible and can be freely downloaded. Specialized literature and standards can be purchased online and often downloaded too. This means that technical information is immediately available in almost anywhere in the world. In fact, getting informed has never been so easy…

Unfortunately there is a huge difference between having documents and being able to apply them in practice. This is why the personnel of the pharmaceutical industry are deeply worried. The amount of information is not only considerable but is also frequently updated. Coping with it is not a straightforward matter. It is complicated for the average technician to develop manufacturing activities and to spare enough time to read and “digest” the necessary documents. It is true that big companies have many resources and can reduce the importance of this problem, but small and medium-size firms are often extremely affected by it. According to my own practical experience, basic doubts are very common and to be able to obtain a global vision and an integrated approach of all the elements composing GMP is far from being widespread.

This book provides an answer to this common worldwide problem. It exposes GMP topics as simply as possible. They are described in an integrated way and as straightforward and as practical as possible. It responds openly to the “frequently asked questions” about hot topics such as the Pharmaceutical Quality System, qualification, process validation, cleaning validation, lifecycle, documentation, training, risk management, etc. Many tables and figures help in making the description of these subjects clear and logical.

The global aim is to provide a clear GMP understanding to serve both to face practical everyday manufacturing and to create a steady basis to acquire further knowledge. This follows the GMP requirements of “knowledge management” and of “continual improvement”.

Jordi Botet
Barcelona
Spain
E-mail: jbotefregola@gmail.com
CHAPTER 1

Introducing the Particular World of Pharmaceuticals

Abstract: Pharmaceuticals are specialized products because of their characteristics and use and also because of their meticulous regulation. A failure in the quality of a pharmaceutical can put life at risk. Consequently, a specialized manufacturing standard (GMP) is applied with the intention of ensuring quality. Although still different GMP texts exist, there is a steady effort towards their harmonization. GMP is not just practical pharmaceutical common sense, but also a guideline which determines the organization of a pharmaceutical plant. The aim of the pharmaceutical industry is not only manufacturing products with the purported quality, but also delivering them to the patients timely and without any loss of quality. This is why attention should be paid to the whole supply chain of pharmaceuticals and thus complementary standards (GSP, GDPs, and GTDP) have been developed. The globalization of the pharmaceutical market has not only supposed an increase in complexity of the supply chains, but also of contract manufacturing or analysis (outsourcing). Keeping under control such a complex and global market is not easy and this explains why counterfeiting has become a significant matter of concern.

Keywords: API, bulk, counterfeiting, dosage form, excipient, GDPs, GLP, GMP, GSP, GTDP, harmonization, intermediate, key personnel, MAH, outsourcing, packaging, quality assurance, quality control, route of administration, supply chain.

INTRODUCTION TO PHARMACEUTICALS

Since the dawn of civilization, humankind has tried to cure diseases or, at least, to alleviate their consequences by means of “remedies”. Initially these were empirically chosen products derived from plants, animals or minerals. Later on, with the development of science, it became possible to know the root causes of illnesses and the composition of those products used to treat them. As substances, which were at the source of the activity of the traditional remedies were tracked down and their mechanisms of action were identified, it was possible to prepare specific products intended to treat diseases and injuries.

Nowadays, “remedies” are specialized products manufactured in purpose-build facilities and are known as “pharmaceutical products”, “pharmaceuticals”, “medicinal products”, “medicines” or “drug products”. In this book all these terms are freely used as synonymous.
An introduction to pharmaceutical products has to deal with their three basic aspects: what they are in fact (definition), how they are used (routes of administration) and how they look like (dosage forms).

**Definition**

Currently a pharmaceutical can be defined as *any substance or combination of substances presented for treating or preventing disease in human beings or animals. Any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or in animals is likewise considered a medicinal product* [1].

Or as a finished dosage form that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo [2].

These definitions demonstrate that the scope of contemporary pharmaceuticals is wider than that of the older remedies (Table 1).

**Table 1. From the primitive “remedy” to the modern “pharmaceutical”**.

<table>
<thead>
<tr>
<th>Aspect</th>
<th>(Primitive) “Remedy”</th>
<th>(Modern) “Medicine”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose</td>
<td>- Cure</td>
<td>- Treat</td>
</tr>
<tr>
<td></td>
<td>- Relieve</td>
<td>- Relieve</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Prevent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Diagnose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Restore, correct or modify physiological functions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Use as a placebo</td>
</tr>
<tr>
<td>Composition</td>
<td>Unknown (natural product)</td>
<td>Known (formula/biological entity)</td>
</tr>
<tr>
<td>Action principle</td>
<td>Unknown (empirical)</td>
<td>Known (active entity/active principle)</td>
</tr>
<tr>
<td>Mode of action</td>
<td>Unknown (empirical)</td>
<td>Known (pharmacology/biology)</td>
</tr>
<tr>
<td>Presentation</td>
<td>Variable (empirical)</td>
<td>Dosage form based on pharmacology</td>
</tr>
<tr>
<td>Preparation</td>
<td>Artisanal</td>
<td>Technological</td>
</tr>
</tbody>
</table>

**Route of Administration**

Excepting the particular case of placebos, modern drug products are built on an active substance or, in some cases, several substances, known as APIs (“active
pharmaceutical ingredients”), which have to reach quantitatively and timely their point of action in (or on) the body to produce the intended effect. Access into the body is controlled and limited by physical and chemical barriers. The routes of administration, e.g. the ways through which medicinal products reach the parts of the body where they have an effect, can fall into three groups:

The first one takes advantage of the existence of natural openings (mouth, nose, eyes, ears, urethra, rectum and vagina). Of these, the oral route is the most common. About seventy per cent of the medicinal products use it. Despite the fact that taking a product by mouth is very easy, it is less practical than it might seem, because swallowed substances endure the combined action of the stomach low pH and of the digestive enzymes and are metabolized by the liver. The other routes are, generally speaking, mainly limited to medicines possessing a local action.

The second obvious alternative would be getting absorbed through the skin, but this is a natural barrier, which seriously restricts absorption. This is why it is also chiefly limited to medicines possessing a local action.

The third and last alternative is to overcome all barriers by injecting the product directly into a part of the body. This is a “traumatic” route as it does not use a natural path but pierces teguments. The drug product can reach the point of action without any metabolic transformation, but this route involves a particularly high risk of infection.

Draw a practical classification of the routes of administration is difficult because they are defined by different criteria at the same time, but Table 2 provides a tentative one.

Table 2. Tentative classification of pharmaceutical routes of administration.

<table>
<thead>
<tr>
<th>Type of route</th>
<th>Designation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>(I) Through body openings</td>
<td>oral/enteric</td>
<td>drug is swallowed and reaches the gastrointestinal tract (e.g. tablet or syrup)</td>
</tr>
<tr>
<td></td>
<td>sublabial</td>
<td>between cheek and tongue (e.g. tablet)</td>
</tr>
<tr>
<td></td>
<td>sublingual</td>
<td>under the tongue (e.g. tablet)</td>
</tr>
<tr>
<td></td>
<td>topical</td>
<td>applied on the mouth mucosa (e.g. aphtha lotion)</td>
</tr>
<tr>
<td></td>
<td>inhalational</td>
<td>gaseous form reaching the respiratory system (e.g. spray)</td>
</tr>
<tr>
<td></td>
<td>topical</td>
<td>introduced into the nose cavity (e.g. solution, ointment)</td>
</tr>
<tr>
<td></td>
<td>topical</td>
<td>applied on the eye or eyelashes (e.g. solution, ointment)</td>
</tr>
<tr>
<td></td>
<td>topical</td>
<td>applied in the external ear cavity (e.g. solution, ointment)</td>
</tr>
</tbody>
</table>
The Lifecycle Model

Abstract: The performance of any process is both the consequence of its previous development studies and of the adequate transfer of these experimental concepts into practical operation. This is the lifecycle model which reminds us that quality has to be designed, transferred to real routine operation and then maintained within controlled conditions. There is no other way, at least nowadays, to ensure that quality by design will become produced quality too. In a pharmaceutical unit the lifecycle model can be usefully applied both to pharmaceutical products and pharmaceutical projects (premises, facilities, or equipment) and to processes like documentation and personnel. The different lifecycle stages are united like the links of a chain. Therefore, in order to achieve quality, control has to be exerted in a global way. The significance and management of the lifecycle stages of a project (URS, commissioning, admittance, qualification, maintenance and calibration) are analyzed. The practical organization of a qualification program is described in detail, starting with the redaction of a QMP, following with the writing and executing of qualification protocols and finishing with the qualification reports.

