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GOOD PHARMACEUTICAL MANUFACTURING PRACTICES

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ABSTRACT

In order to assure the quality of medicines and to encourage the implementation of the international system for the certification of the quality of pharmaceuticals, it was deemed necessary to specify the conditions under which pharmaceutical establishments should operate to provide full assurance that their products are safe for public health.

The French Government Order of 1.October.1985 therefore provides for the establishement of new recommendations on good pharmaceutical manufacturing practices:"Bonnes Pratiques de Fabrication et de Production Pharmaceutiques : BPF 1985".

Within the system of quality assurance, good pharmaceutical manufacturing practices represent that part which is concerned with manufacture.

Their implementation requires that the specifications of the raw materials and packaging materials, the manufacturing and packaging processes and the control methods be defined and written beforehand, that the premises and equipment be adapted to the intended uses and that the staff have received appropriate training.

Good pharmaceutical manufacturing practices directly concern production departments and packing area, control laboratories, storage areas, purchasing departments, departments receiving raw materials and dispatching finished products. They also concern departments issuing instructions and written or computerised documents intended for the departments previously mentioned.

Although the collection of recommendations thus published constitutes a detailed document, the possibility of there being different methods for attaining the same objective is recognised.

INTRODUCTION

The "Bonnes Pratiques de Fabrication et de Production Pharmaceutiques :B.P.C. 1985" has been carried out in France by a group of pharmacists on the initiative of the Public Health Ministry (1). This working group that I was presided, included seventeen pharmacists from industry, inspection and university.

Before presenting it, I would like to remind you the reasons of guides of Good Manufacturing Practices which appeared lately in various countries.

Medicines became, as many others, industrial products. If their producing has to follow general rules which lead to quality industrial products, they vary from others through some important differences :

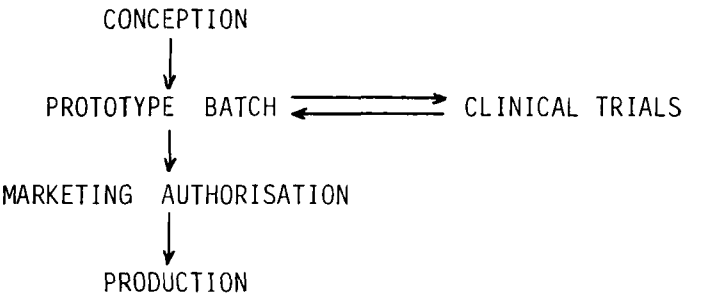
1. In case of medicines, the consumer that is to say the patient is not always able to appreciate its properties. His skill is not large enough to judge therapeutical effects, advers reactions and stability of products.

2. Medicines are generally not chosen by the consumer himself but by a third party: the physician.

3. Concerning the cost, we must notice that the consumer often does not or hardly not take care of it because the medicine will be partially or entirely reimboursed by the health insurance system which take over illness costs.

4.The last difference I will point out comes from the medicine definiton which is "presented as having curative or presentive properties toward illness".

For the medicine, the only real trials are the clinical ones which cannot be repeated on each batch. Trials on man are definitively carried out with the units of prototype batch in view of the marketing authorization of medicinal products.



The prototype is defined in the "dossier of the medicine" (2) by its manufacturing process and by physico-chemical substitution trials. These substitution trials will allow to check the compliance with the prototype when manufacturing.

For all these reasons, the legislation concerning medicines has become especially heavy in each country. National authorities intervene at different levels :

- through the marketing authorisation,
- through prices and reembursement rates,
- and at last through inspections of production sites.

In order fields of industry, it is the management of the company who decides to have or not a quality director and an organisation : system of quality assurance.

In the case of pharmaceutical establishements, the national authorities impose the presence of a qualified person in charge of the quality responsibility and implementation of official rules of Good Manufacturing Practices.

For the writting of the BPF 1985, the working group took into account the following :

1.Rules of Good Manufacturing Practices issued by the World Health Organisation (resolution WHA 22.50 of 25 July 1969 and the subsequent texts pertaining to it).This rules had been adapted in France and became the first issue: BPF 1978 (3).

