DECISION

No. 22/27.11.2009

on the approval of the Guideline on Summary of Product Characteristics (SPC)

The Scientific Council of the National Medicines Agency,
set up based on Minister of Public Health Order No. 1027/22.05.2008, as amended, reunited on summons of the National Medicines Agency President in the ordinary meeting of 27.11.2009, in accord with Article 10 of Government Ordinance no. 125/1998 related to the set up, organisation and functioning of the National Medicines Agency, approved as amended through Law No. 594/2002, as further amended, agrees on the following

DECISION

Single Article. – The Guideline on Summary of Product Characteristics is approved, in accordance with the Annex which is integral part of this Decision, as of 1 May 2010.

PRESIDENT
of the Scientific Council
of the National Medicines Agency

Acad. Prof. Dr. Victor Voicu

ANNEX

GUIDELINE
on the Summary of Product Characteristics
(SPC)

CHAPTER I
Introduction and legal basis

MODULE 1.3 SUMMARY OF PRODUCT CHARACTERISTICS

Art. 1. - This Guideline is a translation into Romanian and an adaptation of the EC/2009 Guideline on the Summary of Product Characteristics (SPC).

Art. 2. – (1) In accordance with the provisions of Art. 702 (4) (j) of Law No. 95/2006 on healthcare reform, as amended, transposing Art. 8 (3) (j) of Directive 2001/83/EC and of Art. 6 (1) of Regulation (EC) 726/2004, a Summary of Product Characteristics (SPC) shall be included in the application for marketing authorisation, issued in accordance with the provisions of Art. 708 of Law No. 95/2006, transposing Art. 11 of Directive 2001/83/EC[1].

(2) In accordance with Law No. 95/2006, transposing Directive 2001/83/EC, on the release of the marketing authorisation, the National Medicines Agency informs the Marketing Authorisation Holder (MAH) about the SPC approved by the latter; thus, the SCP is intrinsic and integral part of the marketing authorisation.

Art. 3. - The SPC sets out the agreed position of the medicinal product as distilled during the course of the assessment process; as such the content cannot be changed except with the approval of the National Medicines Agency.

Art. 4. - The SPC is the basis of information for health professionals on how to use the medicinal product safely and effectively; the Package Leaflet (PL) shall be drawn up in accordance with the SPC. The *Guideline on excipients in the label and Package leaflet of medicinal products for human use* (approved through the Minister of Public Health Order No. 1202/02.10.2006) is also applicable to the SPC.

Art. 5. - It is not in the remit of the SPC to give general advice on the treatment of particular medical Conditions but, on the other hand, specific aspects of the treatment related to use of the medicinal product or its effects should be mentioned; similarly, the SCP shall not contain general recommendations concerning the administration procedures, but any product-specific recommendations should be included.

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[1] Modulul 1.3 constă din RCP.

Art. 6. – (1) This guideline provides advice on the principles of presenting information in the SPC.

(2) Applicants should maintain the integrity of each section of the document by only including information in each section, which is relevant to the section heading.

(3) However, some issues may need to be addressed in more than one section of the SPC and in such situations the individual statements may cross-refer to

other sections when these contain relevant additional information.

Art. 7. - When a guideline exists for the SPC of a specific therapeutic area (e.g. antibiotics, benzodiazepines, vaccines, pegylated proteins or plasma-derived medicinal products), this guideline should be taken into account.

Art. 8. – (1) Separate SPCs are required for each pharmaceutical form and strength by the National Medicines Agency.

(2) Limited references to other strengths or pharmaceutical forms of the same medicinal product may be necessary in an SPC if the dosage regimen is based on the use of several strengths or pharmaceutical forms.

(3) For the purposes of giving information to prescribers, the SPCs of different pharmaceutical forms and strengths may be combined for appropriate products within the same active substance(s).

CHAPTER II
Scope

Art. 9. – (1) This Guideline enters into force starting with the 1st of May 2010 for medicinal products authorised through all types of procedures.

(2) However, applications may also be forwarded based on these recommendations, prior to the mentioned date.

CHAPTER III
Principles on the presentation of the information

Art. 10. – The SPC should be edited in a clear and concise language.

Art. 11. – Each point of the SPC should ensure prioritary care for those aspects which apply to the main public, for which the medicinal product is recommended, following which, if deemed necessary, of that specific information for any relevant special population (e.g. children or elders).

Art. 12. – (1) Public assessment reports provide detailed information concerning the medicinal products and are available on the EMA website as well as on the website of the institution named Heads of the Agencies;

moreover, the National Medicines Agency makes such reports publicly available, upon request.

(2) In case the public may access a public assessment report, the SPC should contain a link to the relevant web pages.

Art. 13. – Medical terminology should be regularly used throughout the entire SPC; e.g. the use of the MedDRA system, in accordance with the presentation in the Annex for point 4.8 „Adverse reactions" (further mentioned in the Guideline, point 4.8), should be employed throughout the entire SPC, mainly in section 4.3 „Contraindications" (further mentioned in this Guideline in section 4.3), section 4.4 „Warnings and special cautions for use" (further mentioned in this Guideline in section 4.4) and section 4.8 „Adverse reactions".

Art. 14. – The SPC provides information concerning a specific medicinal product and, therefore, should not refer to any other product (e.g. via statements such as "Like other medicinal products belonging to the same class ... "), except from the case where this involves a warning concerning a whole class of medicinal products, issued by a competent authority.

Art. 15. – (1) The principles established in this Guideline are available for all medicinal products.

(2) The enforcement of these principles for a specific medicinal product depends on the scientific knowledge of the respective medicinal product, on the juridical grounds of the marketing authorisation and on public health needs.

(3) Therefore, deviations from the provisions of this Guideline should be justified in the General review or in the relevant Summary in the application for marketing authorisation.

(4) Through a national procedure, the applicant is given practical recommendations on the issuing of the SPC, as European templates approved through Minister of Public Health Order No. 399/2006, transposing other templates issued by the Quality Review of Documents (QRD) group in view of the centralised, decentralised and mutual recognition procedures.

CHAPTER IV
Name of the medicinal product

Art. 16. – (1) The (invented) name should be followed by both the strength and the pharmaceutical form; However, when otherwise referring to the medicinal product throughout the SPC text, the strength and the pharmaceutical form do not have to be mentioned in the name.

(2) The International Non-proprietary Name (INN) or the usual common name of the active substance should be used when referring to properties of the active substance(s) rather than those of the medicinal product.

(3) The use of pronouns (e.g. "it") is encouraged whenever possible.

IV.1. Strength

Art. 17. – (1) The strength should be the relevant quantity for identificationand use of the medicinal product and should be consistent with the quantity stated in the quantitative composition and in the posology.

