3.2.1.6.8 Impurities

3.2.1.6.8.1 Related substances (organic impurities)

Monographs should include tests and acceptance criteria for impurities that are likely to occur in substances used in approved medicinal products, insofar as the necessary information and samples (substance and impurities) are available from the producers. Where the required information and samples have not been provided to the pharmacopoeia for a substance synthesized by a given method, the monograph will not necessarily cover the corresponding impurity profile.

Monographs on organic chemicals usually have a test entitled "Related substances" (or a test with equivalent purpose under a different title), designed to control related organic impurities. Impurities to be controlled include: intermediates and by-products of synthesis, co-extracted substances in products of natural origin, degradation products.

Where the counter-ion of an active substance is formed from a lower organic acid, a test for related substances of the organic moiety is usually not considered necessary (for example, magnesium lactate used as a source of magnesium).

Acceptance criteria

Monographs on active pharmaceutical ingredient should take account of the principles and thresholds for control of impurities as defined in ICH guideline Q3A (R2). Justified deviations from this should be explicitly stated. Products of fermentation and semi-synthetic products derived therefrom, should be limited applying the same principles but be covered by thresholds considered appropriate for these products. The same principle applies to excipients.

Monographs should include acceptance criteria for:

- each specified impurity;

- unspecified impurities, normally set at the ICH Q3A (R2) identification threshold where applicable;
- the total of impurities (or a limit for the total of impurities other than a number of identified specified impurities) above the reporting threshold/disregard limit.

Typically, the reporting threshold/disregard limit for substances covered by a monograph is set in accordance with the reporting threshold given by ICH Q3A (R2) where applicable.

The acceptance criteria for specified impurities take account of both:

- qualification data, where applicable, the limit being set at a level not greater than that at which the impurity is qualified;
- batch analysis data, the acceptance criteria being set to take account of normal production; data is provided by the producer for typical batches and checked during elaboration of the monograph on not fewer than 3 batches.

All decisions on impurity acceptance criteria should be based on the real impurity content (meaning after application of correction factors (CF)) in representative batches examined. Impurities need to be specified and located appropriately in the chromatogram if the reported batch values for an impurity are:

- above the applicable limit for unspecified impurities before correction and cross the limit downwards when corrected (overestimation, CF<1), or
- below the limit for unspecified impurities before correction and cross this limit upwards when corrected (underestimation, CF>1).

No correction factor will be given if the reported batch values for an impurity are:

- below the applicable limit for unspecified impurities before correction and below the disregard limit after correction.

867

868 **Enantiomeric purity.** A monograph on an enantiomer includes wherever possible a test
869 for enantiomeric purity by liquid chromatography (LC) using chiral separation to limit
870 the presence of the unwanted enantiomer.

871

872 **Unusually potent or toxic impurities.** In addition to the above mentioned requirements,
873 impurities that are unusually potent or produce toxic or unexpected pharmacological
874 effects, need to be specifically considered. In this context requirements for genotoxic
875 impurities have to be followed (to be completed after adoption of ICH M7).

876

877 **Analytical methods for determination of organic impurities**
878 The most common and preferred method for control of organic impurities is LC; gas
879 chromatography (GC) or capillary electrophoresis (CE) may be the preferred method in
880 some instances. Thin-layer chromatography (TLC) should be reserved for control of
881 specific impurities that cannot conveniently be controlled by LC or GC.

882

883 Monographs frequently have to be designed to cover different impurity profiles because
884 of the use of different synthetic routes and purification procedures by producers. The
885 usual practice is to include a general LC test, supplemented where necessary by other
886 tests (LC, GC, CE, TLC, or other techniques) for specific impurities. It is, however,
887 becoming increasingly impractical in some cases to design a single general test and in
888 such cases more than one general test is included and the scope of the different tests is
889 defined in the tests themselves by cross-reference to the impurities covered (e.g. in an
890 Impurities section).

