

SPECIFICATIONS AND CONTROL TESTS ON THE FINISHED PRODUCT

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SPECIFICATIONS AND CONTROL TESTS ON THE FINISHED PRODUCT

Note for guidance concerning the application of Part 2, section E of the Annex to Directive 75/318/EEC as amended, for the purposes of granting a marketing authorisation.

A glossary of terms used is included in an appendix to this note.

1. SPECIFICATIONS

1.1 Quality characteristics covered by the specifications

Quality characteristics cover the following area:

- general characteristics of the pharmaceutical form, particularly pharmacotechnical; that is to say those characteristics, determined in general by physical tests with limits of acceptance, relating to the product performance or handling (e.g. hardness, friability of a conventional tablet);
- identification of the active substance(s);
- assay of active substances (and also for herbal medicines, quantitative determination of the constituents with known therapeutic activity);
- if necessary, identification and assay of the excipients such as:
- identification of colorants used,
- identification and assay of antimicrobial agents or antioxidant preservatives (with acceptance limits);
- purity tests (if necessary, the investigation of breakdown products, residual solvents or other process related impurities, microbial contamination);
- pharmaceutical tests (e.g. dissolution);
- safety tests including abnormal or specific toxicity tests, where applicable, in particular for biological products.

In order to determine the specifications of the finished product, the quality characteristics related to the manufacturing process should be taken into account.

An appropriate specification for each aspect of quality studied during the phase of development and during the validation of the manufacturing process should be determined. At least those aspects considered to be critical should be the object of specifications routinely verified.

1.2 Relationship between dossier specifications and the Pharmacopoeia

The general provisions of the European Pharmacopoeia describe and define the content and legal weight of the various sections of its monographs and general methods.

Directive 75/318/EEC as amended recapitulates those aspects of quality which must be the object of appropriate specifications by referring to the general monographs of the European Pharmacopoeia or, failing this, to pharmacopoeias of Member States.

Concerning monographs on medicinal products, the European or national pharmacopoeiae define the reference quality level. In the marketing authorisation application, the applicant should determine the most appropriate means for reaching the stated objective, and supply the appropriate analytical validation data. In all cases, routine tests on the finished product at release follow the stipulations of section 1.4.

In addition, as a result of the fact that these monographs correspond to regulatory specifications, they represent the limit values of medicinal product at the end of their shelf life (except for those provisions referring to production). The specifications for release of the finished product must comply with the criteria defined by Directive 75/318/EEC as amended, i.e. $\pm 5\%$ for the assay of active substance(s) except when otherwise justified.

1.3 Relationships between the specification of a finished product at the end of shelf life and at manufacture (at release)

- a) The aim of the application dossier for a marketing authorisation is to set the quality level of the medicinal product as intended for marketing. It establishes specifications, i.e. qualitative and quantitative characteristics, with test procedures and acceptance limits, with which the medicinal product must comply during its intended shelf life.

In Part II F of the dossier, the applicant proposes a shelf life for the medicinal product mainly on the basis of the level of active constituents (efficacy) and the admissible level of any breakdown products or impurities (safety) and consistent pharmacotechnical properties. From the behaviour of the medicinal product the applicant deduces the appropriate storage conditions which will maintain compliance with the specifications of the medicinal product.

- b) The specification limits of the finished product at the time of batch release are set by the marketing authorisation applicant such that the specifications proposed at the end of shelf life are guaranteed; they are established on the basis of a critical detailed review of the data gathered from the batches analysed. Nevertheless, acquired experience is a factor recognised to be very important in terms of good manufacturing practice. One of the basic requirements of GMP (see the Guide to GMP) is the systematic review of all manufacturing processes in the light of experience. Thus, the applicant, in compliance with Directive 65/65/EEC as amended, Article 9. a, shall adapt or refine the specifications at release as a function of experience acquired by the manufacturer(s) of the medicinal product.
- c) The specifications of the finished product at manufacture may be different from those of the medicinal product at expiry.

In certain cases, for characteristics of the medicinal product which may change during storage under the approved conditions, the quality required at the end of shelf life should be taken into account in determining appropriate specifications at the time of manufacture, for example in the case of overages for reasons of stability.

It is desirable that all specifications (characteristics and acceptance limits) of the medicinal product and the finished product at the time of release be presented in the

form of a summary table. In this table, the limits of any likely breakdown products which may form under the approved conditions of storage should be stated.