(2) Different strengths of the same medicinal product should be stated in the same way, e.g. 250 mg, 500 mg, 750 mg.

(3) The use of decimal points should be avoided where these can be easily removed (e.g. 250 microgram, not 0.25 mg); however, where a range of medicinal products of the same pharmaceutical form includes strengths of more than one unit (e.g. 250 microgram, 1 mg and 6 mg), it may be more appropriate in certain cases to state the strengths in the same unit for the purpose of comparability (e.g. 0.25 mg, 1 mg and 6 mg).

(4) For safety reasons, micrograms and millions (e.g. for units) should always be spelled out in full rather than be abbreviated.

IV.2. Pharmaceutical form

Art. 18. – (1) The pharmaceutical form should be described by the European Pharmacopoeia full standard term using plural form if appropriate (e.g. tablets) (see point 3, "Pharmaceutical form").

(2) If an appropriate standard term does not exist, a new term may be constructed from a combination of standard terms, in accordance with "Standard Terms, introduction and Guidance".

Art. 19. – (1) Should this not be possible, the competent authority should be asked to request a new Standard Term from the European Department for the Quality of Medicines (EDQM) of the Council of Europe.

(2) No reference should be made to the route of administration or to the container unless these elements are part of the standard term or where there are identical products, which may be distinguished only by reference to the container.

Art. 20. - For the expression of the name and strength of traditional herbal medicinal products the declaration should be in accordance with the actual *Note for Guidance on Quality of Herbal Medicinal Products*.

CHAPTER V
Qualitative and Quantitative composition

Art. 21. – (1) In section 2 „Quantitative and qualitative composition" (further mentioned in this Guideline, section 2) and, on a case-by-case basis, in section 4.3 or 4.4, full details should be provided concerning the qualitative and quantitative composition of the active substance(s) and excipients, knowledge of which is essential for proper administration of the medicinal product; e.g. to

be mentioned, under a separate title, the qualitative and quantitative composition of the excipients detailed in the Annex to the *Guideline on the excipients in the label and package leaflet of medicinal products for human use.*

(2) A standard statement should be included at the end of the section, i.e. 'for full list of excipients, see section 6.1' (further mentioned in this Guideline, point 6.1).

Art. 22. - In case a solvent is part of a medicinal product, the respective information should be provided under the relevant points (usually, under point 3 „Pharmaceutical Form" (further mentioned in this Guideline, point 3), 6.1, 6.5 „Nature and content of the packaging" (further mentioned in this Guideline, point 6.5) and 6.6 „Special cautions for the release of waste products and other handling instructions" (further mentioned in this Guideline, point 6.6)).

V.1. Qualitative declaration

Art. 23. – (1) The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant, or the European Pharmacopoeial name if that name represents an established name in Europe.

(2) If there is no INN, the European Pharmacopoeia name should be used or if the substance is not mentioned in the pharmacopoeia, the usual common name should be used.

(3) In the absence of a common name, the exact scientific designation should be given.

(4) Substances not having an exact scientific designation should be described by a statement on how and from what they were prepared.

(5) References to the pharmacopoeial quality should not be included.

Art. 24. - Where the medicinal product is a traditional herbal medicinal product, the qualitative declaration should be in accordance with the *Note for Guidance on Quality of Herbal Medicinal Products*.

Art. 25. - When the medicinal product is a radiopharmaceutical kit, the qualitative declaration should clearly indicate that the radioisotope is not part of the kit.

V.2. Quantitative declaration

Art. 26. - The quantity of the active substance must be expressed per dosage unit (for metered dose inhalation products, per delivered dose and/or per metered dose), per unit volume, or per unit of weight and must be related to the declaration of strength, "International Nonproprietary Name" in section 1 (further mentioned in this Guideline under Point 1).

Art. 27. – Quantity should be expressed via an internationally approved standard term, which may be replaced by another term in case the latter is considered more significant for the healthcare professionals.

V.2.1. Salts and hydrates

Art. 28. – (1) Where the active substance is present in the form of a salt or hydrate, the quantitative composition should be expressed in terms of the mass (or biological activity in International (or other) units where appropriate) of the active entity (base, acid or anhydrous material), e.g. '60 mg toremifene (as citrate)' or toremifene citrate equivalent to 60 mg toremifene'.

(2) Where a salt is formed *in situ* during manufacture of the finished product (e.g. formed during the mixing process of a solvent with a powder), the quantity of the active entity should be stated, with a reference to the *in situ* formation of the salt.

(3) In the case of established active substances in medicinal products where the strength has traditionally been expressed in the form of a salt or hydrate, the quantitative composition may be declared in terms of the salt or hydrate, e.g. '60 mg diltiazem hydrochloride'. This may also apply when the salt is formed *in situ.*

V.2.2. Esters and precursors of active substances (pro-drugs)

Art. 29. – (1) If the active substance is an ester or a precursor of an active substance (pro-drug), the quantitative composition should be stated in terms of the quantity of the ester or pro-drug.

(2) When the active entity is an active substance of an already approved medicinal product, the quantitative composition should also be stated in terms of the quantity of this active entity (e.g. 75 mg phosphenytoin equivalent to 50 mg phenytoin).

V.2.3. Oral powders for solution or suspension

Art. 30. – The quantity should be stated per unit dose if the medicinal product is a single-dose preparation or otherwise per unit dose volume after reconstitution; a reference to the molar concentration may also be appropriate in some cases.

V.2.4. Parenterals excluding powders for reconstitution

Art. 31. – (1) For single-dose parenterals, where the total contents of the container are given in a single dose ('total use'), the quantity of active substance(s) should be stated per presentation (e.g. 20 mg etc.) not including any overages or overfill. The quantity per ml and the total labelled volume should also be given.

(2) For single-dose parenterals, where the amount to be given is calculated on the basis of the patient's weight or body surface or other variable ('partial use'), the quantity of active substance(s) should be stated per ml. The quantity per total labelled volume should also be given. Overages or overfills should not be included.

(3) For multi-dose and large volume parenterals, the quantity of active substance(s) should be stated per ml, per 100 ml, per 1000 ml etc. as

appropriate, except for multidose vaccines containing ‘n’ doses of the same dose. In this case, the strength should be expressed per dose volume; overages or overfills should not be included.

(4) Where appropriate, e.g. for X-ray contrast media, and parenterals containing inorganic salts, the quantity of active substance(s) should also be indicated in millimoles; for X-ray contrast media with iodine-containing actives substances, the quantity of iodine per ml should be stated in addition to the quantity of the active substance.

V.2.5. Powders for reconstitution prior to parenteral administration

Art. 32. – When the medicinal product is a powder to be reconstituted prior to parenteral administration, the total quantity of active substance in the container should be stated not including overages or overfills, as well as the quantity per ml when reconstituted, unless there are several means of reconstituting, or different quantities of solvent used, which result in different final concentrations.

