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Annex 7
Guidelines on pre-approval inspections

1. General

The advice provided here extends that given in the "Provisional guidelines on the inspection of pharmaceutical manufacturers" (*1*). The objectives of an inspection, as given in the introduction to the guidelines, are:

— to control and enforce compliance with general good manufacturing practices (GMP) (*2*); and
— to authorize the manufacture of specific pharmaceutical products, normally in response to a licensing application.

These guidelines are applicable mainly to inspections of the first type, whether performed as a condition for the issue of a manufacturing licence/authorization, or on a periodic, routine basis. They are essentially concerned with inspections of manufacturing and quality-control facilities conducted before a marketing authorization (product licence or registration) for a pharmaceutical product is granted.

2. Glossary

The definitions given below apply to the terms used in this guide. They may have different meanings in other contexts.

application
A marketing authorization for a new drug application.

manufacturer
A company that carries out at least one step of manufacture (*2*).

manufacture
All operations concerned with the purchase of materials and products, production (including packaging), quality control, release, storage, the distribution of pharmaceutical products, and the related controls (*2*).

method validation/verification
Method validation is conducted where non-compendial analytical methods are included in the application to confirm that the applicants' proposed analytical methods are suitable for regulatory purposes. A side-by-side comparison with a compendial method, if available, should be included. Method verification is conducted where the methods are compendial, to confirm whether the product as compounded can be analysed satisfactorily by the official method.

pre-approval batches
Pilot or laboratory-scale batches, upon which the application is based, e.g. batches used for pivotal clinical trials and/or those used for bioavailability, bioequivalence and stability studies, and scale-up batches.

3. Objectives

Before any application is approved, it is necessary to determine whether all establishments participating in the manufacture of the finished dosage form are in compliance with GMP and the application commitments. Pre-approval inspections have the following specific objectives:

- Evaluation of the establishment's compliance with GMP requirements, particularly regarding proper environment, quality management, personnel, facilities and equipment.
- Evaluation of the procedures and controls implemented in the manufacture of the product (pre-approval batches), to determine whether they are in conformity with the application commitments.
- Audit of the completeness and accuracy of the manufacturing and testing information submitted with the application, and of the conformity of pre-approval batches with planned commercial batches (process validation protocol).
- The collection of samples for the validation or verification of the analytical methods included in the application.

4. Priorities

Pre-approval inspections are considered to be an important part of the application review and approval process. However, since this represents a considerable workload, inspections are not normally carried out routinely, but rather only in specific cases where non-compliance is possible. Thus inspections may be required for:

— new chemical entities;
— drugs of narrow therapeutic range, and drugs for serious conditions requiring an assured therapeutic response;
— products previously associated with serious adverse effects, complaints, recalls, etc.;
— products that are difficult to manufacture or test, or that are of doubtful stability (and therefore associated with the risk of defects);
— new applicants or manufacturers; and
— applications from manufacturers who have previously failed to comply with GMP or official quality specifications.

For other applications, the drug regulatory authority will rely on the results of recent inspections of the applicant's or manufacturer's facilities for the production of dosage forms similar to that of the proposed product.

5. Preparation for the inspection

An inspection team should, where possible, include analysts and other specialists, e.g. in pharmaceutical technology, or if available, persons with expertise in these fields, when needed. Team members may be assigned to inspect new operations or manufacturing sites associated with product failures. When possible, the analyst involved in the laboratory evaluation of the product under review should participate in the inspection. Pre-approval inspection is often carried out by a single inspector.

It is necessary to verify that the applicant holds an appropriate manufacturing authorization and that manufacturing is carried out in conformity with that authorization (licence).

An essential step in the review of applications is determining whether the commitments made by the manufacturer are reflected in actual practice. A review of the application information is also important in preparing for inspections of firms or processes with which the inspector is unfamiliar. The drug regulatory authority should provide inspectors with relevant information on the application. (Some countries request an additional copy of this information from applicants which is forwarded to the inspection team.) The information

provided should include a copy of the manufacturing and controls section of the application, together with information relating to pre-approval batches.

Reasonable efforts should be made to conduct pre-approval inspections at the earliest possible opportunity, since unnecessary delays will prevent the timely review of applications. However, in some facilities the development or the manufacturing processes may not have been completed. In addition, changes may have occurred in the status of the application, e.g. major deficiencies in the application or the closure of an ancillary facility may affect the need for an inspection. In any case, the timing of the inspection should be coordinated between the inspectorate and the applicant.

For the inspection of major new facilities involving many applications, special coordination efforts are often beneficial.

When desirable, pre-approval inspections should be coordinated with the laboratory scheduled for method validation so as to enable it to participate in the inspection and in the collection of samples.

6. Carrying out the inspection

Emphasis should be placed on the evaluation of the manufacturing process, including data verification and the assessment of compliance with GMP. The production and control procedures described in the application must be compared with those used for the manufacture of pre-approval batches. If warranted by records of past label mix-ups, packaging and labelling control procedures should be evaluated. A programme of ongoing stability testing needs to be addressed.

