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INSPECTION OF PHARMACEUTICAL MANUFACTURING ESTABLISHMENTS

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The inspection of pharmaceutical manufacturing establishments (plant inspection) offers numerous problems of highly diversified nature. This paper is intended as an introduction to the purpose and scope of inspections and to procedures that may be used in its execution. Some attention is paid to the ideal qualifications of the inspector.

1. Purpose and scope

The purpose of plant inspection may be defined as: a Public Health function intended to further the application by manufacturers of good manufacturing practices in the production and quality control of pharmaceutical dosage forms, thereby contributing to achieve sustained and uniform manufacture of drug dosage forms of defined quality.

Since the manufacture of dosage forms is not a simple process, current manufacturing practices may differ considerably, and the

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assessment of their intrinsic value bears therefore a more or less arbitrary character.

Manufacturing is done by people; consistency in manufacturing and quality control can therefore only be achieved by people, and as a consequence the human factor should be given considerable weight in plant inspection.

Next to the human factor the number and nature of the dosage forms produced in the plant are important. Some products are easier to make than others, some are very toxic while others may be very active but not very toxic, some may be easily controlled, while the quality control of other products may be difficult to achieve. It is therefore necessary to have a close look at the products manufactured in the plant.

Next in importance are the housing and equipment used in manufacture. The better the tools are, the easier it may be to make a good quality product, but good craftsmanship and know-how may go a long way in producing a satisfactory drug even when only less-than-perfect equipment is available.

Last but not least attention should be paid to the record-keeping of manufacturing and control operations. Consistency of manufacture and quality control are very much dependent upon paper work. It is on paper that people communicate with each other, it is on paper that we record our experiences and our mishaps, be they subjective and personal or objective and scientific; it is therefore important that manufacturing and control operations are adequately recorded; in this way we may control and improve the standard of operations.

2. The inspector's qualifications

In the first paragraph of this paper, an attempt was made to outline the purpose and scope of plant inspection. The importance of the human factor in manufacture was stressed: it is only logical to direct the same attention to the official designated to inspect and thereby to control plant operations. What qualifications do we expect to find in such a profession?

First, and foremost, he must be a man who is able to make people trust him. He must inspire confidence, and make social contacts easily. He will act as a consultant, paid by the government to give his advice to the manufacturer in order to improve the standard of pharmaceutical manufacturing. Remember always that the motivation of professionals in drug manufacture and control is the best guarantee for the maintaining of proper quality control. If the inspector adopts a policeman's attitude, his access to people's minds will be less, their motivation to follow the lines set down by the law will be less, and the patient will suffer.

Secondly, the inspector must be a man with an aggressive intelligence. Except in those cases where, following laboratory analysis, a drug is shown not to be of the required quality, the inspector will start his tour without exact evidence of faults or shortcomings in the quality control system of the manufacturer. Therefore, he will have to look for such evidence, and this requires a highly active mind.

This brings us to his third asset: the inspector should be patient and inclined to maintain a systematic procedure of investigation in an environment which is not his own, and where everybody knows his way around better than the inspector does.

If the inspector is given a high degree of independence by his government, it will be necessary that his professional qualifications are no less than the requirements set by law, written or unwritten, for the qualifications of experts who are in charge of manufacturing and quality control.* It should not be necessary to dwell on this point. Furthermore, in order to understand the practical problems in manufacturing and quality control, he should have practical experience, accumulated whilst working in a manufacturing establishment, preferably medium sized, since specialization in manufacturing and quality control responsibilities usually is not excessively developed in such establishments.

3. The inspection procedure

After this brief introduction, a look at the methodology of plant inspection seems indicated.

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* vide World Hlth Tech.Rep.Ser. no 418, 1969, page 18 and 19.

Plant inspection as a matter of routine begins behind the inspector's desk. The first stage consists of bringing together the data which are relevant to the planned inspection.

Such data include (1) name and address of the firm (location of plant), (2) names and titles of managing directors, (3) names and qualifications of experts supervising manufacture and quality control, (4) list of items produced, with adequate details such as specification of dosage form, composition, quality control specifications, (5) if necessary, a lay-out of the plant facilities, and/or a brief description of these, (6) any information on plant performance as witnessed by such particulars as analysis reports on the firm's products, past recalls, complaints received, law enforcement action taken and results of such action, etc.

It is recommended that a special inspection dossier be compiled containing the elements specified above, since the inspector may feel a need to consult these during the inspection.

The next step in planning consists of determining the kind of inspection to be carried out. There are several possibilities:

(1) preliminary inspection: this type of inspection is necessary in large plants and may be useful in medium-sized plants to get acquainted with the firm's officers, the plant lay-out and the type of its operations.