V.2.6. Concentrates for parenteral solutions

Art. 33. - The quantity should be stated as the content per ml in the concentrate and as the total content of the active substance; the content per ml when diluted as recommended should also be included unless the concentrate is to be diluted to within a range of different final concentrations.

V.2.7. Transdermal patches

Art. 34. - The following quantitative details should be given: the content of active substance(s) per patch, the mean dose delivered per unit time, and the area of the releasing surface, e.g. ‘Each patch contains 750 micrograms of estradiol in a patch size of 10 cm^2, releasing a nominal 25 micrograms of estradiol per 24 hours'.

V.2.8. Multidose solid or semi-solid medicinal products

Art. 35. - Quantity of active substance should be stated, where possible, per unit dose, otherwise per gram, per 100 g or percentage, as appropriate.

V.2.9. Biological products

Art. 36. – (1) In case of ***biological products***, **strength (**quantity of biological product) is expressed in terms of mass units, biological activity units or International Units, depending on the medicinal product and in accordance with the use of the European Pharmacopoeia, if relevant; for pegylated proteins, reference is made to the CHMP Guidance on the description of composition of pegylated (conjugated) proteins in the SPC.

(2) The nature of any cellular system(s) used for production, and if relevant the use of recombinant DNA technology, including the use of the expression ‘produced in XXX cells <by recombinant DNA technology>’should be mentioned in the SPC, in a pattern as set by the following examples:

- ‘produced in human diploid (MRC-5) cells’,

- ‘produced in *Escherichia coli* cells by recombinant DNA technology’,
- ‘produced in chick-embryo cells’ and
- ‘derived from human plasma donors’.
- ‘derived from human urine’,
- ‘derived from <animal> blood’,
- ‘derived from swine pancreatic tissue’,
- ‘derived from swine intestinal membrane’.

(3) **The special dispositions for normal immunoglobulins** include a declaration concenring the distribution of the IgG subclass within the total IgG percentage, following which the upper limit of the IgA content is indicated.

(4) **The special dispositions for vaccines** specify the fact that: the content of active substance per unit dose is stated (e.g. per 0.5 ml), if any, adjuvants should be stated in terms of quality and quantity, relevant residues shall be indicated (e.g.

ovalbumin in egg-derived vaccines); specific additional recommendations can be found in the CHMP Guidelines on biotechnological medicinal products, e.g. in the CHMP Guideline on the pharmaceutical aspects of the information concerning medicinal products for vaccines for human use.

V.2.10. Herbal medicinal products

Art. 37. – The quantitative declaration should be in accordance with the recommendations concerning the quality for herbal medicinal products.

CHAPTER VI
Pharmaceutical form

Art. 38. – (1) The pharmaceutical form should be described by the European Pharmacopoeia full standard term (see section 1). The term used in this section should be the same as the term used in section 1.

(2) However, where a European Pharmacopoeia short standard term is used on small immediate packaging material, the short term should be added in brackets in this section.

Art. 39. - It is recommended that a visual description of the appearance of the product (colour, markings, etc.) is given, in a separate paragraph to the standard term, including information on pH and osmolarity as required e.g.

-*„Tablet White, circular flat bevelled-edge tablets marked ‘100’ on one side”*

Art. 40. - In case of tablets designed with a score line, information should be given whether or not reproducible dividing of the tablets has been shown. e.g. ‘the scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses’, ‘the tablet can be divided into equal halves’.

Art. 41. - Information concerning the pH and osmolality shall be provided, on a case-by-case basis.

Art. 42. - In case of medicinal products to be reconstituted before use, the appearance before reconstitution should be stated in this section, while the appearance of the medicinal product after reconstitution should be stated in section 4.2 “Doses and route of administration” (further mentioned in this Guideline, section 4.2.) and 6.6.

CHAPTER VII
Clinical data

VII.1. Therapeutic indications

Art. 43. – (1) The indication(s) should be stated clearly and concisely and should define the target disease or condition distinguishing between treatment (symptomatic, curative or modifying the evolution or progression of the disease), prevention (primary or secondary) and diagnostic indication.

(2) When appropriate it should define the target population especially when restrictions to the patient populations apply.

Art. 43. – (1) Study endpoints should not normally be included unless such mention is specified as being appropriate for the indication in CHMP Notes for Guidance or Points to Consider Documents.

(2) The objective of a prevention indication may be mentioned in general terms only. This should also be done for the target population.

Art. 44. - Where results from subsequent studies provide further definition or information on a licensed indication, such information, provided it does not itself constitute a new indication, may be considered for inclusion in section 5.1 “Pharmaceutical properties” (further mentioned in this Guideline, section 5.1).

Art. 45. - Mandatory conditions of product usage not covered more appropriately in other parts of the SPC may also be included when relevant, e.g. concomitant dietary measures, lifestyle changes, or other therapy.

Art. 46. - When the product is indicated in a specific age group such as children/adolescents, the indication should state the age limit e.g. ‘X is indicated in <children> <adolescents> from the age of X <months><years >‘.

Art. 47. - In case the medicinal product’s indication depends on a certain genotype/gene expression/phenotypic expression, the fact should be stated in the therapeutic indication.

VII.2. Posology and method of administration

Art. 48. - In case of restricted medical prescription, this section should be started by specifying the conditions.

Art. 49. – In case of a special safety need, the recommendation in view of restriction of the use in specific surroundings (e.g. „to be used only in healthcare areas" sau "recommended for use only in the presence of adequate resuscitation equipment") is also mentioned.

VII.2.1. Doses

Art. 50. – The dosage has to be clearly specified for each method/route of administration and for each indication.

Art. 51. - Where appropriate, a reference to official recommendations should be made (e.g. for primary vaccination and antibiotics as well as for booster dose).

Art. 52. – (1) Specify dose recommendations per dose interval in an appropriate way (e.g. mg, mg/kg, mg/m2) for each dosing interval and age category where appropriate (specify age ranges/weight/body surface, as required), i.e. children as specified.

(2) The frequence of administration is expressed in time units (e.g. once/twice a day or every 6 hours) and, in order to avoid misunderstandings, abbreviations such as OD/BID shall not be employed.