Keywords: Admittance, calibration, commissioning, discontinuation, DQ, IQ, maintenance, OQ, PQ, project design, QMP, qualification, qualification protocol, qualification report, qualification testing, requalification, supplier, traceability, URS, verification (checking).

WHAT A LIFECYCLE IS

Pharmaceutical products can be considered a sort of living being. They are initially “conceived” and, after their “birth”, they spend a life, which is more or less long, with variable incidences and changes, until the moment their production comes to an end. Thus, all the phases in the life of a product from the initial development through marketing until the product’s discontinuation [1] are collectively known as “lifecycle”.

All lifecycle phases are closely related. Each one is influenced by whatever happened before and, in turn, has an influence on whatever will happen afterwards. Improvement and scientifically sound control are only possible if knowledge and experience gained during one stage are transferred to the next one. This is why the lifecycle model is important.

This model can be usefully applied not only to the products but also to the facilities where they are manufactured and even to the manpower and
documentation used for this manufacture. In fact, any process can be considered in terms of a lifecycle.

A lifecycle is typically composed of four stages.

(1) Development/conception: The process is conceived, invented, and its outlook is decided. It consists in gathering, evaluating, comparing and selecting information. And then, on this base, something new is created.

(2) Transfer/realization: What has been created is practically built, adapted or moved to be used for its routine function.

(3) Manufacturing/operation: The process operates routinely during its lifetime.

(4) Discontinuation: The process is no more necessary or useful (e.g. it is superseded by a better one or it is unprofitable).

THE PHARMACEUTICAL PRODUCT LIFECYCLE MODEL

As represented in the annexed Fig. (1), lifecycles appear intersecting the supply chain, which was considered in chapter 1.

Only two lifecycles are shown in the figure (the first corresponding to the manufacturing of ingredients/intermediates and the second dealing with pharmaceutical products). Practically speaking, these two processes exercise the highest effect on the quality of the pharmaceutical product, as they concern the starting materials and the preparation and packaging of the dosage form. Other processes, however, can have their influence on the pharmaceutical product too (e.g. synthesis, extraction, or fermentation of the raw materials used to obtain the pharmaceutical ingredients; manufacturing of the packaging materials employed in the finished product).

In any case, the driving idea is always the same, without a proper study and a scientific design a product will not be adequately understood and consequently the production process will never be enough sure and robust. Also, if the transfer from the development center to the production plant is not adequately performed the quality of the product is doubtful (in research laboratory conditions the product which was obtained met specifications, but what will happen in different conditions).

The last stage, discontinuation, is considered not by taking into account the product itself but the social consequences of its withdrawal. The aim is keeping
patients protected (e.g. information on the product will continue to be available, there will always exist an alternative product, etc.). Pharmaceutical products are not just another commodity, but health assets.

Fig. (1) Intersection of supply chain and lifecycles.

The pharmaceutical product life-cycle is discussed in detail in chapter 11.

THE PREMISES, FACILITIES AND EQUIPMENT LIFECYCLE MODEL

The lifecycle model is usefully applied to a whole plant (with its premises, facilities and equipment), to a definite part of it, or even just to a single system or equipment.

In this case the first stage of development/conception is usually known as “project” and the third one of manufacturing/operation as “service-life”. The other two stages can be denominated by the usual general names. See Fig. (2).
CHAPTER 3

Risk Management

Abstract: The quality of pharmaceutical products is permanently threatened by hazards that are potential sources of harm. And hazards have an associated risk, defined as the combination of the probability of occurrence and of the severity of that harm. Therefore, it is necessary to keep these hazards under control by diminishing as much as possible the related risks. This approach to quality assurance is known as risk management. Different tools allow for the assessment of risk. Then, risk can be routinely monitored. Yet, there are no magic tools. Risk assessment requires a good amount of knowledge on the matter submitted to study. This does not exclude, however, that by skillfully using the existing tools it is possible to appraise adequately the level of risk and decide on its acceptance. A high residual risk is, in principle, unacceptable and requires the implementation of measures for its reduction (changes in the process or system or in the way it is monitored), whereas a low residual risk can be accepted. And this allows for the introduction of continual improvement, understood as the progressive diminution of the residual risk level. The whole process of risk management is explained step by step and the most useful tools used in risk assessment are described providing practical examples.

Keywords: Cpk, Fishbone diagram, FMECA, FTA, HACCP, Hazard, HAZOP, histogram, Pareto chart, PHA, process capability, risk, risk assessment, risk communication, risk control, risk monitoring, risk review, RRF, specific tools, unspecific tools.

INTRODUCTION TO RISK MANAGEMENT

Risk management designates an approach to the organization and monitoring of items (premises, facilities, processes, etc.) that analyzes the risks which might put in danger their reliability with the aim of applying corrective and preventive measures for ensuring that reliability will be maintained.

An anecdote can help us to understand why risk management is advantageous: Many years ago, we were in the Pyrenees and we wanted to visit a small and secluded glacier lake high up in the mountains. The dirt track leading there was steep and in bad condition. Consequently, we decided to rent a powerful Land Rover adapted to the harsh conditions of our excursion. To our great surprise when we reached the lake we saw a small city car parked beside it. Our Land Rover driver could not refrain from complimenting the proprietary of the car for being so bold as to drive there with such a kind of car. I have always remembered the answer he gave. “You know. This is not a question of boldness, but of sheer ignorance”.
This story reminds us of an approach that we had in the past, pharmaceutical industry included, which ignored formal risk management.

Pharmaceutical products have to be safe and meet approved requirements or, said in other words, they have to possess the purported quality. This was and is out of discussion. Notwithstanding that, different types of “hazards” (contamination, degradation and error or mix-up) loom during their manufacturing and distribution processes and put quality at stake. Thus, if we have to manufacture quality products, we are bound to know and understand these “hazards” in order to take measures to keep them under control. This approach has been fully incorporated into GMP by the WHO [1] and by the ICH [2], which means adoption by the USA, Japan, and Europe (incorporated as Annex 20 to European GMP) [3].

A “hazard” is a potential source of harm and “harm” can be defined as damage to health, including the damage that can occur from loss of product quality or availability. Then, “risk” is the combination of the probability of occurrence of harm and the severity of that harm [4]. See Fig. (1).

![Fig. (1). Relations between hazard and harm.](image)

In our everyday’s life we often talk about “risk” and, unconsciously, we apply this definition. Thus, we say that a given activity is risky because we estimate that there is a significant possibility of being seriously injured. Or we do not want to go on board of a very old and rusty aircraft, whereas we might happily seat in a brand-new airplane. The reason is clear: although the severity of an accident might be about the same, its probability seems to be much higher in the first case!

