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MANUFACTURING CONTROL AND RECORDS

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Past and present attempts to ensure a proper quality control of pharmaceutical preparations have been based, in most countries, on an assumption that specifications of quality relating to each final product could be written down and that compliance with these specifications would give the guarantee required. In some countries final product specifications are to be found in pharmacopoeias only and are very limited in scope. Certain countries, on the other hand, have published extensive detailed specifications of certain classes of pharmaceutical products e.g. FDA (USA) in relation to antibiotics, but in fact very few, if any, of these specifications, taken alone, can guarantee that the quality is what it purports to be. It is doubtful whether final product specifications are possible which would allow an independent control laboratory to verify that formulated products have been prepared from separate ingredients, each of which complied with its own particular minimum specifications.

Most final formulated product specifications in pharmacopoeias, FDA Regulations, and in the files of manufacturers assume that individual constituent materials, each complying with their own specifications, have been used and the final product specifications are usually only

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sufficient to ensure that proper mixing and distribution of the active principle between doses has been achieved. It is often impossible, by examination of the final product in the laboratory, to ensure that material of a certain specified minimum purity was used in the formulation, nor of course can the stability of the product be predicted. The security that can be assured by a national control laboratory restricting itself to an examination of the final product may therefore be illusory.

In the case of preparations which are specified in pharmacopoeias, when limitations are applied to the nature of the various diluents, buffering agents, excipients, colourings, coatings, etc. it is probable that a method of assay should enable an assurance to be given that a minimum quantity of active principle is contained in a given dose. This is of course a useful check and a highly desirable one to ensure efficacy but it may be quite insufficient to ensure safety.

With many specialities produced only by a given company even this assurance of correct dosage may be difficult for the unaided national control laboratory to guarantee without extensive development of analytical techniques specifically tailored to the particular speciality. Recognition of the vulnerability of the quality control of drugs at a national level when based only on an examination of the final product has been largely responsible for the drawing up and publication by WHO of recommendations relating to "Good Practices in the Manufacture and Quality Control of Drugs" (WHO, 1969).

This document is an international recognition of the fact that only the manufacturer of a drug is in a position to ensure that the drug is prepared from components of adequate purity, compounded in such a way that their quality is not adversely affected by processing and that, when distributed to the patient, the final form will provide a safe and efficacious dosage. For many modern formulated drugs, where it is impracticable for the national authority to guarantee the safety and efficacy, then the national authority must ensure that this safety is guaranteed by the manufacturer himself.

"Good Practices in the Manufacture and Quality Control of Drugs" is a set of recommendations only and is directed to advise the manufacturer as well as the national control authority. If these guide lines are accepted and properly implemented by a manufacturer then "Finished product specifications" as defined by the WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO 1969) Annex 1, pg 16 may be sufficient "criteria on the basis of which the designated control authority determines the acceptability of finished drugs".

It cannot be too strongly stressed that without an assurance that "Good Practices" are being adequately affected, "Finished Products specifications" are of very limited value. The necessary assurance of implementation of "Good Practices" can only be obtained if a National Authority can restrict the manufacture of drugs to licensed manufacturers; the license being granted by the National Control Authority only after it is convinced that "Good Practices" can be followed by the particular manufacturer. The license should be allowed to remain effective only as long as "Good Practices" are implemented. The granting and continuation of the license should be dependent on satisfactory inspection by suitable government inspectors. In this way "Finished Product" control can be supplemented by the necessary "in process control" to ensure a satisfactory end product.

This procedure of manufacture under government license with inspection to ensure proper manufacture was found necessary as early as the 1920s for biological products such as vaccines and sera and has been the subject of many detailed recommendations by WHO (See report of WHO Expert Committee on Biological Standardization (WHO 1969) pg 61. The increasing complication and potency of modern therapeutic agents, of non-biological origin, which are commonly compounded into the final dosage form by the "manufacturer" rather than the pharmacist requires that these products receive equal attention by national authorities during manufacture to ensure that they are of proper quality.

The WHO "Good Practices in the Manufacture and Quality Control of Drugs" is a set of guide lines, it does not attempt to, and could not, instruct the manufacturer how to do his job properly. It does, however, lay down minimum requirements, which if followed, will allow a national authority to obtain maximum security in relation to the safety and efficacy of drugs manufactured within its territory. It is important to recognize that ultimate responsibility must rest with the manufacturer but legislative implementation of a licensing of manufacture based on "Good Practices" will enable the National Authority to ensure that the manufacturer accepts the responsibility.