(3) Where appropriate, the following points should be addressed:

- the maximum recommended single, daily and/or total dose,
- the need for dose titration,
- the normal duration of use and any restrictions on duration and, if relevant, the need for tapering off, or advice on discontinuation of treatment,
- advice on action to be taken if one or more dose(s) is (are) missed, e.g. in case of vomiting (the recommendation should be as clear as possible and take into account the recommended administration frequency, as well as the relevant pharmacokinetic data),
- advice on preventive measures to avoid certain adverse drug reactions (e.g. administration of antiemetics) with cross-reference to section 4.4,
- the intake of the medicinal product in relation to food and beverage intake, with cross-reference to section 4.5 "Interactions with other products and other forms of interaction", in case of a specific interaction, e.g. with alcohol, grapefruit, milk;
- advice regarding repeat use, with any information on intervals to be observed between courses of treatment, as appropriate,
- interactions requiring specific dose adjustments with cross-reference to other appropriate sections of the SPC (e.g. section 4.4, 4.5, 4.8, 5.1, 5.2 "Pharmacokinetic properties", further mentioned in this Guideline, section 5.2.), and
- The recommendation against the premature stop of the treatment in case of specific non-serious adverse reaction(s) which are frequent/temporary/easy to handle by dose reduction.

Art. 53. - Where relevant to the particular product, an entry such as the following should appear ‘The potency of this medicinal product is expressed in <invented name> units. These units are not interchangeable with the units used to express the potency of other <active substance name> preparations’.

VII.2.2. Additional information on special populations

Art. 54. – Where deemed necessary, dose adjustments or other dose-related information and information related to the relevant route of administration for specific groups of patients shall be mentioned, under specific points, ordered in accordance with their rank, e.g. concerning:

- elders; it should be clearly understood whether dose adjustment is necessary or not for any subgroups of elder patients, with cross-reference to other sections providing information about the elder population, e.g. section 4.4, 4.5, 4.8 or 5.2.

- renal insufficiency; the dose recommendation should relate as precisely as possible to the cutoff values for biochemical markers of renal impairment clinical studies and to the results of these studies;

- liver disease, specified according to the patients included in studies, for instance ‘alcoholrelated cirrhosis’ and the definitions used in the studies, for instance Child-Pugh score/grade of the patients, and

- patients with a certain genotype, with cross-reference to other relevant section for other details, as required;

- other special patient groups (e.g. patients with other simultaneous diseases or obese patients).

Art. 55. - Where required, relevant recommendations in view of dose adjustment shall be provided, e.g. those issued from the monitorisation of symptoms and clinical signs and/or laboratory investigations, including the medicinal product’s blood concentrations, with cross-reference to other sections.

VII.2.3. Children and adolescents

Art. 56. - When the medicinal product is to be used in children, a specific sub-section ‘paediatric patients’ should be identified and the provided information
should cover all subgroups of children and adolescents, using a combination of potential situations described below, on a case-by-case basis.

Art. 57. – (1) If the medicinal product is indicated for children or adolescents, dose recommendations shall be provided for each relevant subgroup.

(2) The age limits should reflect the assessment of the risk-benefit balance of the available documentation for each subgroup.

Art. 58. - In case children and adolescents are given the same dose, a statement is sufficient; it is not necessary to repeat the given dose.

Art. 59. – (1) Recommendations concerning doses (e.g. mg, mg/kg, mg/m^2) should be specified for each dosing interval required for the subgroups of children and adolescents for which the respective medicinal product is recommended.

(2) Different subgroups may require different dosage information.

(3) If deemed necessary, recommendations should be provided to premature neonates, taking into account the more suitable age, e.g. gestational/premenstrual age.

Art. 60. – Depending on the available subgroups, clinical data and formulations, the dose shall be expressed depending on weight/body surface, e.g. „Children between 2 and 4 years old, 1 mg/kg, 2 times a day".

Art. 61. – Where required, the information on the product's ingestion schedule should take into account the child's daily schedule, e.g. school/sleep schedule.

Art. 62. - In case a medicinal product is indicated to children and no adequate formulation can be developed, detailed instructions concerning the manufacturing process of an extraporaneous preparation should be mentioned in section 6.6, with cross-reference to section 4.2.

Art. 63. – Doses and the route of administration for different subgroups may be exposed in tabulated form.

Art. 64. – In case there is no indication provided in some/all subgroups of children/adolescents concerning the respective medicinal product, no dosing recommendation can be done, but the available information should be summarised by using the following standard statements (a single statement/combination of several statements, as required):

- <Safety> <and> <efficacy> X in children aged between x and y <months, years> <*or any other relevant subgroup, e.g. weight, adolescence, sex*> <have> <not> <been> <yet> established.

  One of the following statements should be added:

  - <No available data>.

  or

  - <Presently available data described in section <4.8> <5.1> <5.2>, but no dose-related recommendation can be provided>

- X is not recommended for use in children aged between x and y <years, months> <*or any other relevant subgroup, e.g. weight, adolescence, sex*>

due to <safety> <efficacy> issues < *which are about to be specified*, with cross-reference to the sections exposing detailed data (e.g. 4.8 or 5.1)>.

- X does not have relevant use in <children and adolescents><children aged between x and y><years, months>><*or any other relevant subgroup, e.g. weight, adolescence, sex*> for the indication(s) < please specify)>.

- X is contraindicated in children aged between x and y <years, months>< *or any other relevant subgroup, e.g. weight, adolescence, sex*><indication …> (cross-reference to section 4.3).

Art. 65. – In case of certain strength(s) and/or more adequate pharmaceutical forms in view of administration to some or all subgroups of children and adolescents (e.g. oral solution for toddlers), these may be specified in section 4.2 in the SPCs of those less adequate, *e.g. Other pharmaceutical forms/strengths may be more proper for the administration to this group of patients.*

VII.2.4. Route of administration

Art. 66. – In this section, with a specific subtitle, any special safety measure related to the handling/administration of the medicinal product shall be mentioned (e.g. cytotoxics) by healthcare professionals (including pregnant medical staff), patients/caretakers (<*Cautions to be taken prior to the handling or administration of the medicinal product*>), with cross-reference to point 6.6 (or 12 „Instructions on the preparation of radiopharmaceuticals" (further mentioned in this Guideline, section 12)).

Art. 67. – (1) The route of administration shall also hereby be mentioned and relevant instructions shall be briefly formulated in view of proper use and administration.

(2) Information on the manufacturing/reconstitution should be introduced in section 6.6 (or in section 12, if applicable), with cross-reference to this section.

Art. 68. – When support data is available, clear information concerning any alternative manner(s) of the facilitation of the administration/acceptability of the medicinal product should be provided (e.g. the possibility of fragmentation/division of a tablet/transdermal patch, tablet spraying, capsule opening, mixing with food, dissolution into liquid food – while mentioning whether a part of the respective dose may be administered), especially in case of the administration via tubes.

Art. 69. – Any specific recommendation concerning use related to the pharmaceutical form, e.g.:

- „The hard candy should not be chewed, due to its <unpleasant taste>,
- „The gastroresistant film-coated tablet should not be fragmented should not be fragmented because the film stops the <pH-sensitive degradation> <irritant effects> in the intestine",

- „The hard candy should not be broken, because the covering layer is meant to ensure a prolonged release (see section 5.2)".