Medicinal products supplied to patients have to correspond exactly to the marketing authorization and possess the purported quality, but as we are bound to accept that the quality of products and processes is always at risk (because hazards are ordinarily there, independently from our wishes), it is evident that we have to manage that risk. Risk management is the systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk [5].

Therefore, risk management is a methodical and cyclical process (Fig. 2) that starts by identifying the hazards and assessing their risk. Then, once the risk is
known, it is necessary to decide if it is acceptable or not. If the answer is negative that means that either we modify things in order to reduce the risk or we have to stop what we are doing. If the answer is positive, than we have to put into practice measures for keeping it under control. The accepted risk can be communicated to third parts (e.g. inspectors, clients) and submitted to periodic revision to see if it can be further reduced by applying improved procedures.

Risk management can be applied both to production and to supporting processes.

Let us then see risk management in detail.

![Risk management stages](image-url)

**Fig. (2).** Risk management stages.

**Risk Assessment**

*Risk assessment is a systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards [6].*

Before starting any risk assessment it is necessary to have a well-framed process, where its inputs, outputs and stages are well known. A detailed flowchart is essential for doing this. Then, in a first step, it is possible to detect the hazards and their causes and effects (harm) and, in a second one, risk can be assessed.

This is an important bottleneck, because there is not always sufficient information at disposal. If this is the case, it is evident that our assessment will just be tentative and subject to further improvement when more information will be available. It
CHAPTER 4

Quality Hazards in the Pharmaceutical Industry

Abstract: Pharmaceuticals are manufactured in purpose-build premises which are provided with controlled environment, with specialized equipment and with the necessary utilities. There, trained personnel following approved procedures transform inputs (materials) into outputs (pharmaceutical products). Therefore, the quality of these pharmaceuticals is linked to the quality of the above mentioned aspects. This was long understood and became the base of GMP: “keep the factors influencing quality under control and you will get quality”. Nowadays it is possible, and necessary, to implement risk management to better recognize and control these quality factors. But, be that as it may, it is evident that without knowing and understanding the hazards which threaten quality, any quality assurance policy is doomed to failure. Thus, premises, utilities, equipment and personnel are analyzed in order to detect which hazards loom on the quality of pharmaceutical products. Then, these quality hazards are described and their causes determined with the aim of proposing measures for reducing their likelihood or keeping them under control. It is interesting to underline that changes in systems and equipment and in approaches to hazard handling have contributed in diminishing the risk, but most of the hazards remain basically the same. There is a wide coverage of the hazards linked to harmful products and microorganisms and the preventive measures, according to the risk level.

Keywords: Airlock, biohazard, BSC, clean area, contained area, contamination, cross-contamination, dust exhaust, environmental contamination, equipment, error/mix-up, degradation, HEPA filter, HVAC, OEL, personnel, PPE, premises, utilities, waste disposal.

QUALITY AT BAY

Long before the formal introduction of risk management in pharmaceutical manufacturing it was understood that the quality of the products depended on the elements which intervened in their fabrication, traditionally known as the 5 Ms (Machines-Medium-Men-Methods-Materials).

It was also perceived that often a single mistake might, perhaps, not be significant, but that the coupling of several mistakes could easily lead to an accident. Thus quality was seen as the result of having good procedures and then “doing things well”, which excluded that a series of mistakes might constitute a chain of events leading to an accident (e.g. entrust a task to a new operator is, maybe, not very dangerous in itself, but if he is not adequately trained, supervised and has not a written procedure to follow, we would easily agree that it becomes very perilous indeed). This is, by the way, why GMP was born. GMP pointed out the main
quality mistakes affecting pharmaceutical manufacture and proposed “good procedures” to overcome or control them [1, 2, 3]. Nowadays we have advanced a step forward, as we use science-based approaches and risk management, but essentially quality hazards remain the same and have to be well known and understood prior to any quality management policy. This is why in this chapter the hazards linked to pharmaceutical manufacturing are described and analyzed in a systematic way. In fact, just five categories of hazards endanger product quality: contamination (“external”, “crossed” and “environmental”), error/mix-up, and degradation. Once potential hazards are known it is necessary to identify the items which are going to be analyzed to see if these possible hazards did exist and then identify the possible causes and propose control measures. The items which are analyzed can be usefully classified using the method proposed in chapter 2 while describing the QMP (qualification master plan) and that can be summarized here by saying that manufacturing processes are performed in premises by means of equipment supplied with utilities and that in spite of the impressive progress of automation, the “human factor” still plays an important role.

**Quality Hazards**

**Contamination**

“Contamination” is defined as the undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a raw material or intermediate during production, sampling, packaging or repackaging, storage or transport. Whereas “cross-contamination” is the contamination of raw material, intermediate product or finished product with another raw material or product during production [4].

Even accepting that starting materials meet specifications (yes, they can be already contaminated prior to its reception, but it is not considered here), within a pharmaceutical plant products can be contaminated by the most varied impurities. Although any contamination is, by definition, external to the substance which is contaminated, “contamination” by sand, dust, fibers, hair, pollen, pesticides, cleaners, lubricants, microorganisms, etc. can be dubbed “external contamination”, whereas “cross-contamination” is produced by other materials or products. This distinction is important because, as we are going to see, both types of contamination involve different preventive approaches.

Besides, some materials and microorganisms manipulated in pharmaceutical plants are harmful for the operators and, if they break out from the premises, they
cause pollution of the environment by their physico-chemical or biological toxicity and this can be called “environmental contamination”.

**Error/mix-up**

Although both words design the same fact (*i.e.* procedures were not followed), error is a more general term used to design that something is done in a wrong way, whereas mix-up refers usually that one thing is changed for another. Errors and mix-ups can affect different products, different batches of the same product or different stages in the production of a batch of a product.

**Degradation**

The quality of a material or product can be affected if exposed to inappropriate conditions (*e.g.* temperature, humidity, sunlight, illumination, radiation).

**Pharmaceutical Plant Items**

These above mentioned hazards threaten premises, utilities and operations (which include equipment and personnel), as shown in Fig. (1).

**Premises**

Pharmaceuticals are manufactured in premises which:

- Provide physical support to the production (installation of equipment, storage of products, setting for the operations, *etc.*) and adequate conditions for the products (temperature, humidity, illumination, *etc.*);

- Facilitate the development of processes and prevent mix-ups (separation of operations in different rooms, appropriate flows, delimitation of zones, *etc.*);

- Shelter products from contamination, coming from outside and generated inside (“cross-contamination”);

- Protect the environment from contamination by products manipulated inside.

A plant has different areas, which can be either service areas without GMP requirements or areas where GMP-regulated activities are developed. These latter can be subdivided into “gray” and “clean” areas (depending on the existence or
CHAPTER 5

The Pharmaceutical Quality System: The 21st Century Approach

Abstract: The Quality System is the nervous system of the GMP-body. The ruling brain is the Quality Manual, whereas the procedures which develop it are the nerves that control this GMP-body. The Pharmaceutical Quality System (PQS), as proposed by ICH Q10, has a slightly wider scope than GMP, as includes pharmaceutical development too. In terms of responsibility the senior direction of the company is a key factor of the quality system because determines its policy and objectives. The PQS is composed of two enablers and four elements. Enablers facilitate the attainment of the PQS objectives. A couple of elements were already in place relatively long ago (change management and CAPA system), whereas the other two are newcomers and focus on control on processes and products and on the PQS itself. The different approaches to the Quality Manual and its contents are described and commented. As a modern quality system is based on continual improvement it is necessary to identify and analyze the processes in the manufacturing plant. Processes can be kept in state of control by monitoring of variables/indicators. The latter can be monitored either during the same process (on-line or off-line) or after it by evaluation of data. Thus, improvement means variable/indicator improvement. The performance of the quality system itself must be reviewed by the management in order to ensure that it remains appropriate. The practical organization of the system is developed in documents known as general procedures of the system. The contents of these procedures are commented and their interrelations are analyzed.