The summary table could be presented as follows:

SUMMARY PRESENTATION OF THE SPECIFICATIONS OF THE MEDICINAL PRODUCT AND THE FINISHED PRODUCT (AT MANUFACTURE)

Characteristics	Methods and Acceptance Limits	
	of the medicinal product up to the end of shelf life	of the finished product at release
1. Characteristics of the pharmaceutical form	Indicate with an asterisk the specification limits which may require updating in the light of experience acquired after the first "n" production batches	
2. Identification and assay of active constituents		
3. Purity tests		
4. Excipient: Identification for example of colorants, preservatives, limit values of preservatives etc.		

Details should be given of specification reference number and signature and date of approval.

This presentation of the complete series of specifications does not affect the choice and the frequency of the testing which will effectively be carried out on the finished product at manufacture (or possibly on the bulk product or intermediate product) (see 1.4).

1.4 Specifications and routine tests for the release of batches of finished product at the time of manufacture (at release)

1.4.1 Relationship between validation of the manufacturing process, GMP and establishment of specifications

The compliance of each batch of finished product with its specifications at manufacture should be guaranteed by GMP (see Guide to GMP). Nevertheless, those features of the batch documentation required by GMP may not be included in the marketing authorisation dossier.

In the marketing authorisation dossier, it must be shown that the manufacturing process used in compliance with GMP is capable of producing the finished product consistently in compliance with the specifications chosen; these specifications take into account:

- development studies described in Part II A 4 of the marketing authorisation dossier (see note for guidance *Development Pharmaceuticals and Process Validation*) which will have led to the identification of the features of the formulation and the manufacturing process, which are essential for the quality of product;

- the validation of critical steps in the manufacturing process described in Part III B 3 of the marketing authorisation dossier which enable scale up and batch reproducibility to be monitored.

1.4.2 Routine tests and periodic tests

Different types of tests may exist:

- a) tests to be carried out batch by batch on the finished product or, possibly, on the bulk product;
- b) tests whose performance during a manufacturing step (intermediate products or in-process controls) will contribute a greater guarantee of finished product compliance than their performance on the finished product or on the bulk product;
- c) periodic tests (not carried out batch by batch on the finished product or, possibly on the intermediate product or bulk product), where the frequency of performance is highly dependent on other parameters of GMP (e.g. microbiological quality);
- d) tests whose performance on the finished product or possibly on the bulk product at manufacture can be replaced by the verification of another highly dependent specification (for example replacement of the test for uniformity of mass with the test for uniformity of content);
- e) tests which are not carried out routinely once the guarantees of compliance are furnished by the manufacturer; these specific cases are exceptional (e.g. identification of colorants);
- f) tests corresponding to critical points in the manufacturing process to be monitored particularly during the first “n” production batches and temporarily in the course of any substantial modification (for example changing the manufacturing site, materials, etc.). Subsequently, as a function of acquired experience and especially validation of the production process, their batch by batch performance can be omitted (e.g. residual solvents).

There may exist situations other than those described above.

1.4.3 Scheme for verifying specifications

As a function of the conclusions of parts II A 4 and II B 3, the dossier must clearly indicate the individual tests to be carried out for the release of the finished product and state whether they are done routinely on each batch of finished product, or indicate the periodicity of testing (batch by batch, every “n” batches, the first “n” batches etc.).

Two cases are possible depending upon whether or not the products are known and for which the manufacturer has available substantial production experience.

In the first case, for example a new dosage strength of an already authorised product, or a new conventional formulation (solution, compressed tablet etc.) of a well known pharmacopoeial active substance, tests carried out routinely and periodically can be stated at the time of application.

In the second case, for example with formulations of a new active substance or new dose delivery system such as modified release tablets, adjustments as a result of product experience should also be described, where possible, and the regulatory authorities informed of appropriate developments based on the results obtained.

The tests proposed in both cases should be presented in the form of summary tables as indicated below (Tables 1 and 2). Whenever necessary, the tests proposed during the first “n” batches (Table 1) should be distinguished from those envisaged in a routine industrial situation (Table 2).

Table 1

Proposed scheme for testing during the initial period of industrial production

Tests	Frequency of Testing (Surveillance of the first “n” batches)

The applicant should state the number (“n”) of batches involved where applicable.