891

892 For pharmacopoeial purposes the objective of a purity test using a separation method will
893 usually be the control of impurities derived from one or more known manufacturing
894 processes and decomposition routes. However, the experimental conditions are chosen
895 for the test, especially the detection system, so as not to make it unnecessarily narrow in
896 scope. Chromatographic purity tests may often be the best means of providing a general

screening of organic impurities derived from new methods of manufacture or accidental contamination.

Monographs should provide a reliable means of locating all specified impurities on the chromatogram. Identification of unspecified impurities is necessary if a correction factor is to be applied. Peaks may be located using:

- a reference standard for each impurity;
- a reference standard containing some or all of the specified impurities, provided with a chromatogram;
- location by relative retention is not generally considered sufficient for pharmacopoeial purposes, notably for gradient elution.

General considerations applying to separation techniques:

- high concentrations/loadings are normally used since the symmetry of the principal peak or shape of the spot is not critical in impurity testing so long as there is no interference. When using an external standard in quantitative determinations the response of the principal peak need not be in the linear range of the detector;
- in general tests for related substances, the substance to be examined should not to be chemically modified (e.g. derivatization) before purity testing since the impurity pattern may be modified;
- similarly, extraction of the free base or acid prior to impurity testing is to be avoided.

3.2.1.6.8.1.1 Thin-layer chromatography

TLC methods should only be used for control of a specified impurity and where liquid chromatography, gas chromatography or capillary electrophoresis methods are inappropriate (usually due to a lack of a suitable detection system).

Commercially available precoated plates are to be used; the trade name of the plate found suitable should be made available to the public but leaving some flexibility to the user for using another brand of material if demonstrated to be suitable. The monograph describes the type of plate (not the commercial name) and includes system suitability criteria for verification of the separation capacity and of the sensitivity. Often the substances that would be best suited for a system suitability test will not be readily available individually; a sample of the substance to be examined containing them as contaminants or even a deliberately spiked sample may then be prescribed. Permissible variations to the different parameters are indicated in a general chapter on *Chromatography*.

If any pretreatment is required or if the chromatography is carried out in unsaturated conditions for the satisfactory conduct of the test, then this information is included in the text of the monograph (especially applicable to the use of reverse-phase plates).
One or more dilutions of the substance to be examined will often prove adequate for reference purposes, provided the impurities to be compared exhibit a similar behaviour under the chosen chromatographic conditions. This implies that the spots to be compared are sufficiently close in R_F value to minimize errors introduced by different diffusion of the substances during their migration. Otherwise, reference solutions containing the specified impurities are to be employed.

3.2.1.6.8.1.2 Liquid chromatography

Defining the appropriate chromatographic system will often be one of the major problems to be dealt with in elaborating a pharmacopoeial purity test based on LC. The matter is further complicated by the existence of numerous variants of stationary phases, especially amongst the chemically bonded reverse-phase materials for which not only brand-to-brand but occasionally also batch-to-batch variations occur that can influence a given separation. During the validation of the method several types of stationary phase should be tested and the brand names of materials found to be suitable should be made available to the public through appropriate means but leaving some flexibility to the user for using another brand of material if demonstrated to be suitable.

In describing the chromatographic system, mention is made of the column dimensions (length and internal diameter), nature of the stationary phase (in detail) and its particle size including any steps to prepare or pretreat it, composition and flow rate of the mobile phase including elution programme (if any), column temperature (if differing from ambient or especially if thermostated), method of injection (if important), injection volume and method of detection. Permissible variations to the different parameters are indicated in a general chapter on *Chromatography* or in the individual monographs.

Test and reference solutions are wherever possible prepared using the mobile phase as the solvent in order to minimize peak anomalies.

For the sake of simplicity and reproducibility, isocratic elution is to be preferred. If the chromatography is not carried out at normal room temperature (15 °C to 25 °C), the temperature is specified (≥30 °C).

When a gradient system is described, all necessary parameters are clearly given, e.g. composition of mobile phases, equilibrium conditions, gradient conditions (linear or step), etc.