2.The French legislation which principles come from the law of 21 Germinal Year XI (11 Avril 1803) that is to say just after the French Revolution. This law :

-entrusted to the pharmacist the manufacturing and sale monopoly of medicines,

-made out pharmacy schools,

-and founded a body of pharmaceutical inspectors.

Even before the word existed, this system was a system of quality assurance which still works by which should be modified owing to manufacturing process of medicines which from handywork became industrial work.

3.The quality management evolution in other industries which bases relied mainly on :

-the board management implication in quality,

-the staff participation in development,

-the substitution of oral transmission by written documents,

-the quality improvement through defects exploitation.

4.The GMP already published in other countries and particularly the 1983 issue of GMP of United Kingdom. Compared with the last one, the French text shows several differences,two of them are important:

-The quality of a medicine is what is described in the dossier of this medicine for the application of a marketing authorisation.

-The responsible of the quality in pharmaceutical establishments is a pharmacist called "Responsible pharmacist".

So as to give a legal form to the BPF, their publishing caused a government order of 1st October 1985. They have been

addressed officially on the same day to all the pharmacy inspectors in pointing out the following:

"The Pharmacy Inspectorate shall see, as before, to the application of these fundamental principles designed both to give a more accurate interpretation of general, legal and regulatory provisions and to form a basis for dialogue between the industry and the relevant authorities".

The PREFACE recalls the WHO resolutions, the Law of Germinal and the articles of the Code of Public Health to which reference is made in the text. It highlights that BPF 1985 are applicaple to industrial production of medicines intended for human use and to medicines prepared in advance in hospital pharmacies.

The INTRODUCTION gives the BPF 1985 content:

-22 chapters of recommendations,

-A glossary of the definitions of some important terms,

-The articles from the Code of Public Health to which reference.

It finishes with an important sentence: "Although the collection of recommendations thus published constitutes a detailed document. the possibility of there being differents methods for attaining the same objective is recognised. The objectives pursued are indicated at the beginning of each chapter".

It is then the spirit of the text which is all the most important.

I can put forward that general ideas, which guide writers are the followings :

-to avoid all confusion between medicines of various batches,

-to avoid all pollution or all cross-contamination,

-to avoid damages during production or storage,

-to take care on the fact that it is always possible to trace back the source of a defect,

-to take care that products protection can be conciliated with personnel protection.

We are now through the chapters, but only by seeing the essential. We will insist more on the content of some chapters which have a general widerange (4).

DISCUSSION

Chapter 1. Quality and Good Pharmaceutical Manufacturing

This chapter concerns the relationship between the concept of quality and the basic principles of GMP.

"Every pharmaceutical establishement must be implement a policy of quality, the aim of which is to guarantee, in the interest of public health, that medicines released provide and retain the quality required to the intended use .

In order to be in control of quality, the pharmaceutical establishement must devise and implement a system of quality assurance : this system must cover all phases of development, manufacture and distribution of medicines".

This beginning reminds the obligation for a pharmaceutical company to organise itself to guarantee the quality of medicines;

The first chapter then gives the ways to follow to reach this goal.

The starting point is the definition of medicine quality.Like for other industrial products, this quality may be defined as "the ability of a product or a service to satisfy the needs of its users" (5).

In the particular case of a medicine. the specifications are in its dossier of the application for a marketing authorisation. They are drawn up with reference to the scientific data obtained from a fundamental study of the elements of quality which may affect the efficacy. safety and stability of the medicine.

Quality assurance is obtained by implementation of an appropriate series of preestablished and systematic measures intended to ensure that the required quality will be obtained" (5). This serie of measures is called the system of quality assurance.

The system of quality assurance must be worked out on the basis of scientific and technical data concerning the medicines.

It must be adapted to the conditions of production at each establishment and thus constitutes for that establishment the internal rules which are implemented in accordance with the principles of GMP.

Measures should be taken to confirm that quality assurances procedures are being followed by personnel at all levels. It is recommended that self-inspection (periodic and detailed examination by a team of the production plant) or quality audit (examen or assessment of all or part of the system of quality assurance by a specialist or team designed by the board of management) be undertaken.