Keywords: CAPA system, change management, continual improvement, document management, general procedures, incident management, knowledge management, management review, PAT, performance indicator, personnel management, PQS, Process manual, process map, Quality manual, quality objectives, quality risk management, quality policy, quality review, variable monitoring.

WHAT A QUALITY SYSTEM IS

In precedent chapters it has been analyzed why quality is a must for drug products and why different approaches to it have been adopted. Unfortunately, quality, as many other basic and evident concepts, is easier to describe and understand than to put into practice. We noticed that GMP is a basic tool to ensure quality (see chapter 1), but one thing is providing general orientation and another one very different is ensuring continual compliance. This is only possible by setting up a Pharmaceutical Quality System (PQS) which incorporates GMP. This could be expressed by a very simple equation: GMP + PQS = Ensured Quality.
GMP is well known and notwithstanding the fact that there are different texts it is something concrete, but then, what about the PQS?

For a long time there had not been a “pharmaceutical” quality system and general quality system models were adopted by the pharmaceutical companies and tailored to suit their needs. Most popular were the quality systems derived from the ISO 9000 family [1-3]. Consequently, many companies were accredited ISO. This meant that they were ISO audited on one side and GMP inspected on the other. The former was a company stake, whereas the latter was a requirement from the pharmaceutical competent authorities. In any case, the objective was ensuring continued GMP compliance.

This situation evolved at the beginning of the 21st century when, within the frame of the ICH, it was proposed a true and specific PQS model [4].

A “quality system” is the sum of all aspects of a system that implements quality policy and ensures that quality objectives are met [5].

In practical terms a PQS is the last step of a logical process that starts by defining the “quality policy”, that is the overall intention and direction of an organization regarding quality, as formally expressed and authorized by top management [6].

This quality policy is then developed and implemented by the direction of the organization in what is functionally known as “quality management”.

The basic elements of quality management are:

- An appropriate infrastructure or “quality system”, encompassing the organizational structure, procedures, processes and resources;

- Systematic actions necessary to ensure adequate confidence that a product (or service) will satisfy given requirements for quality. The totality of these actions is termed “quality assurance” [7].

As for the rest, a quality system is compulsory (something not surprising because it is necessary for ensuring GMP compliance):

The manufacturer shall establish and implement an effective pharmaceutical quality assurance system, involving the active participation of the management and personnel of the different departments [8].
The restricting factor for the implementation of a PQS is the need of a good knowledge on materials, products and processes, but this can be overcome by understanding that it is better something imperfect than nothing (provided that weak points are well understood and continual improvement is envisaged).

**CHARACTERISTICS OF THE PHARMACEUTICAL QUALITY SYSTEM**

**Objectives**

The basic objectives of a PQS are three [9].

- **Achieve a quality product.** The system should allow the manufacturing of products meeting the specified quality attributes.

- **Establish and maintain a state of control.** The system should exert continued monitoring and control in order to ensure that products and processes are adequate (“continued suitability”) and maintain their aptitude (“capability”).

- **Facilitate continual improvement.** The system should identify and implement the improvement opportunities in order to increase the ability of meeting the quality requirements.

**Organization**

The PQS possesses a defined configuration and is based on essential principles. Two “enablers” help in building a structure based on the integration of GMP with a quality system. See Fig. (1).

(a) **Basic Principles**

1st **The PQS concerns the whole lifecycle of the product**

As seen in chapter 2, the quality of a product can only be controlled if previously it has been created. In other words, just a well known product (i.e. after an appropriate development), manufactured by a robust and well characterized process, can be effectively controlled regarding quality.

Quality depends not only on what is done in a phase of the lifecycle but also on what has been done in previous phases (“domino effect”). This is why in terms of quality lifecycle phases cannot be considered independently.
CHAPTER 6

Documentation

Abstract: Documentation is an essential GMP feature. If the PQS is something like a nervous system, then the documents are the nerves which carry information and which keep an organism alive and operational. This information has to be exact, clear and delivered safely where it is necessary. This is why the lifecycle of documents is critical. It is indispensable ensuring that they are well written and reviewed and approved by the right persons. Personnel using these documents have to receive copies and get well acquainted with them. This is vital, but not easy to ensure. Documents should reflect reality. This is why they have to be kept updated and superseded documents have to be returned to QA. Documents are crucial because they define how operations have to be performed, but also because they allow for traceability in the operations. The documents of a PQS are so numerous that document management requires hard work. Consequently there is always the risk of considering it something unworthy and boring, to be allotted to unlucky novice technicians. As a matter of fact documents reflect so trustworthy reality that is almost impossible doing wrong and showing good documentation or doing right and providing poor documentation, and this is why inspectors pay particular attention to documentation. Disorganized documentation is the hallmark of a disorganized company. Although documentation is usually associated to paper, this is not exact. Documentation is information on any support, ensuring traceability, safety and readability at any time. Tentative lists of the documents which are required in a manufacturing laboratory are given in this chapter.

Keywords: Accessibility, approval, BMR, code, controlled copy, data back-up, drawing, instruction, label, log (log-book), master document, master formula, master record, procedure, record, retention time, review, SOP, specification, version.

WHAT DOCUMENTATION IS

“Documentation” is the general term used to designate the documents of an organization (i.e. a group of people working together in a structured way for a shared purpose). Documents are pieces of information (i.e. data which has a meaning) on a support (traditionally paper but nowadays usually stored electronically or otherwise).

GMP acknowledges that documentation is an indispensable element of the Pharmaceutical Quality System (PQS). It fixes, preserves and diffuses company knowledge (i.e. what has to be done, why, by whom, when, etc.) and, besides, this diffusion is free from the misunderstandings linked to spoken communication. Documentation allows for the traceability of operations. As it was described in the previous chapter PQS requires process monitoring and evaluation and it is evident that this necessitates documentation, either on paper or electronic.
DOCUMENTATION LIFECYCLE

Although documents are simply instruments used to convey information on the processes of an organisation, their production and management constitute a process too. Thus, documentation requires a lifecycle approach (see chapter 2), as shown in Fig. (1).

![Lifecycle of documents](image)

**Design**

Although it is evident that good presentation does not improve a bad document, an appropriate design enhances a suitable document.

Organizations design documentation according to their needs but also consider that documents are a kind of visiting card. This is why internal procedures often describe in detail how documents should be designed, even defining the font to be used, and they are developed on templates for ensuring homogeneity.

Each company has established its “own format” for the documents, which differentiate them from those of other organizations. Although there are not defined models, following is given general orientation on this matter.

Some people prefer documents with pages limited by margin lines, because this ensures to the lector the entirety of the text when printing or photocopying.
Cover Page

The cover page (or first page) is different from the other because it presents the document. A quite practical approach is using this front page for displaying all the general information about the document (identification, signatures, version control and distribution of copies), while the technical contents of the document start on the following page.

