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Good laboratory practice in pharmaceutical quality control

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Abstract: Experience in establishing a system of 'Good Laboratory Practice' (GLP) in the pharmaceutical industry is discussed with respect to the historical development and specific aspects of the system: training, safety, documentation, equipment and personnel management in the laboratory.

Keywords: *Quality control; good laboratory practice; good pharmaceutical manufacturing practice; solvent toxicity; industrial safety.*

Introduction

The subject of Good Laboratory Practice in Pharmaceutical Quality Control seems so wide that it is necessary, as a preamble, to put it into context by first reviewing good drug manufacturing practices.

Historically, the first text dealing with 'Good Manufacturing Practice' (GMP) was an amendment to the US Federal Food, Drug and Cosmetic Act issued in 1962. This decree formalized the cumulative experience and noted, for example, the necessity of recording control operations, of knowing the history of the batches, of ensuring the prevention from contamination, etc.

This concept was established at a meeting of the World Health Organization through resolution WHA-22-50, dated 25 July 1969 [1], in which the 22nd World Health Assembly recommended the member states to adopt "the regulations on good practices applicable to the manufacture of drugs and to the control of their quality" as well as "the certification systems of the quality of the drugs subject to international marketing". This publication, amended in 1972 and in 1975, was produced in response to a number of intelligent people who organized various symposia, such as those of the Fédération International de l'Industrie du Médicament held in Geneva in 1971, or who were responsible for issuing directives, such as those from the European Economic Community, recommendations from the Fédération Internationale Pharmaceutique for Benelux, regulations from the Pharmaceutical Industries Association and publications in numerous countries, mostly under the aegis of national pharmacopeias.

What is 'Good Manufacturing Practice'? GMP is a set of principles or general

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proposals (not regulations), which have to be adapted and applied for each particular situation. In essence, GMP gives the appropriate definitions and makes recommendations for the workshops, warehouses or laboratories of a production unit, satisfactory premises, equipment, hygiene and cleanliness, document storage etc. GMP is achieved by means of planning, monitoring or control.

As regards these principles, there appears to be a new trend: the very concept of 'building quality' has changed. As a result of the complexity of production in pharmaceutical industry, safety can no longer be ensured only by controlling the finished product. In practice, it appears that the logistical support of quality must be obtained at two different levels: 'Quality Control' (QC) and 'Quality Assurance' (QA).

The first, Quality Control, is mainly based on analysis: analysis of all raw materials used in the manufacture, analysis of semi-finished, semi-packaged and finished products, analysis of packaging materials. The quality control department must also define the storage conditions and the shelf-lives of raw materials and semi-finished products. Beyond Quality Control a wider concept has developed, that of Quality Assurance. This deals with production facilities and storage warehouses, as well as control laboratories. QA is concerned with the management and control of all aspects of pharmaceutical manufacture. So, after the euphoria induced by the powerful possibilities of chemical analysis, a more precise evaluation of its limits has led to a revised assessment in the field of industrial manufacture.

More recently, an improved knowledge of the 'imponderable' factors and of those parameters hard to control, coupled with the boom in analytical science, seems now to be leading to a fresh appraisal of the role of analysis. In any case analytical control remains the key-stone for building the quality required by the essential character of the drug.

In 1975 during control operations carried out in pharmaceutical firms and subcontracted toxicology laboratories, the US Food and Drug Administration (FDA) noted major deficiencies or errors in the reports submitted. The FDA set up the first Good Laboratory Practice (GLP) document, published in the Federal Register on 19 November 1976, and entitled "Non-Clinical Laboratory Studies, Good Laboratory Practice Regulations". Based on comments received or presented during public meetings, a final text came into effect after publication in the Federal Register on 22 December 1978, subsequently amended on 4 December 1979. As a historical footnote, the abbreviation "GLP" seems to have been mentioned first in New Zealand in a "Testing Laboratory Act". It should be noted that owing to their origin and their contents, the GLP regulations expressed general recommendations, directed initially at toxicological studies.

Beyond this basic document, the international situation becomes highly complex due to the multiplicity of supranational approaches. In this respect one can quote in particular the statement of the O.E.C.D. principles, the meetings of the pharmaceutical sections of the European Organisation for Quality Control and E.C.E.T.O.C. Also to be noted are the conclusions of the seminar held in Budapest in 1981. In any case, no text has so far received the agreement of the countries concerned. The principles of good laboratory practice are still the subject of discussions; one can mention for example the differences existing between the FDA documents and the E.C.E.T.O.C. proposals.