Art. 70. – For parenteral formulations, information on the rate/speed of the injection/infusion process should be provided.

Art. 71. – For parenteral formulations – in children, especially neonates, in which liquids should be quite frequently restricted – information on the maximum strength which could be administered under safety conditions would be useful (e.g. „no more than X mg of Y ml solution").

VII.3. Contraindications

Art. 72. – (1) Situations where the medicinal product must not be given for safety reasons, i.e. contraindications, are the subject of this section. Such circumstances could include particular clinical diagnosis, concomitant diseases, demographic factors (e.g. gender, age) or predispositions (e.g. metabolic or immunological factors, prior adverse reactions to the medicine or class of medicines).

(2) Such situations must be unambiguously, comprehensively and clearly outlined.

Art. 73. - Other medicinal products or classes of medicinal products, which must not be used concomitantly or consecutively should be stated, either based on data or strong theoretical reasons; if applicable, a cross-reference to section 4.5 should be given.

Art. 74. – (1) In general, patient populations not studied in the clinical trial programme should be mentioned in section 4.4 and not in this section unless a safety issue can be predicted (e.g. use of renally cleared substances with narrow therapeutic margin in renal failure patients).

(2) If, however, patients have been excluded from studies as being contraindicated on serious grounds of safety, they should be mentioned in this section; if applicable, a cross-reference to section 4.4 should be given.

Art. 75. – (1) Only if pregnancy is strictly contraindicated, should it be mentioned here.

(2) In section 4.6 "Pregnancy and lactation" (further mentioned in this Guideline, section 4.6), a crossreference should be given and further information about the background be provided.

Art. 76. - Hypersensitivity to any of the excipients or residues from the manufacturing process should be included, as well as any contraindication arising from the presence of certain excipients (see SCD No. 29/14.07.2006 on the *Guideline on excipients in the label and package leaflet of medicinal products for Human Use* based on the European Commission Guideline).

Art. 77. - For herbal medicinal products, hypersensitivity extended to other plants of the same family or to other parts of the same plant should be labelled as a contraindication, where applicable.

Art. 78. – (1) A simple lack of data should not lead to contraindications.

(2) Where due to safety reasons, the medicinal product is contraindicated in a certain group of patients, e.g. children and adolescents, or in a subgroup of children and adolescents, this fact should also be mentioned in this section, with cross-reference at the section containing detailed information about the safety concern.

(3) Contraindications in children and teenagers shall be stated without a separate subtitle.

VII.4. Special warnings and cautions for use

Art. 79. - Generally, the order of warnings and cautions should be established depending on the importance of the safety information provided.

Art. 80. – The exact content of this section will be different for each product and the therapeutic conditions it is intended to treat. It is however suggested that the following items should be included where relevant to the specific product.

Art. 81. – (1) Information on a potential risk shall not be exposed in section 4.4, unless the specific risk determines a measure of caution in its use or the healthcare professionals should be informed about that risk.

(2) Patient groups in which the use of the respective medicinal product is contraindicated should only be mentioned in section 4.3 and shall not be repeated here.

Art. 82. - The below mentioned particulars should be described:

- The conditions under which use of the medicinal product could be acceptable, provided that special conditions for use are fulfilled; in this section, risk management plan in view of ensuring the use under efficacy and safety conditions (e.g. “Hepathic function should be assessed prior to the initiation of the treatment and on a monthly basis, afterwards”, “Patients are recommended to immediately report any symptoms e.g. depression and/or suicidality”, “Childbearing women should use contraceptive methods”, …)
- Special patient groups, such as elderly and children, that are likely to experience product or class related adverse reactions (ADRs) to the respective medicinal product/class of medicinal products occurring under normal conditions of use e.g. specified age groups, patients with renal/hepatic impairment (including the degree of impairment, such as mild, moderate or severe) patients who have been administered an anesthetic or patients with cardiac failure (including the NYHA classification); cross-reference is made in section 4.8. concerning the differentiated effects of the frequency and seriousness of the respective adverse reaction.

- Serious adverse reactions to which the healthcare professionals need to be alert, the situations in which these may occur and the action that may be required, e.g. emergency resuscitation.

- If there are particular risks associated with starting the medicinal product (e.g. first dose effects) or stopping it (e.g. rebound, withdrawal effects), these should be mentioned in this section, together with the action required for prevention.

- Any measures which can be taken to identify patients at risk and prevent the occurrence, or detect early the onset or worsening of noxious conditions. If there is a need for awareness of symptoms or signs representing early warning of a serious ADR, a statement should be included.

- Any need for specific clinical or laboratory monitoring should be stated; if dose reduction is recommended in such circumstances or conditions, this should be included in section 4.2 and cross-referenced here.

- Any warnings necessary for excipients or residues from the manufacturing process.

- For herbal medicinal products containing alcohol, information on the ethanol content should be provided, in accordance with SCD No. 29/14.07.2006.

- Any needed warnings concerning the transmissive agents [e.g. Summary of Product Characteristics (SPCs) and Package leaflets for Plasma-Derived Medicinal Products (CPMP/BPWG/BWP/561/03)] shall be provided.

- It is possible that subjects/patients with a specific genotype/phenotype do not respond to treatment or present a pronounced pharmacodynamic risk/occurrence of adverse reactions, which may show up due to the failure of enzyme alleles, alternative metabolic pathways, (regulated by specific alleles), or transportation deficiency; such situations should be clearly stated, if known.

- Any specific risk associated with a wrong route of administration shall be presented (e.g. risk of necrosis characterised by extravasation of the intravenous formulation or development of neurological consequences in case of intravenous administration instead of intramuscular administration), accompanied by recommendations concerning the therapeutic approach of such situations, if possible.

Art. 83. - In exceptional cases, especially important safety information may be included in bold type within a box.

Art. 84. – All adverse reactions mentioned in this section or known to result from the affections stated in this section should also be presented in section 4.8.

Art. 85. - Specific interaction with biological test should be mentioned when appropriate, e.g. Coombs test and Beta-lactams; these should be clearly stated under a subtitle, e.g. "*Interference with serological tests*".

Art. 86. – (1) În general, warnings and precautions regarding pregnancy and lactation, ability to drive and use machines, as well as other aspects of interactions
should be dealt with in sections 4.6, 4.7 „Effects on the ability to drive and use machines" (further mentioned in this Guideline, section 4.7) and 4.5, respectively.

(2) However, in cases of major clinical importance, a presentation in this section may be more adequate, namely of specific warnings, e.g. contraceptive measures or reference to the situations in which the simultaneous use of another medicinal product is not recommended, with cross-reference to sections 4.5, 4.6 or 4.7.