Thus, a first page could contain this information (Fig. 2):

(A) Document identification

- The company logo and name;
- The related area of the document (project, plant, unit, department, process, system, etc.);
- A short and concise description (title);
- The type of document (see below);
- Code. It is a set of alphanumerical characters used as a reference for the document. Each organization uses its own system and all are equally acceptable, provided that they allow for the unambiguous identification of the document. They usually consist of three parts. The first one identifies the type of document. The second one the unit, division or department to which the document belongs. And, finally, the third one specifically identifies the document, which is often consecutive numbering. Thus, SOP-WAR-005, would mean: standard operating procedure of the warehouse number 5.
- Version of the document. There is no defined norm for the numbering of the versions of a document. Some prefer to consider that the first writing of a document is version 0 (zero), whereas other consider it version 1 and consequently do not have a version 0. Any option is correct, but it should be indicated in the appropriate procedure.

The version of a document can be included in the code (e.g. SOP-WAR-005-01), but then, when a new version is released (e.g. SOP-WAR-005-02), it is necessary to publish also new versions of all the documents which mentioned the old version. Instead, a code without version does not change when new versions are edited.
CHAPTER 7

Personnel and Training

Abstract: Personnel are certainly the weakest ring of the quality chain of the pharmaceutical industry. On one side, their adequate level of training is difficult both to reach and to monitor. On the other, they are the only known source of contamination and mix-up which is voluntarily allowed to enter a manufacturing unit. It is true that automation and computer-assisted monitoring systems have contributed in diminishing this problem. Nevertheless personnel still holds the center of the scene. Education and a good deal of training can provide an acceptable level of knowledge and skills, but keeping this “state of training” is not easy. Training programs are a must for any laboratory, but ensuring their efficiency requires a good deal of dedication, not to say of ingenuity. It is well known that when the root causes for a deviation are investigated often one of them is “lack of adequate training”, then training is repeated and rather commonly this becomes a vicious circle because the problem was not lack of training but inadequate training. Hygiene is a must too, but can training change behavior? The answer should be yes, of course, but this requires convincing people of the real impact of hygienic practices on the quality of products. This chapter describes the GMP approach to personnel and training, analyses well-known problems and proposes solutions for them. The organization and documentation of training is studied in detail. Particular attention is drawn to the existing methods of training and to the measure of their effectiveness.

Keywords: Analysis of requirements, annual training program, appointment, confidentiality agreement, continuing training, evaluation of effectiveness, general admission training, job description, job specification, personnel lifecycle, personal training matrix, personal training tally, post profile, professional CV, selection, specific admission training, trainees, trainers, training methods, training records.

PERSONNEL: AN UNSOLVED PROBLEM

Personnel are at the same time the hero and the villain of pharmaceutical manufacturing. It is evident, at least for the time being, that in spite of the increasing automation persons still play a key role in production. They are educated and trained to possess the necessary competence for performing and supervising production. They are aided by specifically designed documentation and they work in GMP-compliant premises provided with purpose-build facilities and equipment. And in spite of that, personnel, as it was seen in previous chapters, keep always being a source of hazard because of their intrinsic capacity of microbiological contamination, not to mention how easily they may act as vectors of cross-contamination. Besides, human beings are prone to make errors and mix-
ups. In other words, personnel organize, supervise, perform and monitor production and they are intended to do this with the lowest possible quality risk but at the same time, for the simple reason of being there, they increase significantly the level of quality risk regarding contamination, cross-contamination and error/mix-up.

As we have already considered in chapter 4, this is a hazard which cannot be eliminated. Thus, only palliative solutions can be envisaged:

- Separation of personnel from products (clothing);
- Separation of products from personnel (isolators, RABS, closed systems);
- Education and training to avoid unhygienic practices and errors derived from lack of practice;
- Supervision by other personnel of the critical operations to detect errors/mix-ups.
- Use of automated systems as far as possible.

Automation of manufacturing processes is useful because it allows for an important degree of separation between products and operators, eliminates (at least in theory) mistakes and can be used as an independent supervisor of manual operations. Nevertheless, still many processes rely on critical operations performed by human workers.

**PERSONNEL LIFECYCLE**

As it was described in chapter 2 the lifecycle model can be usefully applied to the management of personnel, as shown in Fig. (1).
Consistent with the important role played by personnel in pharmaceutical manufacturing a policy directed to their management is of paramount importance. The aims of this policy are:

- Determining the manpower needs in terms of quantity and quality (educational and training level).
- Selecting people meeting these specifications.
- Providing selected persons with the initial training to familiarize them with the company organization and the Pharmaceutical Quality System (PQS).
- Prepare them for the concrete tasks they should perform.
- Appointing selected and trained persons to the posts.
- Detecting training needs and providing people with adequate continual training.
- Promote people to different posts to meet new manpower needs or just to fill vacancies.

As it can be seen, these actions correspond to the steps of a lifecycle model which match closely that of the products or of the premises, equipment and utilities. See chapter 2 for more details on lifecycles.

The objective of the PQS is implementing the quality policy and ensuring that the quality objectives are attained and this can be obtained by adequately trained personnel provided with the adequate documentation working in well-designed pharmaceutical plants. As it was described in chapter 6, documentation (or better said, the information that it conveys) is the backbone of the PQS. And in this sense, documents are crucial for the adequate development and control of the personnel lifecycle.

**Analysis and Definition of Requirements**

The need of educated and trained personnel in sufficient amount is not only imperative for logistic reasons, but also because it is a GMP requirement: *The establishment and maintenance of a satisfactory system of QA and the correct manufacture and control of pharmaceutical products and active ingredients rely*
CHAPTER 8

Premises/Clean Rooms

Abstract: Pharmaceutical premises determine the manufacturing flows and provide the setting for manufacturing equipment and for the complementary utilities. Clean rooms, where production operations can be performed within a controlled environment, are the result of combining sanitary internal architecture and HVAC systems. Premises have to be well designed in order to impede the entrance of outside contamination and the diffusion of internal cross-contamination. Moreover, personnel, because of their inherent contamination, put at risk the quality of the internal environment of the premises and therefore their access has to be controlled and performed through changing rooms, where operators put on appropriate clothing for the operations to be performed. When products happen to be potentially harmful, it is necessary to protect operators and outside environment too. This requires specially designed premises where the above-mentioned protection of products is coupled with the protection of operators and environment. This latter requirement is fulfilled by means of two steps of contention, primary within closed devices and secondary within the rooms by a combination of differential pressure and air filtration. Qualification allows for the demonstration that premises perform as intended.

Keywords: Action limits, airborne particles, air changes, airflow, airlock, internal architecture, clean area, clean room classification requirements, clean room conditions, clean room monitoring, clean room qualification, clothing, containment, design, differential pressure, material flow, personnel flow, sanitary construction, turbulent airflow, UDAF.

PREMISES FROM THE GMP POINT OF VIEW

Pharmaceutical premises are not just a physical space where equipment and personnel perform the manufacturing operations. Their layout determines flows and separations. Besides, the internal architecture complemented with the HVAC system allows for the creation of a controlled environment where manufacturing takes place.

A pharmaceutical manufacturing plant is defined by the operations which are or can be performed:

- Scope of operations: Although traditionally in the same premises were prepared many different products with varied dosage forms (multiproduct plants), nowadays the tendency is often towards specialized plants for given dosage forms or for reduced number of
products or production stages. In some cases logistic and economical reasons can even lead to plants dedicated to a single product (single product plants). In other cases plant specialization is a GMP requirement to impede cross-contamination (e.g. penicillanic antibiotics).

- Dosage forms: The characteristics of the premises depend on the dosage form, because of its physical characteristics (solid, semi-solid or liquid) and environmental requirements (aseptic production or not).