The contents of the published documents follow the general idea of GMP: after the definitions of terminology, some general principles follow, concerning laboratory organization, the qualification and training of personnel, facilities, animal breeding and testing room, animal care, reference products, protocols for investigation, and the

recording of results. It should also be noted that in the FDA document the notion of disqualification of laboratories and its public disclosure is mentioned.

In brief, these texts constitute an allegedly exhaustive inventory of the 'parameters' controlling the reliability of results from a toxicological laboratory and prescribe their appropriateness to the intended use. As an example, one can mention the common-sense rules stated as laconic aphorisms: "the personnel shall be adequate in number and background of education, training and experience . . . and should have capabilities commensurate with their assigned functions. Personnel should have a thorough understanding of the control operations they perform".

As regards buildings, GLP requires that their dimensions, construction, location as well as the facilities of testing laboratories be adapted to the appropriate performance of the study. The same lack of specificity applies to comments on laboratory animals, their feeding, their litter and the materials used for cleaning. This lack of specificity, combined with the absence of regulations for physico-chemical or microbiological control laboratories, is quite regrettable and deserves to be taken into consideration.

The following comments on various technical aspects in the field of analytical development or quality control are intended to reflect personal experience in the field of GLP.

Training and Safety

Dealing first with the problem of personnel training, this requires the setting up of a programme applicable to management staff as well as to technologists. Such a programme should include the distribution of journals and internal documents, and participation in lectures or external courses. By way of introduction, information should be given on the drug and the relevant regulations, and on the company considered as being part of the national pharmaceutical industrial system. Then, a more general training should follow in the field of pharmaceutical technology and quality control, with an introduction to economics, statistics, data processing and foreign languages. Finally, there should be technical training concerning the use of equipment, documentation and occupational safety. In connection with the last, detailed information should be given about the toxicity of the substances handled and especially about the solvents.

A few decades ago humanity entered the 'chemical era' which brought a large improvement in the conditions of human life. However, no molecule can be considered *a priori* as free of toxicity and evaluation of the risks has resulted in the 'ecotoxicological anxiety' being experienced now.

It should be recalled that, beyond the very restrictive notion of fatal acute poisoning, the long-range effects, i.e. chronic toxicity caused by repeated intake of small doses of a drug, should be taken into consideration. One should also consider dose accumulation and the accumulation of effects, such as in the example of butter yellow, or the delayed 'hit-and-run' effect, when the toxic agent itself disappears, while its toxic consequences remain and continue to increase. Peculiar forms of toxicity are also related to embryotoxic actions, mutagenesis and carcinogenesis.

The handling of toxic substances is a daily practice in most control laboratories. Although penetration by the oral route is extremely rare, penetration by the pulmonary route is most frequent, its efficiency being comparable to that of the intravenous route, owing to the considerable surface area of pulmonary alveolae and also to the intrinsic sensitivity of the organ itself. The cutaneous route should not be omitted, since accidents

are well known to result from penetration via the palpebral route during the determination of melting points.

In laboratory practice, the handling of poisonous substances cannot be avoided if they are to be tested. As regards reagents, restrictions on their use have been prescribed, and certain legislation has sometimes gone so far as to ban keeping some reagents. Such is the case for benzidine and some amines which are carcinogenic to the bladder. Particular attention has been paid to solvents, owing to their massive use and their volatility. In the following, a brief classification of solvents and the usual reagents is given according to their toxicity.

Among the hydrocarbon compounds, benzene — 'Public Enemy Number 1' as Professor Truhaut called it — was widely used in the laboratory in the past. In addition to its acute toxicity, an insidious and irreversible chronic toxicity has been observed. Under these conditions, the total banning of benzene and benzene-containing mixtures must be the rule when an alternative solution is possible. Otherwise, handling and disposal must be subject to maximal precautions. The following replacement solvents have been recommended: toluene, which can entail acute toxicity but is devoid of chronic toxicity; *n*-hexane or preferably cyclohexane.

The chlorinated solvents are poisonous substances with two critical properties: their volatility and thus their rapid penetration via the pulmonary route, and their solubility in fats, which is the cause of neurotoxicity. Carbon tetrachloride is very poisonous but little used as opposed to chloroform, which is responsible for myocarditis, hepato-nephritis and liver or kidney cancers. 1,2-Dichloroethane is hepato- and nephro-toxic, mutagenic and carcinogenic. Trichloroethylene and tetrachloroethylene cause nervous and cardiac disturbances. On the other hand, methylene chloride and 1,1,1-trichloroethane are considered not to be very poisonous and thus constitute good replacement solvents.