The Good Manufacturing Practices represent, within the system of quality assurance that part, which is concerned with manufacture. They should directly cover production departments and packaging areas. control laboratories, storage areas, purchasing departments, departments receiving raw materials and dispatching finished products. They also concern departments issuing instruction s and written or computerised documents intended for the departments previously mentioned.

Control is " the verification of conformity with pre-established criteria, followed by an evaluation" (5).

Quality control refers to that part of GMP concerned with the operations of verification of quality levels: acceptance or rejections of raw materials, acceptance or rejection of semi-finished or finished products, estimation of stability of products, examination of returned products and supervision of retained sample stores. This department should be under the authority of a person with appropriate qualification and experience, who has at his disposal the services of control laboratories.

Chapter 2. Personnel

The establishment and maintenance of BPF and system of assurance quality relies upon people. This very important chapter concerns organigramme, workforce,duties and delegations, job descrip-

tions, training and hygien instructuions.There must be sufficient qualified personnel to carry out all the tasks which are the responsibility of the manufacturer.

The French legislation demands the presence of a "responsible pharmacist" in every pharmaceutical establishment. He has the responsability of supervising the application of administrative regulations promulgated in the interest of public health which are particularly concerned with the manufacturing, packaging, storage, control and release of medicines.

The board of management and the responsible pharmacist have to draw up an organigramme of the personnel stipulating in writing spheres of responsability and fields of activity. Each person must receive a written job description. All personnel should be aware of the BPF and receive initial and continuing training relevant to their needs.

In this chapter and its appendices are described the tasks of responsible pharmacist. If necessary his responsibilities may be delegated but only to assistant pharmacist or another qualified person.

It is specified "Whatever the organisational structure of each establishment, the functions of head of production and head of quality control must not be assigned to the same person". In other words you can't be judge and party in the same time.

The head of the production department particularly has the responsibility to ensure that production are manufactured according to the GMP in order to obtain the required quality and to assemble all the constituent parts of the batch manufacturing and packaging record and transmit them to the person responsible for the quality control.

The head of the control laboratories has special responsibility to decide whether or not the results conform with pre-established specifications.

The head of quality control has the responsibility to accept or to reject batches of finished products. Within the measures to be taken by the board of management and the responsible pharmacist,

is the implementation of a staff training system : "Every establishment must adopt a staff training scheme concerning GMP. This scheme should not be limited to newly recruited staff but should provide continuing training, which guarantees that employes are up to date with scientific and technical progress. This scheme must be implemented and sustained".

In these two first chapters, we find back the basic principles for the managing of the quality: one responsible person and one organisation.

Chapter 3. Documents

Documents constitute an essantial part of the system of assurance quality.They reduce the risks of error inherent in all spoken communication and should be such that the history of each batch of medicines may be determined. They should be designed and prepared with care. Documents are classified in written instructions and records.

The written instructions for production and control include:
-General procedures required for a production plant that is to say; sampling procedures for manufacturing and packaging, general control procedures, procedures for cleaning, drying, computerised procedures, etc...
-Instructions deriving from the dossier of the medicines that is to say : specification for raw materials and packaging materials, specification for finished products, product manufacturing instructions and control methods for raw materials, packaging materials and products.

The records which collect all information concerning the progress of production and control: the batch record is the set of documents, always available, which constitutes the history of the manufacture, packaging,control and ultimate fate of each batch (distribution, reprocessing or destraction).

In appendice to chapter 3 are given for guidance only, the contents of various documents: written instructions for production and batch record.

Chapter 4. Premises

The buildings, production areas and facilities must be designed, adapted and maintained to suit to the operations to be carried out. They should be chosen so as to limit as far as possible external pollution and nuisances of any kind. Premises must be clean and be kept clean according to written instruction. The routes for the movement of personnel and materials must be rational.

Chapter 5. Equipment

Producing and control equipment should be designed, located and maintained to suit their intended purpose. Maintenance operations should not present any risk to the quality of the products. All parts of the equipment in contact with the products must be cleaned so as to avoid contamination of one product with another.