VII.4.1. Paediatric population

Art. 87. – (1) In case the medicinal product is indicated one or several children/teenager subgroups and if there are special warnings and precautions for use, which specifically refer to children and teenagers or any such subgroup, it should be stated under this subtitle.

(2) Any needed warning or precaution concerning the long term safety (e.g. related to growth, neurobehavioral development or sexual maturation) or specific monitorisation (e.g. growth) of children and teenagers.

Art. 88. – If long-term (not yet available) safety data is needed, it should be stated in this section.

Art. 89. – In case of a potentially significant impact/ long-term impact concerning children's day-by-day activities, such as the learning ability or physical abilities, or in case of an impact on the appetite or type of sleep, warnings should be included.

Art. 90. – In case specific measures are needed for children and teenagers for whom the respective product is indicated (e.g. within a risk management plan), the respective measures should be mentioned in this section.

VII.5 Interactions with other products and other types of interactions

Art. 91. – (1) This point should provide information concerning the possibility of clinically relevant interaction, based on pharmacodynamic properties and *in vivo* pharmacokynetic studies on the respective product, with special emphasis on interactions and which determine the need for recommendations concerning the intake of the respective medicinal product.

(2) This point includes the results of important *in vivo* interactions in view of the extrapolation of a certain effect on a marker („sample") to other medicinal products having the same pharmacokinetic property as the marker.

Art. 92. – The interactions affecting the use of the respective medicinal product shall be firstly mentioned; reference should be made afterwards to

those interactions which determine clinically relevant modifications for the use of others.

Art. 93. - The interactions referred to in other sections of the SPC should be described in this section, which should provide cross-reference to this section.

Art. 94. – The presentation order should include contraindicated associations, those which do not recommend a simultaneous use, and others.

Art. 95. – The following information shall be provided for each clinically relevant interaction:

a) Recommendations: these may be

- contraindications for simultaneous use (with cross-reference to point 4.3),
- simultaneous use is not recommended (with cross-reference to section 4.4), and
- safety measures, dose adjustment included (with cross-reference to section 4.2 or 4.4, as required), while stating the specific situations in which other type of measures may be necessary.

b) Any type of manifestations or clinical effects on plasma concentrations and AUC of parent compounds or active metabolites and/or on laboratory parameters.

c) Mechanism, if known. E.g. the interaction determined by the inhibition/induction of P450 cytochrome as such is stated in this section, with cross-reference to section 5.2 which includes the summary of the *in vitro* results on the inhibition/induction potential.

Art. 96. – In case the *in vivo* unstudied interactions (however anticipated from the *in vitro* studies or issuing from other situations/studies) may determine a change in the use of the medicinal product, these should be described, with cross-reference to section 4.2 or 4.4.

Art. 97. – (1) This section should include the durata de interacţiune in case of discontinuation of the use of a medicinal having a clinically significant interaction (e.g. inhibitor/enzyme inductor).

(2) Consequently, dose adjustment might be required.

(3) Moreover, what requires the need for an elimination period in case of simultaneous use of medicinal products should be equally stated.

Art. 98. – (1) Similarly, this section should provide information concerning other relevant interactions, such as interactions with herbal medicinal products, food, alcohol, smoking or pharmacologically active substances used for purposes other than medical.

(2) Where there is a possibility of a clinically relevant potencies or the occurrence of an additional noxious effect, such pharmacodynamic effects should be stated.

Art. 99. - *In vivo* results assessing a lack of interaction shall not be stated unless they are considered to have a major importance for the prescribing physician (e.g. within a therapeutic field where potentially problematic interactions have been identified, as is the case for antiretrovirals).

Art. 100. – If there are no interaction studies, it should be clearly stated.

VII.5.1. Additional information about special patient groups

Art. 101. – This subsection includes information on patient subgroups; interactions upon these subgroups is more severe or requires a large-scale

interaction, e.g. patients with renal failure (in case renal excretion represents the parallel path), children and teenagers, elders etc.

Art. 102. – If the interactions with other medicinal products depend on the metabolizing enzymes or on certain genotypes, it should be stated in this subsection.

VII.5.2. Paediatric population

Art. 103. – In case there is an indication for a certain paediatric subgroup, information specific to a special age group should be given here.

Art. 104. – The resulted exposure and clinical consequences of a pharmacokinetic interaction may differ from adults to children, or from older to younger children. Therefore:

- Any identified treatment recommendation referring to the simultaneous use in the paediatric subgroup(s) (e.g. dose adjustment, additional monitorisation of the clinical/adverse reaction marker, monitorisation of medicinal products).

- Therefore, if the interaction studies have been performed in adults, the statement 'Interaction studies have only been performed in adults'.

- In case of a certain interaction degree known to be similar in a paediatric group and an adult one, this should be stated.

- If no interaction studies have been performed, this should also be clearly stated.

Art. 105. - The same also applies to pharmacodynamic drug interactions.

Art. 106. - In cases where there is an interaction with food leading to a recommendation on co-administration with a meal or specific food, it should, if possible, be noted whether this information is relevant for children and adolescents (especially newborns and infants) whose diet may be totally different (100 % milk in newborns).

Art. 107. – (1) *Generally speaking*, section 4.5 should be exposed in the most simple manner so that it emphasizes the interactions which determine a practical recommendation concerning the use of the medicinal product.

(2) In case of many and various interactions, just like in antiviral drugs, a presentation in tabulated form may be useful.

VII.6. Fertility, pregnancy and lactation

VII.6.1. General recommendation

Art. 108. - Efforts should be made by the Marketing Authorisation Holder to provide the reasons for recommendations for use in pregnant or lactating women, and in women of childbearing potential.

Art. 109. – This information is available for healthcare professionals providing information to the patient.

Art. 110. – Throughout the general assessment, all available knowledge should be taken into account, as well as the data issued solely from clinical trials and from post-authorisation surveillance activity, pharmacological activity, non-clinical trial results and knowledge about the same class compounds.

Art. 111. - Efforts should be made in view of upgrading the recommendations used during pregnancy and lactation, depending on the high experience in humans concerning exposed pregnancies, which shall ultimately prevail over the data obtained from studies conducted on animals.

Art. 112. – In case of contradiction, this should be included in section 4.3.

Art. 113. – The following should be mentioned:

VII.6.2. Women of childbearing potential/Contraception in men and women

Art. 114. – (1) Recommendations on the use of the medicinal product in women of childbearing potential should be given when appropriate including pregnancy test, contraception.

(2) Where an effective contraception is required for patients or partners of patients during treatment and for a defined period after ending treatment, the rationale should be included in this section (see Annex 1).