- Technology: It is evident that equipment is chosen in function of the type of operations which are needed and that this equipment, then, determines the lay-out of the facility (utilities which are required, space filled by equipment, material and personnel flows, etc.). The separation of the dirty parts of equipment outside the clean production zones in order to allow maintenance and repair without affecting the products is a GMP requirement. This means that production areas have to be complemented with technical zones.

- Other considerations: Adaptability to changes in product and batch size, packaging materials (containers, closures) ready for use or cleaned/sterilized in situ, production and storage requirements. HVAC equipment is bulky and heavy and requires a good amount of space. It is installed above the production rooms in a specially designed technical zone or outside.

The production rooms can be distributed in a single floor or in different floors. In the first case movement is easy because of the even surface. Whereas in the second, starting materials are taken upstairs by elevators and then the operations take advantage of gravity for the displacement of materials and products until attaining the lowest level.

The partitions and false-ceilings of the premises, known as “internal architecture” play a purely passive role, but a very important one. They contribute in controlling and limiting access to the different areas. They allow for the separation of areas within the premises and determine the flows. And they provide a sanitary setup.

The adjective sanitary is applied to the design based on the know-how of engineers and architects in order to control the risk of contamination during operations:
• Smooth surfaces not shedding particles. This is why brick-build walls with plaster or wood coverings are not accepted. The best-suited material for partitions and falseceilings are sandwich panels with external coating of enameled metal or phenolic resin. Floors are covered either with PVC sheets or coated with resins.

• No cracks or open joints. Paneling joints have to be filled with silicon.

• Limitation of shelves. They accumulate dust and therefore they should be absent in the most critical areas.

• Utilities (pipes, sockets, luminaries, etc.) should not have recesses difficult to clean. Whenever possible utilities should be installed outside from the production rooms or fitted in the partitions and embedded.

• Corners with rounded union profiles.

• Flush surfaces (window panes, doors, etc.) to avoid ledges.

• Avoid uncleanable recesses where dust can gather. This is why sliding doors are not recommended. In low risk areas they are often substituted by rolling doors.

• Control of sinks, drains and floor channels. They should be installed in low risk areas (grade C and D) but not in grade A and B areas and be provided with easily cleanable traps and with air breaks to avert backflow. Floor channels should be open, shallow and easily cleanable and be linked to drains outside the area in a way that prevents the access of microbial contamination.

CLEAN AREA/CLEAN ROOM CONCEPT

During manufacturing operations materials and products should only be exposed to the environment in clean areas, which can be described as areas with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area [1]. The rooms composing a clean area are clean rooms (or cleanrooms).

As it can be inferred from the definition, the clean area notion mixes different concepts:
Utilities

Abstract: Utilities are the blood who keeps alive and functional a pharmaceutical plant. Utility systems are very diverse and range from electricity to compressed air but they share the common fact of possessing points of use. They can be divided into “industrial” utilities which may interact with equipment but not with products and “pharmaceutical” utilities that may interrelate with both. These latter are critical and as such they have to be qualified and closely monitored. This is the only way for ensuring that they do not affect negatively the quality of the products. Utilities are normally tailor-made for each plant and as such a good study of their design is essential. Two utilities are particularly relevant: HVAC and water for pharmaceutical use. The HVAC system, in combination with the internal architecture, provides the controlled setting for the development of the pharmaceutical operations. Any failure puts at risk the production environment. The water for pharmaceutical use is a utility which provides water for cleaning but also water for compounding. This latter function turns water into a very particular starting material. It is obtained in situ and differently from other starting materials it is often used before formal sampling, testing and liberation by QC. This explains why it is one of the points of highest level of risk in a pharmaceutical plant. This chapter analyzes all these aspects and provides keys to the most effective approaches for protecting the quality of products.

Keywords: AHU, biofilm, compressed air, dehumidifier, dew point, distiller, dust exhaust, EDI, HVAC, lighting, nitrogen, passivation, pipework, P&IDs, point of use, RO, steam, storage, water for pharmaceutical use, welding.

INTRODUCTION TO THE PHARMACEUTICAL UTILITIES

Utilities are energies or fluids which are necessary for the functioning of equipment (e.g. electricity, gas, steam, compressed air, etc.) or for the appropriate development of the operations (e.g. lighting, HVAC, dust exhaust, etc.). By the collective name of utility systems (or simply, utilities) we design a rather quite heterogeneous group of systems that support production either directly or indirectly. Any factory can have several utilities and as such pharmaceutical plants too. However, from the GMP point of view only “pharmaceutical” or “critical” utilities count. That is, only utilities which may have an influence on the quality of the pharmaceutical products are required to meet predetermined specifications.

Physical contact with the product is usually considered the key factor in determining the criticality of a utility. Thus, for example, compressed air is critical when used to push stoppers into a filling machine (because it might
contaminate the stoppers, which in turn, might contaminate the products), but it is not critical when used just to activate a valve. In the first case compressed air is required to have pharmaceutical quality, whereas in the second its quality doesn’t matter and appropriate pressure is its only requisite.

In a pharmaceutical plant, any utility susceptible of being critical must be considered as such. A quality risk assessment may help to determine it (Table 1).

Table 1. Simplified example of quality risk assessment of utilities.

<table>
<thead>
<tr>
<th>Topic</th>
<th>E.g. electricity</th>
<th>E.g. compressed air</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is it likely any contact between utility and product?</td>
<td>N. a.</td>
<td>Pharmaceutical</td>
</tr>
<tr>
<td>Can this utility affect the quality of the product?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Does a utility failure affect the manufacturing process?</td>
<td>Yes (equipment stop)</td>
<td>Yes (equipment stop)</td>
</tr>
</tbody>
</table>

Key preventive measures

- Install a generator.
- Qualify equipment to show that stop and restart do not affect the product.
- Qualify compressed air. Install a supplementary air-compressor. Qualify equipment to show that stop and restart do not affect the product.

A critical operation is an operation in the manufacturing process that may cause variation in the quality of the pharmaceutical product [1].

Thus the following utilities are normally considered “critical”:

- Electrical supply (it is a particular case, but it should be ensured that critical equipment do not stop because an interruption on mains electricity supply);
- HVAC;
- Dust collection;
- Pharmaceutical water;
- Pharmaceutical steam;
- Pharmaceutical compressed air;
- Medicinal gases;
- Light (it should be considered critical because inadequate lighting can lead to inappropriate work).

**Characteristics of the Utilities**

In a utility system up to three parts or subsystems can be distinguished (Fig. 1):

- **Generation:** The fluid/energy is produced in the same pharmaceutical unit (e.g. steam generation from mains water) or in a specific production factory (e.g. pressurized nitrogen in cylinders).
- **Storage:** When this is possible the fluid/energy is stored to be used when necessary.
- **Distribution:** The fluid/energy is supplied at the points of use. Utilities that can be stored have a closed network or loop, with return to storage, whereas those which cannot be stored have a unidirectional pipe or network which finishes at the use points. The existence of a distribution network is the most visible characteristic of a utility [2].

![Fig. (1). Parts that compose a utility system.](image_url)

In order to avoid recesses, the only elements of the system that are located inside the production zones are normally the use points, whereas the other elements are placed in technical zones. Pipework should be designed and sited to avoid the creation of recesses which are difficult to clean.