Chapter 6. General Organisation of Manufacturing and Packaging

"The general organisation of manufacturing and packaging must be so designed as to ensure that :

-the medicine produced and packaged complies with the acceptance limits specified in its dossier;

-proof is given that the series of methods and procedures provided have been correctly used to the manufacture and packaging of each batch;

-omissions, contamination, errors or confusion during the various operations are avoided".

This chapter contents many recommendations concerning:choice of suppliers, receipt of raw materials and packaging materials and different steps of manufacturing: preliminary operations, weighings of raw materials and operations of manufacturing.

Chapter 7. Packaging

"The packaging is a delicate and important pharmaceutical operation. The variety of operations carried out and the large number of products and materials used can lead to errors prejudicial to public health. Consequently, the almost rigour must be

exercised from the design of the materials to the dispatch of the medicines".

"When setting up a programme for a packaging operation, particular attention is needed to avoid risks of cross-contamination, mix-ups" or substitutions arising during the simultaneous packaging of medicines in cases when their pharmaceutical forms or their packaging materials make this particularly likely (similarity of apperance between products to be packaged and between packaging materials)".

It is recommended that a quality audit be carried out at the suppliers of packaging materials and particularly printed ones (cases, labels and leaflets).

Chapter 8. Storage

Warehouses must be designed and laid out to ensure that products are well preserved and to allow efficient management of different categories of stored products. Distinct areas or administrative segregation must be provided for raw materials, packaging materials, semifinished or finished products, thermolabile substances substances sensitive to moisture or light, flammableproducts, toxic substances... products in quarantine and products accepted or refused.

The storage facilities should be cleaned according to procedures specifying the means to be used and frequency.

Chapter 9. Control Laboratories

The personnel mus t be particularly appropriate to the task assigned to them. The techniques used must be defined and validated. The results of the controls must be transmitted to the person responsible for quality control so that he can, after examination of the batch records, make a decision of acceptation or rejection.

Recommendations are given concerning reference substances and various reagents : chemical, microbiological, cellular and animal ones.

Chapter 10. Validation

Validation is an "operation intended to demonstrate that every process and procedure used for production, packaging or control of products does actually lead to the expected results.

Validation is an element of the system of quality assurance which guarantees for a given medicine:
-the reliability and reproducibility of the principal processes described in the dossier,
-the attaintment of the provided quality.

In view of the variety of problems posed by each of the pharmaceutical operations, only general recommendation can be made in cases of validation of a new production process, retrospective validation and revalidation after modifications in manufacturing conditions. An example is given: the validation of sterilisation processes using moist and dry heat.

Chapter 11. Distribution

Distribution should be designed so as to avoid any confusion and allow retrieval of the consignee's identification in case of pointed out defects.

Chapter 12. Complaints,Recall of Medicines,Returns

At the company level, an organisation and preestablished procedures must exist which define the methods by which complaints are to be examine, medicines recalled and returns examined.

It is evident that the inquiry done after a complaint and the study of returned medicines, have to end at a judgment on the efficiency of quality assurance system with the view to improve it.

Following chapters 13, 14, 15 and 16 are devoted to special pharmaceutical forms. They contain only specific recommendations for these forms which are of course concerned by the other chapters.

Chapter 13. Liquids, Creams and Ointments

For these pharmaceutical forms, the principal risks are the microbial contamination which may be carried by the water used and the insufficient cleaning of vessels and systems of transfer pipelines, circulation pumps...)

Chapter 14. Oral Dry Forms

These forms pose mainly the problem of cross-contamination by emission of dust. The best solution is prevention by closed systems of manufacture and transfer or by use of special equipment to capture the dust at its source. Likewise, two different products should not be manufactured at the same time in the same area.

Chapter 15. Sterile Preparations

This chapter is very important. Sterile preparations, more than any other medecine, must be manufactured according to procedures carefully established and rigorously applied in order to guarantee their sterility and to prevent particulate and pyrogenic contamination.