(2) full inspection: this expression is used to connote an inspection which is intended to check compliance with the rules of Good Manufacturing Practices (hereafter referred to as WHO-GMP); such an inspection is useful to define problem areas of manufacturing and quality control operations of the plant to be inspected.

(3) special inspection: this is an inspection serving to have a closer look at one or more problem areas defined by an earlier full inspection.

The quality defects of drugs may be classified into two categories:

(a) the systematic defects, which occur through shortcomings of the manufacturing operation itself, such as poor miscibility of tablet granulations, of doubtful sterility of injectables because of

incorrect sterilization procedures, and which occur therefore in all or many lots of the same product; and

(b) the accidental defects, which are usually brought about by human error in spite of intrinsically adequate manufacturing operations. Such defects include accidental mislabeling, mix-up of identical-looking but in reality very much different products, misreading weighing data, calculation errors, etc. The possibilities in this field are without limitation. An important part of the WHO Guidelines for Good Manufacturing Practices was developed to exclude this type of defects as far as possible.

It should be borne in mind that plant inspection is chiefly useful in eliminating possible causes of accidental defects: such inspection is essentially directed to the prevention of mistakes.

The detection of systematic defects is a task that, depending on the nature of the defects, is best accomplished by collaboration between the inspector and laboratory experts.

The third stage in planning an inspection, which is necessary when a full inspection is envisaged, is an examination of the list of items produced by the plant to be inspected, with a view to choosing a number of products as a guide into the firm's manufacturing and control operations.

It may be useful to select products which present special quality control problems. In this way, while providing a convenient starting point for the inspection, possibilities for both accidental and systematic defects of products or control procedures may be checked; the latter type of defects may be confirmed through verification by the official laboratory.

Some quality control problems are listed in the table below.

dosage form	quality control problem
capsules and tablets with low (less than ± 5%) active substance content	uniformity of content
sugar-coated tablets	color reproducibility (check for other products in same line with same specified color), stability of active ingredient
coated tablets, with active substance incorporated in coating	uniformity of content
enteric-coated tablets sustained-release tablets and capsules	disintegration in specified media reproducibility of sustained-release properties
suspensions for oral use (active ingredient suspended)	particle size distribution, re-suspendability, uniformity of filling
solutions for injection, small volume	filling volume adequate for taking out and administering full dose
solutions for injection, large volume (25 cc and up)	extraneous particles, pyrogenicity, sterilization, stability
dry solids for injection	uniformity of filling, stability
suppositories (active principle insoluble in fatty base)	conformity of content with label declaration
suppositories (active principle soluble in fatty base)	release of active principle from suppository base

The last stage in planning an inspection is the fixing of a date. Unless there are special reasons for paying an unannounced visit to a firm for inspection purposes, inspection dates should be fixed in common agreement with the responsible company officials. In this way, the persons that the inspector will wish to see will be present and he may expect a helpful attitude of the manufacturer's key personnel, having shown due regard for their working interests. The name of the senior official, responsible for the overall operation of the plant, should be verified, so that this person may be visited first.

In starting a full inspection, the inspector should present himself to the senior plant official and explain the purpose of the inspection to him. At this time, the names and responsibilities of the key personnal engaged in manufacture and quality control should be verified, so that no misunderstanding will occur later as to who is responsible for what operational detail. Paragraph 3 of the WHO-GMP may serve here as a guide. A point should be made of ascertaining whether manufacturing personnel are subjected to periodic health checks (see para 8.4 of WHO-GMP).

Furthermore, the operations of the firm should be exactly defined:

(a) production of pharmaceuticals to be marketed under the firm's own brand;
(b) production of pharmaceuticals for other firms,
(c) packaging only of bulk products obtained from other firms for sale under own label;
(d) packaging only of bulk products for other firms;
(e) sale only of products finished by other firms, under own label;
(f) sale only of products finished by other firms, not under own label.

The names of the products, should be noted or verified, as the case may be, according to each category of operation specified.

From his list of items produced by the plant, the inspector may now select one or two products, and ask the responsible officials for a complete explanation of the production procedure for these products, beginning with the production order.

The inspector may find it useful to ask for blanks of all forms and records used in manufacture. This will help him in familiarizing himself with the manufacturing procedures of the firm. The inspector should ask specifically for those stages of production, which are subject to in-process controls. Sometimes these controls are executed under the responsibility of the expert, responsible for the manufacture; this is, as a rule, not objectionable. It is, of course, necessary that the results of such in-process controls be adequately recorded. Paragraphs 8.5 and 8.6 of the

WHO-GMP may be used here as a guide in checking whether the manufacturing procedures are adequately described.