An important parameter to be considered in gradient elution is the volume between the solvent mixing chamber and the head of the column, usually referred to as the dwell volume, *D* (other terms employed include: effective system delay volume, dead volume and delay volume). A method for the determination of dwell volume can be indicated in a general chapter on *Chromatography*. Large differences in dwell volume from one pumping system to another will result in differences in elution of peaks. The greatest effect of differing dwell volumes on retention times is for those substances that are not strongly retained. Thus, gradient systems should be conceived in such a way that analytes are not eluted at or near the beginning of a gradient. It is best if less strongly retained components are eluted with an initial isocratic phase followed by a gradient for elution of the more strongly retained analytes. The effect of differences in dwell volumes is then minimized. In addition, an initial isocratic phase allows correcting for marked differences

in dwell volume from one gradient pumping system to another. The dwell volume of the instruments used during development of the method is given in the monograph or made available to the public by other suitable means (e.g. database).

The quality of water and solvents to be used should be defined.

3.2.1.6.8.1.2.1 Quantification

Quantification is required for limits applied to specified impurities, unspecified impurities and total impurities. It is most commonly achieved using an external standard and less commonly by the normalization procedure.

External standard. A dilution of the test solution/substance to be examined is usually used as external standard. A specific external standard may also be used:

- a solution of the impurity (preferred option);
- a solution of the substance to be examined containing a known amount of the impurity.

Where a dilution of the substance to be examined is used as external standard, correction factors[1] for the impurities should be determined during the development of the method and indicated in the monograph only if they are outside a range of 0.8 to 1.2 and considered relevant in view of the batch results. Correction factors are normally given with only 1 decimal place. It is recommended not to apply correction factors >5 for specified impurities, but to use external standards in these cases where possible.

Normalization procedure. Quantification by the area normalization technique requires that all the solutes are known to be eluted and detected, preferably with uniform response factors, and that the detector response is linear with the concentrations employed. This should be validated. Correction factors are introduced where applicable.

[1] The correction factor is the reciprocal of the relative detector response factor (commonly referred to as *response factor)*, the latter expressing the sensitivity of a detector for a given impurity relative to the substance to be examined.

Peaks due to solvents or reagents or arising from the mobile phase or the sample matrix, and those at or below the disregard limit, are excluded before calculating the percentage content of a substance by normalization. The disregard limit is defined as the peak area obtained with a reference solution. The corresponding numerical value (percentage compared to the test solution) is given in brackets for information.

3.2.1.6.8.1.2.2 System suitability criteria

Several system suitability criteria are to be included in the test. Requirements are given in the individual monograph and/or in general texts that are cross referred to.

Separation capacity. Such a criterion is necessary when separation techniques are employed for assays and tests for related substances. The following approaches are acceptable for a system suitability test for selectivity:

- **Resolution.** As calculated by the formula given in a general chapter on *Chromatography* using 2 closely eluting peaks, preferably corresponding to the substance itself and a potential impurity. However, when the elution times of the 2 peaks are very different, i.e. when the resolution factor is large (>5.0), it is preferable to use another impurity or another substance chemically related to the substance under study, giving a smaller resolution factor. Peaks of different heights may be used for calculation of resolution but extreme differences will compromise the usefulness of the criterion. Saturation of the peaks should be avoided.
- **Peak-to-valley ratio.** Can be employed when complete separation between 2 adjacent peaks cannot be achieved, i.e. when the resolution factor is less than 1.5.

In-situ degradation offers an alternative approach to define the suitability of the system provided that the solution of the substance can be degraded, in mild "stress" conditions within a reasonably short time, to produce decomposition products, the peaks of which can be used to determine a resolution or a peak-to-valley ratio.

A "spiked" or an impure substance can also be employed to define the system. This approach can be employed when it is difficult to isolate an impurity eluting close to the main peak in sufficient quantity to establish a reference substance. In this case a chromatogram can be supplied with the reference substance (for system suitability), or published with the monograph or described in the text of the test for related substances. A requirement for resolution or peak-to-valley ratio is also to be included.

When gradient elution is described, it is preferable to describe a system suitability requirement for each critical gradient step.

