WORLD HEALTH ORGANIZATION

Regional Office for the Eastern Mediterranean

ORGANISATION MONDIALE DE LA SANTÉ

Bureau régional pour la Méditerranée orientale

SYMPOSIUM ON DRUG EVALUATION AND LICENCING

EM/SYM.DRG.EVL.LIC./7

Alexandria, 30 October - 2 November 1978

18 September 1978

QUALITY CONTROL IN MEDICINES LICENCING

by

Mr William Hewitt
WHO Consultant

In the preceding contributions to this symposium we have heard of the requirements of regulatory authorities as regards the information to be supplied in support of any application for the granting of a product licence. That is, a licence to manufacture or import for sale a specific pharmaceutical product. Amongst these requirements is data on the procedures used to ensure the quality of the product. The writer's purpose in this paper is to consider the practical usefulness and significance of the quality control data thus presented and its bearing on the thing that really matters, - the quality of the product that would appear regularly on the market if the licence were granted.

First let us consider purpose and proper functioning of a quality assurance system in pharmaceutical industry. The purpose of a quality assurance system is:

i) to ensure that the company's products arriving on the market are of the correct composition, are of adequate stability, are effective and are pharmaceutically elegant;

ii) to avoid any gross errors such as packing a product under the wrong label etc.

This is only achieved by a comprehensive and coordinated system. In the first place there must be proper product development to devise an appropriate formulation and packaging so as to ensure a stable and effective preparation.

A product specification must be devised defining the quantitative composition for active ingredients and perhaps other constituents such as preservatives, buffers etc, limits of impurities and decomposition products. It will also define appearance and perhaps odour and taste. Depending on the nature of the preparation there may be requirements for weight per millilitre, refractive index, viscosity, disintegration time, dissolution time, weight variation, sterility, pyrogens and toxicity.

The manufacturing process must be defined to ensure uniformity from batch to batch. In manufacture there must be discipline and administrative controls to minimize the chances of error.

./..

To devise a system of control in production it is necessary to anticipate what could possibly go wrong in each operation to institute the appropriate administrative controls to avoid such an occurence to apply appropriate tests to check whether despite the precautions taken something has nevertheless gone wrong in the process. A simple example serves to illustrate this principle.

In the manufacture of injection of dextrose 20% the bulk solution is prepared, - this could be the wrong strength for various reasons, e.g.:

variation in moisture content of the dextrose,
wrong quantity being weighed
diluting to wrong volume,
inadequate mixing after dissolving.

The administrative controls to avoid such errors would be:

calculate the weight required according to the moisture content of the particular batch of dextrose,
require that weights and volumes be checked by a second person who signs the process sheet indicating his responsibility for the checking,
define the apparatus to be used for mixing, the mixing speed and time.

Finally, a simple in-process control would be to measure the refractive index of the solution which could be related by a graph or table to dextrose concentration.

Returning now to the subject of the product licence application, it is unlikely that this will show the complete quality control picture as many Q.C. routines in a well organized factory will be of general application rather than being related to the specific product under consideration. The data that is supplied may refer to some or all of the following stages of manufacture:

raw materials,
intermediate products,
formulated products,
products in their finally packed forms.

For each of these stages the data includes two main components:

specifications,
test methods.

Stability and bio-availability data may also be given.

A critical evaluation of the written information provided by the applicant may give a very good insight into the reality or otherwise of quality control in the manufacturing establishment. Much can be learned from the applicant's specifications. Many of the raw materials used in manufacture are described in the International and other pharmacopoeias. Often, the pharmacopoeial standards may be applied directly for industrial quality control purposes. However, in the cases of substances liable to significant deterioration, more stringent standards would be necessary in order that the formulated product may remain of adequate strength/potency throughout its shelf life. This principle is stated formally in the British Pharmacopoeia with reference to antibiotics in the note "Guidance for Manufacturers"*, which recommends more precise assays and more stringent interpretation of assay results, so as to ensure that the potency of the starting material is well clear of minimum requirements.

* British Pharmacopoeia 1973, Appendix XIV A, page A103.

./..