Table 2

Testing scheme confirmed following stabilised industrial production

Tests	Frequency of Testing

Each batch of medicinal product marketed must comply with all the specifications defining its expected quality level, regardless of the testing plans envisaged, or confirmed after experience.

Testing may be chemical, physical, pharmaceutical, microbiological or biological.

1.5 Acceptance limits

The acceptance limits for specifications of the different quality characteristics (refer to section 1.1) are established by taking into account all significant elements related to the quality of the medicinal product (constancy of its characteristics), its activity (level of active constituent) and, if necessary, its safety (risk of microbial contamination, breakdown products, etc.).

1.5.1 Acceptance limits of pharmacotechnical parameters

For most pharmacotechnical specifications, the European Pharmacopoeia or failing this the national pharmacopoeias of the Member States, describes general test procedures with, in some cases, standards or maximal limits.

In the context of these specifications, it is necessary to establish minimal and/or maximal limits, specific and adapted to the medicinal product which is the object of the marketing authorisation in order to guarantee the reproducibility of the finished product at manufacture.

1.5.2 Maximum acceptable deviation in the content of active substances

Directive 75/318/EEC as amended states “Unless there is appropriate justification, the maximum acceptable deviation in the active substance content of the finished products shall not exceed $\pm 5\%$ at the time of manufacture. On the basis of the stability tests the manufacturer must propose and justify maximum acceptable tolerance limits in the active substance content of the finished product up to the end of the proposed shelf life”.

- Release limits of $\pm 5\%$ are acceptable without further justification.
- Release limits wider than $\pm 5\%$ would need to be justified in the part “Development Pharmaceuticals” with experimental results which are normally based on a confidence level of 95%. The wider limits also include both, the variation of the production and of the test procedure for the assay.
- Use of inadequate manufacturing procedures or inadequate test procedures (low precision) will not be accepted as a justification for wider release limits.
- It is left to the responsibility of the manufacturer if -to satisfy the $\pm 5\%$ requirements- he has to apply an adjustment of the amount of active substance in the production of the finished product (factorisation). In such a case, the overage must be clearly stated in Part II B 1. The release limit will remain within $\pm 5\%$ of the stated content.
- References to pharmacopoeias cannot normally be accepted as a justification for wider limits as monographs do not describe a defined composition of the medicinal product, and do not pertain to release, but to recontrol by official laboratories over the whole shelf life of the product.
- Exceptionally, for certain products with a well known degradation process and which pose no safety problems, an overage at release can be tolerated (vitamins, etc.). This overage, the aim of which is to guarantee a sufficient level at the end of shelf life, must not cause an excessive level at release, and release limits must be adapted accordingly.
- Release limits $\pm 5\%$ primarily concern the manufacturers of the product and not any outside laboratory. At recontrol by official laboratories, the release limits of the manufacturer will be taken into consideration despite the fact that the limits used at recontrol may not be identical to the release limits of the manufacturer (due to interlaboratory variability). Where recontrol tests are carried out by another laboratory, the test procedures must be validated in their hands.
- Overfilling to guarantee the delivery of the theoretical unit dose must be justified in Part II A 4 “Development Pharmaceuticals”. The acceptance limits for determination of unit content are adapted in consequence.

1.5.3 Acceptance limits for excipients

- Excipients which affect the bioavailability of an active substance must be the object of a quantitative determination in each batch, unless bioavailability is guaranteed by other

appropriate tests, established on a case by case basis as a function of development studies.

- In the case of preservatives, content limits of 90-110% at release should be acceptable without further justification except in special cases. On expiry the lower limit of antimicrobial preservatives may be reduced subject to the results of satisfactory preservative efficacy testing. For chemical preservatives (antioxidants), the lower limit may be considerably lower than 90% during the shelf life, because of the preferential degradation of these agents.

2. TEST PROCEDURES

Test procedures must be described in a sufficiently detailed manner to enable any official laboratory to verify the compliance of the medicinal product up to the end of shelf life. Control methods must be validated in accordance with the note for guidance *Validation of Analytical Procedures: Methodology*. The results of such analytical validation must be included in the dossier.

Thus, the description of the test procedure(s) should, if necessary, include the description of the reference substance, including its specifications and the description of the calculation formula or an example of calculation (whether or not the calculations are performed by an automatic instrument), chromatograms and spectra (etc.) furnishing the proof of the results obtained.