(3) If contraceptive measures are recommended, a cross-reference should also be made to section 4.5 (and section 4.4), in case of interaction with oral contraceptives.

VII.6.3. Pregnancy

Art. 115. – Generally speaking, clinical and non-clinical should be followed by recommendation.

Art. 116. – With respect to non-clinical data,

- Only the conclusions of nonclinical toxicity studies on the reproductive function shall be mentioned in this section. Further details should be provided in section 5.3.

Art. 117. - With respect to clinical data,

- the section should include comprehensive information on relevant adverse events reported in the embryo, the fetus, neonates and pregnant women, when appropriate; the frequency of such events (for example the frequency of birth defects) may be specified when available.

- the section should specify the extent of the human experience if no adverse events have been reported in pregnancy.

Art. 118. – As far as recommendations are concerned:

a) Recommendations on the use of the medicinal product during the different periods of gestation, stating the reason(s) of these recommendations.

b) Recommendations for the management of exposure during pregnancy when appropriate (including relevant specific monitoring such as fetal ultrasound, specific biological or clinical surveillance of the neonate).

Art. 119. – Cross-references can be included in sections 4.3, 4.4 and 4.8, as appropriate.

Art. 120. - CHMP/SWP Guideline contains annexes on reproduction and breastfeeding; examples of forms are attached in this section.

VII.6.4. Lactation

Art. 121. – (1) If available, clinical data (for neonates) should be mentioned including the conclusions of the studies on the transfer of the active substance and/or its metabolite(s) into human milk (positive/negative excretion, milk/serum ratio).

(2) Information on adverse events in nursing neonates should be included if available.

Art. 122. - Conclusion on clinical studies conducted on animals on the transfer of the active substance and/or its metabolite(s) into milk should be given only if no human data are available.

Art. 123. - Recommendations should be given to stop or continue breast-feeding and/or to stop or continue the treatment in case where treatment or breastfeeding discontinuation is recommended, the reason should be provided.

Art. 124. – Examples of forms for this section are attached to CHMP/SWP on reproduction and breastfeeding.

VII.6.5. Fertility

Art. 125. – The main information on the possible effects of the medicinal product on male and female fertility must be included in section 4.6.

Art. 126. – This section should include:

a) Clinical data if available.

b) Relevant conclusions from nonclinical toxicity studies if available; further details should be included in section 5.3., “Pre-clinical safety data” (further mentioned in this Guideline, section 5.3.)

c) Recommendations for the use of the medicinal product when pregnancy is planned but fertility might be affected by treatment.

Art. 127. - If necessary, cross-references can be included in section 4.3, as appropriate.

Art. 128. – In case there is no data on fertility, this should be clearly stated.

VII.7. Effects on ability to drive and use machines

Art. 129. – (1) On the basis of the pharmacodynamic profile, reported Adverse Reactions and/or specific studies on a relevant target population addressing the performance related to driving or using machines, specify whether the medicinal product has

a) no or negligible influence

b) minor influence

c) moderate or

d) major influence on these abilities.

(2) If any, other important factors influencing the ability of driving and using machines should be taken into account, e.g. the duration of the noxious effect and tolerance/adverse reaction development in case of further use.

Art. 130. - For situations c) and d), special warnings/precautions for use (for situation d)) should also be mentioned in section 4.4.

VII.8. Adverse reactions

Art. 131. – (1) In this context, all adverse reactions occurred during clinical trials, in post-authorisation safety studies and spontaneous reports which, following a thorough assessment, indicate that they are at least possibly causally related, based for example on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual reports.

(2) Adverse events, without at least a suspected causal relationship, should not be listed in the SPC.

Art. 132. – (1) The information of this section should be explained in the overall clinical review from the marketing authorisation application, based on the assessment of all adverse reactions observed and all facts relevant to the assessment of causality, severity and frequency.

(2) This section should be reviewed periodically and, if deemed necessary, updated in view of ensuring accurate information for healthcare professionals concerning the medicinal product’s safety profile.

(3) Moreover, the whole section may be reviewed on the occasion of the marketing authorisation renewal, when it is likely that the safety profile of most

medicinal products is clearly established as well as, subsequently, of each PSUR every three years.

Art. 133. – (1) It is important that the whole section should be worded in concise and specific language and it should not include information such as claims regarding the absence of specific adverse reactions, comparative frequency statements other than as described below, or statements of general good tolerability such as "well tolerated", "generally, adverse reactions are scarce" etc.

(2) Statements on lack of proof of causal association are not helpful and should not be included.

Art. 134. - In order to provide clear and readily accessed information, section 4.8. should be structured according to the following recommendations:

VII.8.1. Summary of the safety profile
VII.8.2. Table of adverse reactions
VII.8.3. Adverse reactions descriptions
VII.8.4. <Paediatric population>
VII.8.5. <Other special patient group(s)

VII.8.1. Summary of safety profile

Art. 135. – The Summary of the safety profile should also include information on the most severe and/or most frequent adverse reactions.

Art. 136. – (1) If known, stating the moment when adverse reactions occur may prove useful.

(2) E.g. in view of preventing the early interruption of a treatment, the information concerning non-serious adverse reactions which are important during the treatment's onset, but which might disappear after its continuation, might prove useful.

(3) Another example would be to provide information concerning adverse reactions associated with prolonged use.

(4) The frequency of mentioned adverse reactions should be stated as accurately as possible.

(5) This summary of the safety profile should be compliant with the identified significant risks stated in the Safety Specifications from the Risk Management Plan as well as in the table of adverse reactions (see section „Table of adverse reactions").

(6) In case this section recommends relevant measures in view of risk reduction, cross-reference should be done in section 4.4.

Art. 137. – A compliant statement is presented below:

„During the treatment's onset, epigastric pains may occurr, as well as nausea, diarrhea, headaches or dizziness; these reactions usually disappear within a few days, even if the treatment is continued. The most frequently

reported adverse reactions during treatment are dizziness and headaches, both being encountered in approximately 6% of patients. In rare cases (less than 1 case in 1000 patients) severe acute hepatic lesions and agranulocytosis may occurr".

VII.8.2. Table of adverse reactions

Art. 138. – (1) All adverse reactions should be stated in a single table (or organised list), while stating the respective frequency category.

(2) In case of frequent/very frequent reactions and when deemed necessary in view of the accuracy of the information, frequency numbers may be included in the table.

Art. 139. – In exceptional cases, when the profile of the adverse reactions are significantly different, depending on the medicinal product's use, separate tables are accepted, e.g. when using in case of using a medicinal product for different indications (e.g. a oncology/non-oncology indication) or with different doses.

Art. 140. – The table should be preceded by a brief paragraph mentioning the safety data source (e.g. clinical trials, post-authorisation safety studies or spontaneous report).