The granting of a license should be dependent on the manufacturing establishment possessing minimum facilities for production and control such as those suggested in the WHO recommendations on "Good Practices". An adequate Analytical Control Laboratory is essential and this laboratory should be closely involved at all stages from development of a new product to its final marketing. Satisfactory quality must be planned into the product and the Control Laboratory should carry out stability studies on new formulations before they are marketed or on established ones if any significant change is made in production procedures. The laboratory should accept responsibility for the quality of "starting materials" and lay down those analytical procedures to be carried out at various intermediate stages of manufacture which cannot be performed on the final product. In many instances it will be necessary to develop methods of analysis specific to a particular product. The more extensive the analytical control carried out at different stages of manufacture the less extensive are the tests which must be applied to the final product. Tests for impurities in the components of the preparation should be performed before compounding and if undesirable degradation products or residues may be introduced during manufacture they should be examined for at the appropriate stage in manufacture. The Analytical Control Laboratory should also be responsible for monitoring manufacturing facilities, to minimize and control adventitious contamination of the products either of microbial or chemical origin.

It is self evident that the quality of the final product will be related to the quality of the staff of the control department. However, efficient staff, working in good laboratories may be rendered ineffective if the expert

responsible for the quality control function does not possess adequate authority. The expert responsible for quality control should not be responsible at the same time for organizing and managing production, but should have authority at least equal to that of the expert responsible for production. All samples necessary for quality control examination within the manufacturing establishment should be taken by quality control personnel, no product should pass from quarantine to the market without the consent of the expert responsible for quality control. This expert carries the major responsibility for ensuring the safety and adequacy of the products released onto the market and should be given as much support as possible by the appropriate national authority. A license granted to a manufacturer entitling him to manufacture drugs should preferably name the expert scientific staff who are responsible for different functions including quality control. Changes which are made in these staff appointments should be notified to the national authority for its approval.

The WHO "Good Practices in the Manufacture and Quality Control of Drugs" recommends, pg 19 that expert staff:- "should preferably not have any interests outside the manufacturers organization that (a) prevent or restrict their devoting the necessary time to their assigned responsibilities or (b) may be considered to entail a conflict of financial interest." These restrictions to the interest of expert staff should be absolute and not just preferred. They should apply equally to the staff of the "National Control Authority". It is possible that in a particular situation a shortage of adequately trained scientific staff may be a complicating factor but the degree to which the restrictions are observed will seriously affect the degree of confidence that can be placed in the products of a particular company or country.

The WHO "Good Practices" details the various records that should be kept by a manufacturer of drugs e.g. 8.5, 8.6, 8.7 and 10, 12 and 13. It should be stressed that the recommendations are minimum ones. Records should also include details of the evidence justifying the formulations used, e.g. their stability, the methods of manufacture and analysis when these have been developed for a specific situation. It is probably unwise

to attempt to define in detail for a particular manufacturer what records he should keep. Any information which an independent scientific expert (e.g. government inspector) needs to evaluate the history of any batch of drug from the reception and testing of the raw materials used to the distribution of the formulated product to the market should be available in the files of the manufacturer. It should be made clear that the responsibility for ensuring the adequacy of the records is a responsibility of the manufacturer. The records should be kept in a durable form, readily available and intelligible to the inspector of the national authority. Records relating to all batches of material manufactured should be retained for a period of time defined by the national authority or should only be destroyed with the permission of that authority.

The value of the records does not only lie in allowing the proper evaluation of a specific batch of a drug, when necessary, but also in providing evidence of consistency of quality from batch to batch. For this reason it should be a requirement that records relating to all batches should be kept including those batches which have been rejected because they are not suitable to be released for sale. From such complete records it is often possible to detect trends in change of quality an investigation of which might lead to an improvement of specifications and manufacturing procedures.

References

WHO Good Practices in the Manufacture and Quality Control of Drugs, WHO Expert Committee on Specifications for Pharmaceutical Preparations 22nd Report. Wld Hlth Org. techn. Rep. Ser., 1969, 418 Annex 2, 17.
WHO Expert Committee on Biological Standardization 21st Report, Wld Hlth Org. techn. Rep. Ser., 1969, 413 Annex 3, 61.