Sensitivity. The method should be designed to achieve sufficient sensitivity. A S/N ratio ≥10 at the disregard limit/reporting threshold has to be observed by the user. It may be necessary to add a specific sensitivity criterion for specified impurities, e.g. for impurities with high correction factor. Example: impurity X specified at 0.15 %, correction factor 5, general disregard limit 0.05 %. For the considered impurity X, the sensitivity of the method is sufficient if (1) a S/N ratio of minimum 10 is obtained with a 0.05 % (relative to the test solution) solution of impurity X, when impurity X is available as reagent/CRS or (2) a S/N ratio of minimum 50 is obtained with a 0.05 % solution of the active substance when impurity X is not available. Option (2) is preferred when only limited amounts of the isolated impurity are available.

System repeatability. A requirement for the maximum permitted relative standard deviation (calculated for a series of injections of the reference solution(s) used for quantification) is included in the monograph or given in a general text that is cross referred to.

Peak symmetry. A requirement for the symmetry factor (also known as the asymmetry factor or tailing factor) of the peak in the chromatogram obtained with the reference solution(s) used for quantification is included in the monograph or given in a general text that is cross referred to.

3.2.1.6.8.1.3 Gas-liquid chromatography

The difficulties met when defining the appropriate chromatographic system are similar in GC purity tests to those mentioned under LC although the emphasis may be on other points. In describing the chromatographic system, mention is made of essentially the same factors as mentioned under LC with appropriate variations, e.g. temperature programme (if any) instead of elution programme, injection port and detector temperatures, etc. The nature of the stationary phase, i.e. the composition of the coating material (including its concentration) and the inert support (including its particle size and any pre-treatment) are also given here in general terms but the brand names of material found to be suitable should be made available to the public through appropriate means (e.g. database or general chapter). Use of packed columns should be avoided. Permissible variations to the different parameters are indicated in a general chapter on *Chromatography*.

For the sake of simplicity and reproducibility isothermal operating conditions are preferred. Quantification is usually based on an internal standard technique or on the area normalization procedure.

3.2.1.6.8.1.4 Capillary electrophoresis

CE may be employed to separate and control a large number of impurities of vastly different polarities. It is also suitable to control the content of the unwanted enantiomer in chiral therapeutic substances.

For the control of impurities or assays, the use of an internal standard is recommended to achieve appropriate precision.

For chiral analysis, a chiral reagent is added to the running buffer. The chiral reagent should be carefully described in the monograph or as a reagent, particularly for cyclodextrin derivatives and the brand names of materials found to be suitable should be made available to the public through appropriate means (e.g. database or general chapter).

Experimental parameters to be considered for inclusion in the monograph:

- instrumental parameters: voltage, polarity, temperature, capillary size (diameter and length – total and effective – to the detector);
- coating material of the capillary (where applicable).(if a coated capillary is used, the trade name of the capillary found suitable during elaboration of the monograph should be made available to the public through appropriate means (e.g. database or general chapter);
- buffer: pH, molarity, composition;
- sample solvent;
- separation: pole outlet, separation voltage U or current I;
- injection: time t, voltage U or pressure Δp;
- detection: wavelength, instrumentation;
- temperature;
- shelf-life of solutions
- rinsing procedures (time, reagents, pressure Δp) needed to stabilize the migration times and the resolution of the peaks:
  - preconditioning of a new capillary,
  - preconditioning of the capillary before a series of measurements,
  - between-run rinsing.

In order to minimize the electro-osmotic flow (EOF) signal, test and reference solutions are, wherever possible, prepared using water for injections or the running buffer as the solvent.

It is recommended to make cross-reference to an internationally harmonized general method (see 3.2.1.10.).

3.2.1.6.8.2 Inorganic impurities

Inorganic impurities include reagents, ligands and catalysts, metal impurities, inorganic salts and other materials such as filter aids (where relevant).

Known impurities, likely to be present, are typically covered by specific tests.
Metal impurities: (to be drafted after adoption of ICH Q3 D)

3.2.1.6.8.3 Residual solvents

Control of residual solvents is typically provided for in the pharmacopoeia by a:

- General chapter that takes into consideration the classification and acceptable limits of the ICH Guideline Q3C;
- General method for the identification and determination of residual solvents which contains the default methods to be applied.