Any wet surface is prone to be colonized by microorganisms (unless protected by the addition of biocides) [3]. Colonies that adhere to a surface are known as “biofilm” (i.e. biological film). Some utility systems offer good possibilities for
CHAPTER 10

Equipment

Abstract: Equipment plays an active role in a pharmaceutical unit by conveying, transforming and protecting from the environment materials and products. Pharmaceutical equipment should observe hygienic rules in its design, construction, installation, utilization and maintenance, as stated by GMP. As most equipment is controlled by computerized systems, it is necessary restricting access to them and ensuring that these can provide the same level of safety than operators (in fact higher). Equipment is as varied as existing operations and technical approaches for performing them, but it can be practically distributed into several groups. The first one is represented by weighing/measurement equipment. The second one is very large and comprises preparation equipment which is basically defined by the physical type of dosage form (liquid, semi-solid, solid). A third group would include secondary packaging equipment. Then a fourth group would be constituted by the booths, cabinets, benches and RABS, which provide limited protected operational environments. And finally we could still mention a fifth group collecting up other varied items of equipment. With the exception of disposable equipment, it is essential securing appropriate cleaning. Qualification, maintenance, calibration and, as required, requalification are essential activities for ensuring appropriate equipment performance.

Keywords: Access control, audit trail, BSC, cleaning, closed systems, computerized systems, materials of construction, dead leg, drainage, isolator, labeling, PLC, qualification, RABS, requalification, sanitary connection, sanitary design, SCADA, smooth surfaces, UDAF.

FUNCTION OF EQUIPMENT IN A PHARMACEUTICAL PLANT

Whereas internal architecture plays passive role providing overall protection and the physical frame for the processes, equipment actively transforms input materials (or products) into output materials (or products) or, simply transports them. Equipment is supported by the adequate utilities. Furthermore, equipment should also protect materials and products from contamination and minimize the risk of error and mix-up. These latter objectives are met by appropriate design, construction, and installation.

Additionally, there is also a specialized type of equipment known by the general name of “measuring instrumentation” which determines process parameters. These instruments can be either parts of manufacturing equipment or self-standing pieces of equipment. Thus, for instance, dosage machines or packaging lines are usually combined with weighing devices, whereas in weighing areas scales are basic items of equipment for weighing materials. It is important to emphasize that
pharmaceutical manufacturing control implies parameter monitoring and this usually requires measuring. This is why it can be said that product quality is impossible if there are no quality measures.

From the logistical point of view equipment can either be “dedicated” (used for a single product or for a specific group of products) or simply “multi-product” (used for different products, as necessary). In the first case, cross-contamination usually is not a major concern, but it should not be neglected, however, because degraded residues or bioburden from one batch might contaminate the following one. In the second case, cross-contamination is always lurking. Thus, ensuring proper cleaning is always a priority. In order to overcome this problem disposable equipment has been proposed, but for economical reasons, it still remains limited to particular cases [1].

**GMP REQUIREMENTS FOR EQUIPMENT**

Here are summarized the essential conditions for equipment as indicated in GMP:

1. **Design and construction**: Equipment should be designed and built to be appropriate for its function and to minimize the risk of contamination and errors. It should be of adequate size and make easy the operations (production, cleaning and maintenance).

2. **Absence of dead spaces**: Equipment should not have hollows where dust, dirt and materials can accumulate and promote microbial proliferation. These points, known as dead spaces, can be limited by good design and construction of equipment. The golden rule of sanitary design is avoiding them.

3. **Absence of threads, bolts or rivets**: Grooves and flutes are in general dead spaces and, as such, should be eliminated from critical parts of equipment (that is, from surfaces contacting products).

Screwed pipe connections are not acceptable. If necessary, connections can be made in two ways (never threaded fittings!):

- **Permanent connections**: welding without additional material (autogenously) and in an inert atmosphere to avoid oxidation (TIG orbital welding). See chapter 9.

- **Temporary connections**: sanitary fittings (triclamp® system or equivalent).
(4) Adequate radius of internal corners: Angles and corners should have sufficient radius to ensure that materials will not accumulate there and that they will accessible for cleaning.

(5) Smooth surfaces: Critical parts of equipment should be free of both microscopic irregularities (“bug traps”) and macroscopic ones.

(6) Full (100%) drainage: Equipment should be self-draining. It must be designed to avoid stagnation spots (Fig. 1).

Fig. (1). Self-draining equipment.

(7) Dead leg control: Dead spaces created by the blind branch of a pipe are known as “dead legs”. In the main pipe liquids flow, but in a dead leg they stagnate. Thus, products can accumulate there and deteriorate, not to mention the possibility of biofilm growth. Materials within a dead leg escape from the action of cleaning or sanitizing agents. This is why equipment should be free of dead legs (Fig. 2).

Fig. (2). Dead leg concept.

If any blind branch of a pipe was a dead leg, then, all instruments or valves should be considered as such. Traditionally, however, it is thought that what really matters is not the existence of a blind branch, but the stagnation produced in this piece of pipe.
CHAPTER 11

Products

Abstract: The application of the lifecycle model to the pharmaceutical products has modified existing approaches to quality assurance. The quality of a product is not simply the outcome of a GMP-compliant manufacturing, but the result of a GMP-compliant lifecycle. Product development means devising a formula and a manufacturing process, but most importantly, understanding thoroughly the product. This, known as quality by design, goes from defining its quality target profile to identifying the quality attributes of the starting materials and the quality parameters of the manufacturing process. Critical variables are the hallmark of a product during its lifecycle. They are identified and studied during the development stage and knowledge on them is increased during the product’s lifetime. Technological transfer means confirming that what worked in the development center will also work in the manufacturing plant, but also increasing and improving knowledge on the critical variables under industrial-scale conditions. Validation means verifying that the production process can be successfully controlled by means of the critical variables and that if these remain within proven acceptable ranges the process can be deemed under control and consequently yielding quality products. Thus, by monitoring critical variables each batch can be considered concurrently validated. The application of the above described approaches will enhance the level of quality assurance of the new products, but what happens with legacy ones? The model can be usefully applied to these latter too by using the same principles but proceeding step by step in a reverse approach, from knowledge to development instead of development to knowledge.

Keywords: Analytical validation, commercial manufacturing, computerized systems validation, CPP, CQA, critical variable, DAME, design space, development, discontinuation, DoE, evaluation, monitoring, PAT, process validation, proven acceptable range, QbD, QTPP, RTRT, technological transfer.

PRODUCT LIFECYCLE

Following the lifecycle model described in chapter 2, Fig. (1) shows the four lifecycle stages of a pharmaceutical product (i.e. development, technological transfer, manufacturing and discontinuation).

Although the phases of a product life-cycle have always been recognized, only recently they have acquired their fully developed outline. Besides, nowadays these stages are purely seen as different faces of the same reality and, consequently, it is acknowledged that they have to be considered in a global way because together they build quality.
New approaches came as a consequence of understanding that in practice there are not and may not exist two separated parts in the life of a product and of its manufacturing process (the first one devoted to obtaining knowledge and the second one of simple exploitation of this knowledge), because the process of increasing of knowledge is a never ending one and this includes manufacturing too.

**Development**

*The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product...*

*It should describe the knowledge that establishes that the type of dosage form selected and the formulation proposed are suitable for the intended use [1].*

**Periods**

Fig. (2) shows the periods of development and the standards which are applied (GLP and GCP). Postapproval studies (standard: GCP) and control (standard:
GVP) are also included to get a better understanding of the matter. For comparative purposes manufacturing (standard: GMP) is also incorporated.

Development is composed of three periods, which can be partially superposed. The total duration of this first stage of a product life-cycle is very variable but it is generally considered that usually averages ten years.