Alcohols are in general not very hazardous, except for methanol, which is a cumulative poison whose aggressive effect on the optic nerve is well known. Ether and tetrahydrofuran are slightly poisonous but their tendency to form peroxides and their inflammability require particular precautions. Dioxane is highly carcinogenic. Also to be avoided are aniline, pyridine, *o*-toluidine, quinoline, acetonitrile, carbon disulfide and hexamethylphosphoric triamide (HMPT, hexametapol).

The recommended substitute solvents once again are: cyclohexane, methylene chloride, 1,1,1-trichloroethane, ethanol, propyleneglycol, acetone, tetrahydrofuran, dimethylsulfoxide. Among the carcinogenic reagents, benzidine should be replaced by 3,3′,5,5′-tetramethylbenzidine which is neither mutagenic nor carcinogenic. While repeating the recommendation to ban some of them from the laboratory, the handling of solvents requires particular precautions: the wearing of glasses, the use of bulbs with pipettes, protection of the skin, operation under a hood; not forgetting to keep solvents away from any source of heat or static electricity and to minimize the amounts stored. But sometimes in trying to make things better, one ends up by making them worse. Thus by extending the list of substances considered carcinogenic, one can in fact create a further problem by omitting to call into question the possibility of carcinogenesis. Isoniazid, a hydrazine derivative, is an example; at the height of its use, it no doubt had a major tuberculostatic activity.

Mention should also be made of the anonymous leaflets, which have been put into circulation in several countries of the European Economic Community during recent years. The classification of food additives was accompanied by erroneous if not false statements: in fact, citric acid was the most dangerous.

With regard to training related to safety in general, written directions should be prepared, distributed and displayed. It is appropriate to remind the personnel from the outset that safety is 'everyone's business'; this should be a permanent reflex response. Safety concerns the labelling of any container and closure, the essential individual precautions, the checking of equipment and materials at the end of a day's work, the removal of waste. More technical are the instructions dealing with the removal of peroxidizable substances and the risks of implosion. The list of incompatible chemicals, i.e. those giving violent, uncontrollable or hazardous reactions, should be widely distributed.

Other instructions are concerned with discipline at work, but in order to avoid a long listing, consider, for example, the cleaning of general equipment after work, including perhaps the polarimeter and spectrophotometer cuvettes, potentiometric electrodes and so on.

Documentation

Another section of good laboratory and quality control practice deals with the documents made available to the technicians. For the testing of raw materials, whether or not subject to a monograph in the European or a national pharmacopoeia, the relevant specifications and methods appear not to be always sufficient. In order to be efficient, the working document should contain additional information and remarks which can help the operator, starting with the relevant indications, if required, concerning the toxicity or any hazardous characteristic, i.e. data not mentioned in the European Pharmacopoeia, followed by any other suitable explanation likely to be useful for handling, e.g. the reagents to be used, the method of destruction after testing.

Another particular point concerns the training of technicians. It often seems advisable and perhaps even essential to supplement the instructions with an explanation; this can help the operator perform better. Two examples selected from the French pharmacopoeial methods can be cited to illustrate this.

The limit test for sulphates includes the addition to the test and standard solutions of a highly dilute suspension of barium sulphate. It is known, of course, that this is aimed at priming the crystallization during the reaction of sulphate ions with barium cations. But somebody could be surprised and just in case, an explanation should be given in the working document detailing the general procedure.

As regards the heavy metals test, a foreword should draw attention to several points. First of all, the determination is imperative for active principles subject to long-term administration at high doses. Some tests have shown that determination of heavy metals from ash or even sulphated ash residues, as performed in the past, is a bad procedure because of the occasional loss of the elements to be tested. It has also been observed that in the presence of cations loss does not occur if the calcination is run at a temperature not exceeding 500°C. The methods currently described in the pharmacopoeias for the destruction of the organic residue mention the use of magnesium oxide or magnesium sulphate and sulphuric acid. The final phase of the determination of heavy metals includes the addition of a small amount of the test solution to a standard solution. The reason for this is to check that the test solution does not contain any heavy-metal-complexing substance which might inhibit the formation of sulphide. If this problem occurred, it would be observed with the standard solution.

Equipment

In order to avoid a long listing, mention should briefly be made of the directions for equipment use. It should be remembered that in the detailed explanations which have to be made available to the technicians, in addition to the instructions for cleaning, the maintenance of spectrophotometers, potentiometers, polarimeters, chromatographs etc. should be monitored at two levels: in-house, by a systematized, programme of action carried out according to a maintenance log-book; and periodic checking performed by the after-sales service of the equipment manufacturer. The need for proper calibration of laboratory equipment was expressed recently in the European Pharmacopoeia by the introduction in the general monograph on visible and ultraviolet light absorption spectrometry, of a measurement of the resolving power of the apparatus and of the technique for selecting the slit width.