Where the limits to be applied are in line with the general monograph, tests for residual solvents are not specifically mentioned in individual monographs since the solvents employed may vary from one manufacturer to another.

A test and limit for a Class 1 solvent is included in the individual monograph if it is potentially present in an approved product.

Tests and limits for Class 2 solvents are not included in monographs since the limit may be set using option 2 of the ICH guideline/General chapter, whereby all the ingredients of a pharmaceutical preparation are taken into account.

A test and limit for a Class 3 solvent is included in the individual monograph if it is potentially present in an approved product at a level higher than 0.5%.

3.2.1.6.9 Foreign anions and/or cations

Since strong inorganic acids and bases are widely used in syntheses, the contents of foreign anions and/or cations in a substance can be indicative of the extent to which it has been purified. They can also reveal whether contamination with closely related

substances has taken place. On the other hand, the usually ionic impurities can often be removed from poorly water-soluble substances by treatment with water without necessarily removing the organic impurities. Tests for anions and cations therefore cannot replace a test for related substances in organic substances but they may constitute a useful supplement in the case of the water-soluble organic substances. For inorganic substances, which are usually prepared from other inorganics, a much broader range of tests for foreign ions are contemplated.

Where the introduction of tests for foreign anions in organic substances is considered then a single one, either for chlorides, sulfates or – less commonly – nitrates, will usually suffice even when several could theoretically be present. The test is then to be carried out on the most abundant anion.

Certain cations are stringently limited because of their toxicity or catalytic activity. They are treated separately under Heavy metals. Unless there are special reasons for limiting the presence of cations, individually or in smaller groups, in organic substances, the majority are adequately controlled via a determination of sulfated ash (see further).

3.2.1.6.10 Loss on drying

A General chapter includes sets of standard conditions that are referred to in monographs using conventional expressions. If other conditions are used, they are described in full in the monograph. Drying is carried out to constant mass, unless a drying time is specified in the monograph. When a drying time is prescribed, this should have been validated. Where a drying temperature is indicated using a single value, a tolerance of ± 2 °C is understood. For temperatures higher than 105 °C, a larger tolerance should be indicated in the monograph, if necessary. Drying in an oven at 105 °C is to be preferred when the product is sufficiently stable at that temperature. Otherwise, drying over P_2O_5 at 1.5–2.5 kPa at room temperature or at a specified temperature is usually applied. It should however be remembered that organic solvents are not always easily removed (e.g. organic solvents in colchicine).

Generally an upper limit for loss on drying is given. If the substance is a hydrate (or solvate), upper and lower limits are indicated. Limits lower than 10 % should be given with 2 significant figures and limits of 10 % or greater should be given with 3 significant figures. The sample size is chosen to give a difference of 5–50 mg before/after drying and is indicated with 4 significant figures.

When only class 3 solvents are used, a test for loss on drying with a limit at 0.5% may be included to control water and residual solvents at the same time.

The test can be carried out on a semi-micro scale, in which case the accuracy with which the test sample is to be weighed should be specified accordingly.

Thermogravimetry

Loss on drying can be determined by this method when the amount of substance has to be restricted, for example to reduce exposure for the analyst or if the substance is very expensive (e.g. vincristine sulfate and vinblastine sulfate).

3.2.1.6.11 Water

3.2.1.6.11.1 Semi-micro determination of water (Karl Fischer)

The sample size is chosen to obtain a titration volume of about 1 mL and should be given with 3 significant figures Commercial reagents without pyridine are now used instead of *iodosulfurous reagent R*; stoichiometry and freedom from interference are to be verified (data may be provided by the supplier of the reagent for the substance in question).

Commercial reagents found to be suitable should be made available to the public through appropriate means (e.g. database or general chapter).

Limits lower than 10% should be given with 2 significant figures and limits of 10% or greater should be given with 3 significant figures.

Semi-micro determination is not recommended for a water content of less than 0.5%.