The inspection team will determine whether the application provides the scientific data justifying full-scale production procedures and controls. The validation of pertinent manufacturing procedures, including equipment qualification, will also be evaluated.[1] However, inspectors should not recommend withholding approval of applications based on a lack of complete full-scale, multiple-batch validation of sterile and non-sterile processes, unless the data submitted in the application are found to be of questionable validity or completeness. It should be understood that full-scale validation may be completed after approval of the application, but before shipment of the first commercial batches. Nevertheless, certain data must be included in the application to demonstrate that the sterilization or aseptic fill process has been qualified. The inspection team is expected to audit the data to determine their authenticity, accuracy and completeness.

[1] For details of recommended validation programmes, see reference *3*.

Investigational products are often produced in facilities other than those used for full-scale production (*4*). These facilities and the associated manufacturing and control procedures are not routinely inspected unless validation of the transfer of the methods from the "investigational" facilities to the full-scale facilities is lacking or questionable. The facilities may be periodically inspected when this is required by national legislation/regulation.

All suppliers and manufacturers of starting materials used in the formulation of pre-approval batches should be identified. The physical characteristics and specifications of the drug substance should be reviewed. This is particularly important for solid oral dosage forms where the physical characteristics of the drug substance often affect uniformity, dissolution and absorption of the dose.

When a pharmaceutical manufacturer replaces the supplier or manufacturer of the drug substance used for the manufacture of the pre-approval batches by another supplier or manufacturer, the application should include data demonstrating that the dosage forms formulated with the drug substance from the two different sources are equivalent in terms of conformity with established specifications, including those given in the application. Specifications should also cover the physical characteristics of the drug substances.

The addition of any new drug substance and/or dosage form to a production environment must be carefully evaluated in terms of its impact on other products already under production. Any changes that may be necessary in the building and facility must be assessed for their effect on overall compliance with GMP requirements. For example, a new toxic, potent or highly sensitizing product may require additional measures against cross-contamination, and facilities already operating at full capacity may not have adequate space for additional products. The evaluation should also include an assessment of whether any change in the manufacturing authorization is necessary.

Laboratory equipment and procedures must be qualified and validated. Every pre-approval inspection should include an evaluation of laboratory controls and procedures, and a review of some of the raw data used to generate results. The authenticity and accuracy of the data used in the development of a test method should be reviewed.

The inspection team should pay special attention to any newly established facilities, newly installed equipment and/or new raw material suppliers. If unapproved facilities are in use, this should be reported immediately. Inspections of these facilities are not normally required.

7. Sample collection and testing

The pre-approval inspection may include the collection of samples for validation of the analytical methods. Normally the sample size should be sufficient for three full analyses. Unless otherwise indicated by the laboratory, samples of the following sizes may be taken, depending on the dosage form of the product:

— tablets and capsules: 300 units of production;
— injections (single component): 100 units of production;
— injections (combination): 100 units of production plus 10 samples of each component;
— oral powders for reconstitution: 10 units of production;
— oral liquids: 1 litre.

It is important to collect, with the samples, the relevant manufacturer's analytical documentation, namely a copy of the analytical methods used by the inspected laboratory and the report of the analyses performed by the applicant on the batch sampled. A method validation report may be of some use in better understanding and reproducing the analytical methods. Problems encountered in the performance of the analyses may be resolved by an exchange of information between the applicant and the government laboratory.

Samples are tested in accordance with methods described in the application. If there are problems with the methods that require additional information from the applicant, the laboratory director must review the situation and decide whether the applicant should be contacted. The written request should be included in the documentation submitted to the review analyst.

Each method validation/verification report should contain the following:

- The identification of the test samples received, a description of the product tested, and confirmation of conformity with the product described in the application.
- The original analytical worksheets with calculations, the results of all tests performed, comments by the analyst(s), associated spectra, chromatograms, etc., and a comparison of the results obtained with the applicant's data and with the applicable specifications.
- An evaluation of each test performed by the applicant and the laboratory.
- A recommendation as to whether the methods are acceptable, acceptable only after specified changes have been made, or unacceptable.

If samples have not been collected in the course of a pre-approval inspection, the results of the analytical examination of the samples

submitted by the applicant may nevertheless be used as supporting information.

The reserve samples, associated documentation and copies of laboratory reports should be stored in an orderly and retrievable way for a time period specified by national regulations. It is usually recommended that all material should be kept for a minimum of 3 years or for 1 year after the expiry date of the finished product.

8. Follow-up regulatory/administrative decisions

The inspectorate (inspection group of the drug regulatory authority) should recommend withholding approval when significant deviations from GMP requirements and other application commitments have occurred having an adverse effect on the product covered by the application. Examples of significant problems are:

- Misrepresentation of data or conditions relating to pre-approval batches.
- Pre-approval batches not manufactured in accordance with GMP.
- Inconsistencies and/or discrepancies raising significant questions concerning the validity of the records.

If applications are refused because of significant non-compliance with GMP, action must be taken to ensure that the necessary corrective measures are taken.

The drug regulatory authority is expected to advise the applicant that the inspectorate has recommended withholding approval of the application and give the reasons for this recommendation.

References

1. Provisional guidelines on the inspection of pharmaceutical manufacturers. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992, Annex 2 (WHO Technical Report Series, No. 823).
2. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2. Good manufacturing practices and inspection*. Geneva, World Health Organization, 1999.
3. Good manufacturing practices: guidelines on the validation of manufacturing processes. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996, Annex 6 (WHO Technical Report Series, No. 863).
4. Good manufacturing practices: supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996, Annex 7 (WHO Technical Report Series, No. 863).