It should be emphasized that in a laboratory guide everything ought to be mentioned, from the smear-free operation of burette taps in the determination of non-saponifiable matter, to the development of a thin-layer chromatogram, or the explosion risk associated with chloroform–acetone–ammonia mixtures.

Laboratory and Personnel

Good cooking requires good ingredients. Likewise, good drugs require good raw materials and good testing requires good equipment and good reagents. But this also requires 'know-how' and a 'willingness to do well'.

It is an accepted fact that 75–80% of operating deficiencies can be controlled by the management responsible for solving problems relating to defective equipment, inadequate procedures or any lack of technical training. But the 20–25% remaining must be the responsibility of the operating personnel, who should be motivated to assume this task.

"By the sweat of your brow shall you earn your daily bread", as in *Genesis*, is a material reality for man. The moral notion of labour, based on the doctrine of Luther and Calvin, has been carried on through the industrial revolution to the 20th century. Since the end of the Second World War numerous changes have occurred in the economic and social fields, with the result that the individual's behaviour and aspirations in professional life have been changed. Frederick Taylor, in his "Principles of Scientific Management", stated that "employees" are uniformly motivated by the desire for money, whereas other motives are inconsequential. More analytically, A.H. Marlow notes that the needs of man have their own hierarchy: first come the physiological factors (food, clothing, leisure), then the factors of safety and environment of workplace. If these needs are not provided for, any attempt at motivation will be inefficient. The motivating factors are respectability, career development and the level of responsibility. Consideration should be given to the quality of professional life, as produced by a pleasant environment, implying more authentic human relations.

What course of action shall be taken in the context discussed? The management staff of a control laboratory is constantly concerned at the gravity of the consequences that potential mistakes could entail. Beyond the factors that can be controlled, another notion appears, that of confidence in personnel. In the author's experience, lack of integrity and unfairness are very rare and can in fact be rapidly detected by cross-checking.

From the outset it is necessary to give employees the necessary background

information on the drug concerned. Emphasis should be given to the importance of quality in the development of the drug, of its consequences and of its necessity at the final control stage. Such notions may seem obvious, nevertheless they require to be regularly repeated.

The laboratory manager should then do his best to make work more meaningful and satisfying for the employees. The rotation of personnel performing different tasks is recommended, but is contradictory to the specialization which has now become essential. The manager should also participate in dialogue on decisions made about the content of work and its criteria for evaluation.

The question arises as to whether the wider use of instruments entails any danger? Apart from the greater reliability and convenience of equipment, does not the continuous use of a chromatograph, for example, lead to monotony? Twenty or thirty years ago, analytical laboratory technicians applied procedures that directly involved following a chemical reaction in an Erlenmeyer flask or in a beaker, the chemical scheme being before their very eyes. Such a situation had many advantages, the most direct being the opportunity to understand the importance of operating conditions and thus to be able to monitor them, thereby detecting more rapidly the causes of any errors. It could be said that the use of sometimes fully automatic equipment is not conducive to intellectual involvement? However, it is advisable for laboratory managers to fight against the undesirable evolution of the analytical technician. In order that his task does not lose its soul, the chemical intellect must remain.

A second example concerns the microbial assay of antibiotics and bacteriostatic substances. Standardization of the turbidimetric procedures has resulted in the design and marketing of special computer-aided equipment, to give automated control, the detection of errors, feed-back and auto-regulation. After statistical analysis of the raw data, the equipment prints out the results with a statistical assessment of their quality. As far as the technician is concerned, the work is then reduced to some manual operations. The balance could be redressed if all preliminary operations such as weighing, dilution and distribution were performed by the same operator, who would use the elementary statistical data to make the most appropriate decision as regards the results of analysis. The computer should make no decision for approval or rejection, but should only supply the analyst with the best information, so that the best possible objective decision is made. In this way, work can be personalized and made less tedious. It may be interesting to note that a recent survey performed in the analytical control laboratories of an important pharmaceutical firm gave the following results, when technicians were invited to express themselves freely about their aspirations. They only mentioned the loss of interest resulting from automation of their work.

On a more optimistic note, the following anecdote comes to mind. In the Middle Ages a bishop was inspecting the building site of a big church. Noticing three workers who were cutting stones he asked each of them in turn, "What are you doing?" "I work to eat" answered the first; and the second answered "I have a lot of children and I work to feed them". The third said, "I am building a cathedral".

There is no doubt that there will always be cathedral builders.

Reference

[1] World Health Organisation Expert Committee on Specifications for Pharmaceutical Preparations. *WHO Organ. Tech. Rep. Ser.* 418, Annexes 1 and 2. Geneva (1969).

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