3.2.1.6.11.2 Micro determination of water (coulometric titration)

Coulometric titration is restricted to the quantitative determination of small amounts of water. The sample size is chosen to have a water content of 10 µg to 10 mg; titration of quantities of the order of 10 µg are prescribed only where the water content is very low or the sample size is limited by the cost of the substance. The sample size should be stated with 3 significant figures.

No detailed description is given for the composition of the electrolyte (anolyte and catholyte) reagent, as almost all laboratories use commercially available ready-to-use reagents. Commercial reagents found to be suitable should be made available to the public through appropriate means (e.g. database or general chapter).

Limits should be expressed with 2 significant figures.

3.2.1.6.12 Sulfated ash/Residue on ignition

This test is usually intended for the global determination of foreign cations present in organic substances and in those inorganic substances which themselves are volatilized under the conditions of the test. Thus the test will be of little value as a purity requirement for the majority of inorganic salts of organic substances, due to the resulting high bias.

The limit in a test for sulfated ash is usually set at 0.1%, unless otherwise justified. The amount of substance prescribed for the test is such that a residue corresponding to the limit will weigh not less than 1.0 mg and the prescribed mass of substance is then given with the appropriate precision (1.0 g). The use of an internationally harmonized general method (see 3.2.1.11) is recommended.

3.2.1.6.13 Residue on evaporation

The amount of a liquid material prescribed for the test is such that a residue corresponding to the limit will weigh at least 1.0 mg. The appropriate mass or volume of the substance will normally be in the range of 10 g to 100 g (or mL).

3.2.1.6.14 Sterility

A test for sterility is prescribed wherever such control is necessary e.g. when it is known that the substance is intended for use in the manufacture of sterile dosage forms without a further appropriate sterilization procedure.

A cross-reference to a general method describing the test for sterility, preferably the general method internationally harmonized (see 3.2.1.11) is then included.

3.2.1.6.15 Microbiological purity

Individual monographs give acceptance criteria for microbiological quality wherever such control is necessary (total aerobic microbial count (TAMC), total combined yeasts/moulds count (TYMC), specific microorganisms).

Microbial examination is performed according to methods given in general chapters that will be referred to in the individual monograph. The use of an internationally harmonized method (see 3.2.1.11) is recommended.

3.2.1.6.16 Bacterial endotoxins

If the substance is offered as bacterial endotoxin-free grade, the limit and test method (if not Gel-clot method: limit test) are stated in the individual monograph. The limit is calculated in accordance with a general chapter of the pharmacopoeia unless a lower limit is justified from results from production batches or is required by the competent authority. The use of an internationally harmonized method (see 3.2.1.11) is recommended.

Abnormal toxicity

A test for abnormal toxicity may be included in some specific cases, e.g. new substances of biological origin.

3.2.1.7 Assay

Assays are included in monographs unless:

- all the foreseeable impurities can be detected and limited with sufficient precision;

- certain quantitative tests, similar to assays, are carried out with sufficient precision (specific optical rotation, specific absorbance);
- specific profiles of relevant substances such as composition of the fatty acid fraction or composition of the sterol fraction of a fat or fatty oil have been established;
- the tests performed are sufficient to establish the quality of the substance, usually a non-active ingredient, for example ethanol and water.

In certain cases, more than one assay may be necessary when:

- the substance to be examined consists of a combination of 2 parts that are not necessarily present in absolutely fixed proportions, so that the assay of only 1 of the 2 constituents does not make it possible correctly to determine the substance as a whole;
- the results of the quantitative tests do not fully represent the therapeutic activity, in which case a biological assay is included.

In the case of well-defined salts, the assay of only one of the ions, preferably the pharmacologically active component, is generally considered sufficient.

When the identification and purity tests are sufficiently characteristic and searching, a non-specific but precise assay (as volumetric analysis) may be used rather than a specific and less precise assay (as LC).

Every assay method proposed is validated.

3.2.1.7.1 Ultraviolet and visible spectrophotometry

Spectrophotometric assays may be carried out directly in the ultraviolet or visible range or after a suitable chemical reaction, though the latter are less precise. Other methods (especially LC methods) are usually preferred.