Specific recommendations are given concerning the training of staff, the premises, equipment, raw materials, the environment in the productions areas and the manufacturing process, specially the sterilisation by filtration, heat, gas or radiation. The validation of process is very important.

Four appendices of this chapter concern:

1.Sterile preparation not sterilised in the final container. The preparation and filling phases of these products must be carried out under conditions of controlled asepsis.

2. Injectable preparations for infusion sterilised in the final container. Particular problems are posed by the quantities of water used, by the control of homogeneity and good running of sterilisation and by of pyrogenic and particulate contamination.

3. Controlled environment zones. Different zones are defined according to the nature of pharmaceutical operations. Some values of particulate and microbial contamination levels are given for each of the zones. The most important point is to determine trends and detect possible deviations from the fixed mean level. Special recommendations concern clothing, working methods and patterns of movement, cleaning and decontamination of the premises, monitoring of controlled environment zones and control protocoles.

4. Validation of sterilisation process by heat. The sterilising value and the reproducibility of a thermal treatment should be determined by trained and experienced staff using validated equipment. An example of practical application is given.

Chapter 16. Homeopathic Preparations

Medicines for homeopathic use is most often concerned, with infinitesimal doses which make analytical control of the finished products impossible. The guarantee of the quality can be obtained only by the implementation of GMP.

Chapter 17. Sampling

Generally controls cannot be carried out on the entire batch. To avoid risks to give a false sense of security, steps must be taken to ensure that samples withdrawn are as representative as possible. In this chapter, rules are given for sampling of raw materials, packagingmaterials and finished products. Special attention should be paid to defining batches of raw materials.

Chapter 18. Electronic Data Processing

The replacement of manual operation by data processing systems and programmable controllers must not entail an increase in the risk or error. Measures of security must be adapted to these systems and a procedure describing the operations of validation must be established.

Chapter 19. Manufacture of Products Hazardous to Personnel

It is the only chapter which the main reason is not the products protection. Dispositions adapted to each situation must be taken to prevent risks to the personnel who handle them: toxicity, physiological action at low dose or sensitization. Particular attention should be paid to cytostatics products.

Chapters 20 and 21. Reprocessing, Recovery

Reprocessing is the return of all or part of a non conforming batch of medicines. Recovery is the introduction of all part of earlier batches into a batch of the same medicine.

These operations must be done according to a defined procedure after estimation of the risk encurred.

Chapter 22. Sub-Contracting

Sub-contracting is the "execution by an independent person or organisation, the contract acceptor, of an operation or vertification for another person or organisation, the contract giver".

Sub-contracting can lead to risks of misunderstandings and consequently of unsatisfactory quality.

This should be a written contract between each party which clearly establishes the responsibilities.

Sub-contracting concerns manufacture, packaging, control and maintenance.

CONCLUSION

Here are the main points of the BPF 1985. They essentially concern, as you could notice, industrial production of medicines.

Nowadays a working group of the Commission of the European Communities prepares an European guide of GMP. This guide should be used as a reference for the examination of the application for marketing authorisation of medicines and for inspection. The draft for consultation which has been given to study to the pharmaceutical industry of the member states of the EEC had been written from the British and French GMP.

In France, this year an another guide aimed at the officinal preparation of medicines in a pharmacy has just been published : "Bonnes Pratiques de Préparation Officinale" (6). In a pharmacy, means for developing are not on the same scale and problems are not so complex as in industry. But the pharmacist has to take care of the quality assurance.

The individual preparation is personnalized. It replies generally to a medical prescription in view of the necessary therapeutical adjustment for a certain patient. It must be carried out under the pharmacist monitoring with all traditional care.

The batch preparation can not be talked about without having first made out a dossier relying on scientific basis. The pharmacist

should have qualified collaborators. He must be sure of the quality of raw materials. The preparation must be done according pre-established procedures in correct premises and equipment.

In hospital pharmacy, the recommendation either from one or another guide can be applied due to circonstances and to manufacturing scale.

In any case, the system of assurance quality of medicines rely on the pharmacist ability, who must keep in touch with the evolution of scientific knowledge by the means of an appropriate training course.

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