The key points of the explanation should be noted. Then the responsible quality control expert should be asked to explain the role of his department. At this time, also, blanks of analysis reports and forms used should be asked for. A point should be made of verifying whether, at the time the finished product is submitted for final analysis, the production protocols are available to the analyst. If possible, this should be discouraged. Whenever possible, production and quality control reports should be submitted separately to the director of production and verified for conformity with established specifications under his direct responsibility. Paragraph 10 of the WHO-GMP may serve here as a guide to the inspector in verifying whether the quality control system of the firm is adequate.

After this preliminary information session, the actual inspection of the plant may now be started.

It is a good idea to start with the inspection of the finished products storage area, which should be - generally speaking - in conformity with the specifications given by para 4.1 of the WHO-GMP. If this area is also used for other purposes, the inspector should use his good judgment in determining whether this is objectionable or not.

In this area a number of samples (consult list of items mentioned earlier) should be taken; the writer advocates to choose at least 10 and a maximum of 20 products. The size of the samples should be predetermined by consultation with the official laboratory officials.

A list of the products, including lot numbers, should be presented to the company official accompanying the inspector with the request to have the corresponding batch manufacturing records (see para 8.6 of WHO-GMP) taken from the files for later verification.

Unless specifically and conspicuously marked as unreleased by quality control, stocks of finished goods should not be stored in the finished products storage area, in view of the risk of distribution of uncontrolled finished products.

Another problem occurring frequently, is constituted by the firm's procedure with returned goods. It is often found that such goods are placed in the finished products storage area with a view to redistribution without proper examination and prior quality checks. In view of the fact that the reason for returning merchandise by the client lies often in questionable quality, such practices are highly objectionable.

After inspecting the finished products storage area, attention may be given to the starting materials storage area. A number of points requiring checks are given by paragraph 7 of the WHO-GMP.

While visiting in turn each area, either intended for storage or manufacturing operations, a check of the points enumerated by the paragraphs 4 (Premises), 5 (Equipment), and 6 (Sanitation) of the WHO-GMP may be made. The points raised by paragraphs 8.1, 8.2 and 8.3 of the WHO-GMP are also important whilst the inspection of manufacturing areas is carried out. Unsatisfactory details should be noted for discussion with the management later.

It is useful to compare batch manufacturing records with the instructions for manufacturing contained in the master formula cards. (see paragraphs 8.5 and 8.6 of the WHO-GMP). This may be done in the production manager's office, when the required samples of finished products are brought together and the lot numbers are compared with the batch manufacturing records. Here, errors in transcription from the master formula cards may show up, as well as calculation errors, occurring when batches of variable size are put into production.

Labelling and packaging operations are to be considered equally important as the activities concerning the manufacture of the dosage form itself. Paragraph 9 of the WHO-GMP may serve as a guideline during inspection. In looking over storage facilities for labelling materials, attention should be paid to the precautions taken in order to avoid mix-up. If a number of issued labels remains unused, care should be taken that all labels which bear batch code identification data are destroyed.

Labelling and packaging operations should be supervised directly by a competent and responsible person. Here, meticulousness and experience are important factors in determining whether an individual is qualified to fill the position. It is important that no packaging and labelling materials which are irrelevant to immediate operations are lying around in the working area. Generally speaking, it is best that labels are supplied in the form of rolls, since this practically exclude the possibility of mix-up in labelling.

After completing a packaging or labelling run, the number of finished containers should be checked against the theoretical output. Broken or damaged containers should be set aside by personnel and destroyed after checking by the supervisor. The losses should be taken into account in determining whether the yield obtained compares well with the expected production figure. The packaging line or, as the case may be, the packaging area should be completely checked to remove all traces of the previous run. The finished containers should be put in quarantine before releasing them for distribution. It is absolutely necessary that at this stage the control laboratory intervene again, if only - depending on what tests have been carried out earlier - for a last identification check.

The control laboratory should, as a rule, be visited last. The analytical instrumentation available and the use of special analytical techniques are points of interest. However, the inspector should not comment off-hand on the adequacy of the methods or apparatus used. This may be saved for a later day, when the reports of the sample analysis are available. Care should be taken to ask whether any special controls to be performed are given to outside laboratories. Names and addresses of such laboratories should be noted for later reference.

It is advisable that the inspector, before taking his leave, discuss the highlights of his tour with the senior plant official. The detailed findings should be communicated to the firm later by letter. Generally speaking, the firm should be left free to devise ways and means to correct shortcomings and to propose these to the designated authority for comment or approval. It is important for later reference that this be done in writing.

In conclusion, it may be said that through his influence on plant manufacturing and control operations, the inspector fulfills a highly important function, constituting an essential link in the range of measures to ensure proper quality of the drugs made available to the population.