3.2.1.7.2 Volumetric analysis

The amount of the substance taken for the assay is such that the final titration, using automatic titration equipment, will consume less than 10 mL – preferably between 7 and 8 mL – of titrant in order to permit the use of standard titration equipment. In the case of back-titration, the fixed volume of the first titrant added is, furthermore, adequate so that the result of the assay will not be based upon a small difference of volumes.

Either a potentiometric end-point detection or a visual colour change indicator can be specified in the monograph. The potentiometric mode of end-point detection is applicable in almost all cases and is to be preferred. Where potentiometric detection is specified, the appropriate combination of electrodes for that purpose is, whenever useful, to be given in the text. The number of inflexion points to be evaluated is given. Exceptionally, other modes of detection are specified, such as the amperometric method. Whichever mode is used, it is known to be appropriately reproducible and preferably stoichiometrically exact.

3.2.1.7.3 Chromatography

The chromatographic methods on which assays may be based are in pharmacopoeial practice normally limited to LC and GC. Such methods require the use of a reference standard with an assigned content of the analyte. The addition of an internal standard in GC is recommended. Requirements for the maximum permitted relative standard deviation (calculated for a series of injections of the reference solution) and the symmetry factor of the analyte peak are included in the monograph or given in a general text that is cross referred to.

3.2.1.8 Storage

Although the statements given under this heading in a monograph of the pharmacopoeia do not constitute pharmacopoeial requirements, the appropriate information to safeguard the quality of a pharmacopoeial material during storage is to be given here where appropriate.

The terminology used should be defined in a general text.

Manufacturers should be requested to provide stability data. In considering the guidance to be given in the monograph, the behaviour of the material towards exposure to atmospheric air, various degrees of humidity, different temperatures and daylight are to be taken into account.

3.2.1.9 Labelling

In respect of the fact that the labelling of medicine is subject to international agreements and supranational and national regulations, the indications given under LABELLING are not exhaustive and cannot be harmonized: they may consist of mandatory statements (for example, those necessary for the application of the monograph) and other statements that may be included only as recommendations. When, for example, a starting material has to comply with additional requirements (sterility, etc.) the label states, where appropriate, that the contents of the container are suitable for that use. Furthermore, when the inclusion of certain stabilizers or other additives is authorized by the monograph, their presence will generally have to be declared on the label.

3.2.1.10 Impurities

Monographs on organic chemicals should have a transparency list defining all specified impurities covered by the monograph. In addition, it may be useful to include information on other detectable impurities (impurities that are known to be detected by the monograph tests but that are not known to occur routinely in current production batches *above the identification threshold*).

The transparency list gives at least the chemical nomenclature of each impurity (of the base/acid where applicable). Trivial names may be included in parenthesis in the rare cases where they are considered to be informative. If the chemical structure is given, impurities are represented in a similar manner to the parent substance to make it clear that they are structurally analogous.

3.2.1.11 General methods

A number of general methods mentioned above have been harmonized by the PDG and are currently under implementation by *The International Pharmacopoeia*. Their prospective use for future monograph elaboration is encouraged.

3.2.2 Monographs for finished products

[*as received from* BP, Ph.Eur., Russian Pharmacopoeia (sterility), USP]

3.2.2.1 Concept

Specifications in pharmacopoeias are one facet of the overall control of the quality of medicinal products and their constituents. The monographs for finished products provide a publicly available standard that a product or a component of a product is expected to meet at any time during its period of use. Pharmacopoeial specifications are used within pharmaceutical product licensing or authorization systems and by manufacturers, suppliers, purchasers and those acting on behalf of consumers of medicinal products.

Before the process of writing a monograph for a finished product can begin, it is important to consider the Tests that are required to demonstrate the quality of a given pharmaceutical form; product-specific tests should be avoided, where possible. These tests should be applied consistently in monographs across all participating pharmacopoeias.

The format for the inclusion of tests may vary regionally. For example, certain regions specify compliance with manufacturing based testing (usually measures of the physical or physicochemical acceptability) in the specific monograph, while others incorporate these requirements in General monographs for a particular pharmaceutical form.