Except for those officially included in the European Pharmacopoeia, e.g. sterility tests, it is not necessary to describe the sampling procedures, which are the domain of GMP and depend on inspection services.

A test procedure may use either an official reference substance (European Pharmacopoeia, national pharmacopoeias, WHO) or a working standard, providing the latter is standardised against the official reference substance (see note for guidance *Validation of Analytical Procedures: Methodology*).

It is to be remembered that an analytical result cannot be dissociated from the method used. Thus in a pharmacopoeial monograph, it is assumed that the specifications adopted for the tests and assay are established from the methods described in the Pharmacopoeia.

Methods other than the methods described in the Pharmacopoeia may be used for control purposes providing that these methods are validated with reference to the official method and providing that these methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monograph would be achieved if the official methods were used (see general provisions of the European Pharmacopoeia).

In addition, the general methods described in the Pharmacopoeia may be used for products not described in the Pharmacopoeia or for specifications not described in a monograph. Utilisation of these methods requires validation for the specific case envisaged.

3. BATCH ANALYSIS

The data which must be produced are summarised in the Notice to Applicants. The section “batch analysis” must include the results obtained for all specifications at release, whether or not they are intended to be verified batch to batch.

Where possible, the consecutive batches should correspond to production scale batches manufactured by all manufacturers and at all manufacturing sites declared in the marketing authorisation, according to the process described in Part 1 A of the dossier. If these data are not available for industrial scale batches, they should be supplied to the competent authorities as soon as possible after the marketing authorisation is granted.

APPENDIX

Glossary

The following definitions are applicable to the terms used in this note for guidance.

Analytical Validation (Refer to note for guidance *Validation of Analytical Procedures: Methodology*)

Batch (Refer to Directive 75/318/EEC as amended, Annex, Part 2 E)

For the control of the finished product, a batch of a proprietary medicinal product comprises all the units of a pharmaceutical form which are made from the same initial mass of material and have undergone a single series of manufacturing operations or a single sterilisation operation or, in the case of a continuous production process, all the units manufactured in a defined period of time.

Bulk Product (Refer to Guide to GMP)

Any product which has completed all processing stages up to, but not including final packaging.

Factorisation

Adjustment by calculation of the mass of an substance (usually the active substance) added for the manufacture of a batch of a product on the actual potency as determined by assay of that particular batch of substance. For example, if the theoretical batch quantity of an active substance in a batch of product is 100 gram, and the assay "as is" of the batch of substance being used is 92.0% m/m, then the factorised mass to be added would be $100 \text{ g} \times 100/92.0 = 108.7 \text{ g}$.

Finished Product

A medicinal product which has undergone all stages of production including packaging (refer to Guide to GMP).

In-Process Control (Refer to Guide to GMP)

Controls performed during production in order to monitor and if necessary to adjust the process to ensure that the finished product conforms to its specifications.

Intermediate Product (Refer to Guide to GMP)

Partly processed material which must undergo further manufacturing steps before it becomes a bulk product.

Overage

An additional amount of an substance (usually the active substance) over and above the amount stated in the unit formula, added to prepare a batch of product in order to compensate for losses incurred during manufacture and/or storage in the finished pack. It is usually expressed as a percentage.

Quality Assurance (Refer to Guide to GMP)

For the medicinal product, it is the sum total of the organised arrangements made with the object of ensuring that manufactured medicinal products are of the quality required for their intended use.

Routine Tests and Periodic Tests

Routine tests are carried out on each industrial batch of the intermediate product, the bulk product or the finished product.

If necessary, these tests are extended by special tests called “periodic tests” which are carried out according to a certain periodicity defined in each case; they are mentioned separately.

Specification

Qualitative and/or quantitative characteristics with test procedures and acceptance limits, with which a given product must comply.

Specifications of the Finished Product (At Release)

Monograph defining qualitative and quantitative characteristics with test procedures and their acceptance limits, with which the finished product must comply at the time of the manufacture (at its release).

Specifications of the Finished Product (Up to the End of Shelf life)

Monograph defining qualitative and quantitative characteristics with test procedures and their acceptance limits, with which a medicinal product (on the market) must comply throughout its valid shelf life.

Validation of Manufacturing Process (Refer to Guide to GMP)

Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results.