![Diagram of pharmaceutical development periods](image)

**Fig. (2).** Pharmaceutical development periods.

The period of discovery of an active molecule is very variable. In large research centers it is the result of the examination of huge quantities of candidates. It is well known that only a few of the molecules which are analyzed show interesting pharmacological effects. And from these latter it is necessary to eliminate those which show toxic side-effects. Only these rare molecules which are thus selected can pass to the second period of development. Another approach is starting with natural products of well-known effects in order to isolate the active principle and use it or a derivative with improved properties.

The non-clinical period is composed of toxicological and pharmacological studies developed in animals or in-vitro. Pharmakinetic and biodisponibility tests can also start. The former study the behavior of the molecule in the organism (*i.e.* its distribution, transformation, effect and elimination), whereas the latter determine how quickly and at what concentration the active principle is available to the organism, verifying, for instance, the evolution of its concentration in blood along the way (Fig. 3).
Global Quality

Abstract: Current pharmaceutical quality requires a global approach based on a quality system established on GMP and on risk analysis. Quality can be only ensured if hazards are identified and controlled to be kept at an acceptable risk level. Consequently, nowadays quality audits are not seen anymore as a simple compilation of checklist questions (yes/no/n. a.), but as an investigation to see if existing problems are detected and solved/controlled satisfactorily. This requires good knowledge and deep analysis on processes and products. As for the rest, it is also necessary to ensure that those pharmaceutical products which are dispatched from the warehouse, after being certified and released, maintain their quality when they reach their final consumers. Thus, it has been paid progressively attention to the hazards that waylay them in the often very complex distribution chain, including the risk of theft and counterfeiting. Taking into account the successful experience of GMP equivalent GDPs (good distribution practices) have been developed. It is also necessary to ensure the soundness of studies on drug products which are performed in different laboratories. And this requires a homogeneous quality approach. This is why, following again the same track, GLP (good laboratory practice) was prepared. And, finally, it is necessary to bear in mind that once a drug product has been licensed it is used by much more people than when it was tested during development, and this opens the door to unexpected reactions. Thus a pharmacovigilance system is necessary to keep updated its benefit-risk safety profile.

Keywords: ADR, counterfeiting, dispatch, GCP, GDPs, GLP, GVP, FEFO, pharmacovigilance, pharmacovigilance centre, PQS, sponsor, study, study director, study plan, supply chain, test substance, reference substance, transportation, warehousing.

CONCEPT

The different elements which make possible manufacturing quality pharmaceuticals have been analyzed in previous chapters. These elements are so varied (documentation, premises, equipment, personnel, etc.) that they require to be studied separately. Notwithstanding that, all these elements have to be designed for building together a precise system of global quality.

Although each case is different, in a general way it is possible to say that pharmaceutical plants can belong to two categories. In the first one appear those which do possess quality and in the second one those which do lack it. This way of putting things might seem surprising and too reductionist, but using current quality thinking it is rather correct, because possessing quality does not mean that everything is done faultless and there are no problems. It means, on the contrary,
that hazards linked to processes are known and understood, that a system is in place to monitor them and, most important of all, when problems arise this system can provide the adequate response to keep processes going under control. This is what makes the big difference; only pharmaceutical plants that know how to handle adequately problems have quality. A company managing satisfactorily several problems can be relied upon, whereas a firm just having a couple of problems, but not conducting them appropriately is very dangerous. This is why it has been said that having problems is not the problem; the problem is having problems and being unable of reacting adequately.

Thus, global quality means possessing a quality system capable of preventing most of problems, handling them satisfactorily and, thanks to continual improvement, reducing progressively their occurrence. Unfortunately the alternative to global quality is simply lack of quality. Let’s suppose a plant manufacturing hundreds of batches and all of them meeting requirements, but where every now and then a batch happens to be out-of-specifications and nobody knows why or detects it. Would it be possible to say that this plant has global quality?

Nowadays a global quality system should be capable of detecting and handling all problems and then finding out the root causes of these problems and implementing actions which improve the system in order to impede relapsing.

GLOBAL QUALITY ORGANIZATION REVIEW

The global review of the organization of a pharmaceutical plant from the quality point of view requires a grouping of the intervening topics in logical areas:

- Quality Assurance (QA);
- Supply chain (manufacturing processes);
- Personnel;
- Premises, Facilities & Equipment;
- Quality control (QC);
- Hygiene, security and environment.

Although this does not intend to be an audit guide it is recognized that can be used as such. In fact it means to be used as an “aide-memoire” to analyze a
pharmaceutical plant in terms of quality assurance compliance. Topics which have
to be considered are numerous, varied and difficult to group in a coherent way,
but some degree of systematization is indispensable not to get lost and in a maze
of matters (Table 1).

Table 1. Global quality organization aide-memoire.

<table>
<thead>
<tr>
<th>Area</th>
<th>Topic</th>
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| (1) Quality Assurance (QA)          | • Organization of the Pharmaceutical Quality System (PQS);
|                                     | • Administration of the Pharmaceutical Quality System (PQS);
|                                     | • Batch certification.                                               |
| (2) Supply chain                    | • Supplier qualification and purchase;
|                                     | • Warehousing of starting & packaging materials;
|                                     | • Weighing of starting materials;
|                                     | • Preparation of packaging materials;
|                                     | • Production;
|                                     | • Process validation;
|                                     | • Cleaning validation;
|                                     | • Warehousing of intermediate, bulk & finished products;
|                                     | • Shipping & distribution of finished products                       |
|                                     | • Outsourcing (vendor/contractor management)                         |
| (3) Personnel                       | • Organization;                                                     |
|                                     | • Management;                                                       |
|                                     | • Training.                                                         |
| (4) Premises, Facilities & Equipment| • Area classification;
|                                     | • Management;                                                       |
|                                     | • Qualification;                                                    |
|                                     | • Maintenance;                                                      |
|                                     | • Calibration.                                                      |
| (5) Quality control (QC)            | • Sampling;                                                         |
|                                     | • Testing;                                                          |
|                                     | • Environmental monitoring;                                         |
|                                     | • Water, steam and compressed air monitoring;                        |
|                                     | • Approval/rejection;                                               |
|                                     | • Cross-contamination & mix-up control;                             |
|                                     | • Retain & reference samples;                                       |
|                                     | • Stability management;                                             |
|                                     | • Pharmacovigilance.                                                |
| (6) HSE (hygiene, security, environment) | • Hazard detection and security measures |
|                                     | • Waste and effluent disposal                                       |
|                                     | • Outdated product disposal                                         |
|                                     | • Vermin control                                                    |
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Dr. Jordi Botet is a graduate in Biology as well as in Pharmacy. He attained Ph.D. degree in Pharmacy. Currently, he works as a consultant providing world-wide GMP guidance and training.

He has been involved in pharmaceutical manufacturing and in public health laboratories in Europe, Russia and South America.

Since 1997, he has been contributing to pharmaceutical projects, providing advice and training on GMP-related topics (quality risk management, pharmaceutical quality systems, quality audits, qualification and validation, clean rooms, process performance and product quality monitoring, documentation systems, etc.).

Dr. J. Botet has written more than thirty papers on microbiology, parasitology and on different pharmaceutical topics (utilities, premises, quality assurance, change control, risk management, validation, training, etc.).

He has published several books on GMP, pharmaceutical projects and quality systems. One of them including “Good practices in pharmaceutical premises and equipment”, has been published in French, English and Portuguese. Besides, he has made contributions in one chapter to an international book on Risk Management, published in 2012, which has been extensively downloaded in its electronic version.

Dr. J. Botet can use several languages and this has allowed him to give many lectures and courses across different countries of Europe, America, Africa and Asia.