In the case of formulated products corresponding to a pharmacopoeial monograph recognized in the country, if at any time during its normal shelf life it is examined by an analyst, then it must conform to the pharmacopoeial standards. Thus, in order to allow for normal deterioration during storage,, the product must be well within pharmacopoeial limits for potency and decomposition products at the time of leaving the factory. Similar considerations would apply to formulated products that are not described in pharmacopoeias but in these cases the manufacturer would have to set his own standards for the product as it leaves the factory and the product as it may be found on the market. It is important to realize that provided appropriate in-process controls and tests on intermediate products have been carried out in accordance with a logical programme, there may be no need to apply full tests, (even though described in a pharmacopoeial monograph) to the final product. To make this point clearer, consider injection of benzylpenicillin. It is logical that before expending labour and packing materials and occupying plant on the filling operation the manufacturer would wish to satisfy himself that the materials were of satisfactory potency and conformed in every way to official requirements. Since there is no reasonable possibility that significant decomposition could occur in the 24 hours or so of the filling operation, it would seem pointless to retest the content of the filled vial for potency. It would be necessary of course to recheck the moisture content which could increase significantly. Naturally uniformity of content of the vials, mean content and sterility would have to be checked.

Pharmacopoeias describe tests and standards that can be applied by an independent analyst having no background information on the particular batch of product such as is available to the manufacturer. The pharmacopoeial requirements are thus designed for direct application by the independent analyst. They are not necessarily suitable for direct application in the quality control laboratory of a manufacturer and it is often possible to design a more convenient specification for the control of production. For example, in the control of fortified injection of procaine penicillin of the B.P. it would be more convenient to define procaine content in terms of upper and lower percentage w/w limits on the bulk mixture (an intermediate stage). Narrower limits than described in the pharmacopoeia would be appropriate since the latter are in terms of actual content of procaine in an individual vial and so make allowance for variation in fill weight in addition to variation in composition.

Specifications for formulated products permit a reasonable latitude in the amount of active ingredient found on analysis.

This latitude takes into account variation in the quality of ingredients, variation in the manufacturing process, analytical errors and, when appropriate, variation in fill weights and volumes. No allowance should be made for deterioration of the product in a manufacturing specification.

The permitted latitude is normally between $\pm$ 5% and $\pm$ 10% according to the difficulties in manufacture and the precision of the assay method.

Many products are manufactured to a formula that includes an average to allow for deterioration during the shelf life. This is usually the case with vitamin products. It follows that if a product contains for example a 25% excess of an active ingredient, then a realistic manufacturing specification would indicate permissible limits of say 115% to 135% of the nominal content.

Unfortunately some manufacturers appear not to realize this and quote lower limits of, for example, 90%.

./..

From these few examples it will be seen that the written data on quality control procedures needs to be evaluated by an experienced analyst, - preferably an analyst with some knowledge of first class pharmaceutical industry. It is not sufficient to merely check that the manufacturer has written methods of analysis, it is necessary to establish that he is doing the right test on the right sample at the right time and applying the right specification. The methods themselves must be looked at critically, - those written methods provided by some applicants have never been used! Sometimes it is obvious from a theoretical appraisal of the method that it is unworkable. In other cases it is only when the method is tried out in the laboratory that its failings are revealed.

In some countries examination of a sample submitted by the applicant is a routine part of the evaluation and licencing procedure. It is a worth-while exercise as, surprising though it may be, some manufacturers may submit a sample for licencing purposes which fails to conform to the standards implicit in the declared formula. Neither is it unknown for a major international company to provide a method of analysis which proves to be unworkable.

Those products for which licences are granted will perhaps be examined several times over the course of a few years by the laboratory of the Regulatory Authority. The occasion of first examining a sample for evaluation purposes provides an opportunity to place in the laboratory records all information relevant to analytical testing. Thus, the laboratory can make use of the test methods submitted by the applicant. Specifications and schedules of testing can be prepared appropriate to control of the product as it is on the market, i.e. making due allowance for permissible deterioration. Examination of the product formula will reveal whether any excipients might interfere with assay methods.

In conclusion, whilst the laboratory of the regulatory authority plays a vital role in keeping the manufacturer "on his toes", it is only the manufacturer's own quality control system that can continuously ensure reliability. It is then surely worth making every effort to evaluate the manufacturer's quality assurance programme at the time a product is submitted for licencing.