Art. 141. – (1) The table should be presented in accordance with the MedDRA classification system (systems, organs and classes).

(2) The system organ classes (SOCs) should be presented in the order shown in the Annex.

(3) Adverse reactions descriptions should be based on the most suitable representation within the MedDRA terminology; this will usually be at the Preferred Term Level, although there may be instances where the use of Lowest Term Level or exceptionally group terms, such as High Level Terms may be appropriate.

(4) As a general rule, any ADR should be assigned to the most relevant SOC related to the target organ; for example, 'Liver function test abnormal' should be assigned to the SOC 'Hepatobiliary disorders' rather than to the SOC 'Investigations'.

(5) Within each system organ class, the ADRs should be ranked under headings of frequency, most frequent reactions first.

(6) Within each frequency grouping, adverse reactions should be presented in order of decreasing seriousness.

(7) In view of describing each frequency grouping, the Romanian standard terms should be followed, in accordance with the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000).

Art. 142. – (1) If for a specific ADR a frequency cannot be estimated or a frequency category not be chosen an additional category frequency ‘not known’ may be added.

(2) In case of using the syntagm „unknown frequency” with reference to the frequency, the following text, explaining the frequency groupings: „unknown frequency (which cannot be estimated from the available data)”, should be added to the list of terms.

(3) The expressions isolated/single cases/reports should not be used.

Art. 143. - Where additional details about an adverse reaction is exposed in section “Description of selected adverse reactions”, the reaction concerned should be highlighted, for example with an asterisk, and ‘see section “Description of selected adverse reactions” ’ should be included as a footnote.

Art. 144. – At the end of this section, there are recommendations concerning the manner of estimation of an adverse reaction’s frequency.

VII.8.3. Description of selected adverse reactions

Art. 145. – This section should include the information which characterise a certain adverse reaction and which can be useful in view of preventing, assessing or handling the occurrence of an adverse reaction in clinical practice.

Art. 146. – (1) This section should include the information which characterise serious individual/frequent adverse reactions, or those which needed serious reports.

(2) The information should state the frequency; features such as reversibility, onset, gravity, duration, reaction mechanism (if clinically relevant), relation with dose, relation with the duration of exposure or risk factors should be stated.

(3) Measures to be taken in view of avoiding specific adverse reactions or actions performed in case of the occurrence of a specific reaction should be mentioned in section 4.4. and with cross-reference here.

Art. 147. – In this section, the information about the occurrence of withdrawal reactions can be mentioned as well, with cross-reference to section 4.2, in case the gradual reduction of the treatment/recommendations concerning its discontinuation is imposed.

Art. 148. – Any differences between various dosage forms concerning adverse reactions shall be mentioned in this section.

Art. 149. – In case of combinations, this subsection should include information stating which adverse reactions may commonly be linked to a certain active substance of the given combination, if known.

Art. 150. - Any adverse reactions resulting from an interaction shall be mentioned here, with cross-reference to section 4.5.

Art. 151. – (1) This section should also provide information concerning less-frequent adverse reactions or adverse reactions with late-onset symptoms, which might have passed unobserved when in relation with the medicinal product, which are considered to be connected with the same therapeutic/chemical/pharmacological class.

(2) It should also be stated that this is a class feature.

Art. 152. – Any adverse reactions specific to the excipients/wastes resulted from the manufacturing process are included.

VII.8.4. <Paediatric population>

Art. 153. – There should always be a sub-section entitled "paediatric patients" (except when not relevant).

Art. 154. – (1) Size and age characteristics of the safety database in children (e.g. issued from clinical trials or pharmacovigilance data) are presented.

(2) Uncertainties determined by limited experience should be stated.

Art. 155. – In case the safety profile observed is similar in children and adults, this fact may be stated as follows: e.g. "Frequency, type and seriousness of adverse reactions in children <are> <assumed to be> the same as in adults".

Art. 156. - Moreover, it is necessary to mention whether safety profiles of different subgroups of children and teenagers are similar or not.

Art. 157. – (1) Any clinically relevant differences (as regards the nature, frequency, seriousness or reversibility of adverse reactions) between the safety profiles in adults and those in the groups of children and teenagers, or in any other relevant age groups, should be described and presented on relevant age groups.

(2) If specific monitorisation is required, it should be emphasized by cross-reference to section 4.4.

(3) As regards clinically relevant differences, if deemed necessary, a separate table may be added, stating such adverse reactions depending on the frequency, and it should be presented on relevant age groups.

(4) If certain adverse reactions occurring in children and teenagers are considered frequent (≥ 1/100 and <1/10) or very frequent (≥ 1/10), frequencies should be mentioned between brackets.

(5) In case of a major difference from the safety profile in adults, in order to facilitate the exposure of information, a summary of the product characteristics in children may be presented.

(6) The available information, issued from a scientifically valid source, concerning the long-term safety in children (e.g. related to growth, mental development and sexual maturation) should also be briefly described, regardless of its positive/negative character, with cross-reference to section 5.1, if necessary.

(7) Any risk factors such as treatment duration or period of risk should be stated.

Art. 158. – If relevant, a separate paragraph shall list the withdrawal symptoms in newborns, with cross-reference to section 4.6.

VII.8.5. < Additional information on special populations>

Art. 159. – This section may include information concerning clinically relevant differences (in other terms, those concerning the nature, frequency, seriousness or reversibility of adverse reactions or need for monitorisation), particularly encountered in special groups of patients, as well as in elders, patients with renal failure/hepatic impairment/other diseases/specific genotype; cross-reference may be added to other sections, on a case-by-case basis, e.g. sections 4.3, 4.4 or 4.5.

Art. 160. – (1) Adverse reactions may also be connected to the medicinal product's genetically determined metabolization.

(2) Subjects/patients who lack specific enzymes may present a different rate of adverse reactions or other degrees of seriousness.

(3) This fact should be stated and, depending on its relevance, correlated with clinical trial data.

VII.8.6. Other recommendations concerning the estimation of the frequency of adverse reactions

Art. 161. – (1) The estimation of an adverse reaction's frequency depends on the data source (e.g. clinical trial, post-authorisation safety study or spontaneous reports), data gathering quality and causality assessment.

(2) In case the option for the frequency category is based on different sources, the cathegory indicating a higher frequency should be chosen, except for the case in which a higher-specificity method has been enforced, leading to an obviously superior estimation, e.g. a centralised analysis of all corresponding studies.

Art. 162. – Data sources should include a population exosed to the doses and duration of treatment recommended in the SPC.

Art. 163. - Usually, in order to avoid the dilution or dissimulation of the real effect, reactions reported in different terms, but which represent the same phenomenon (e.g. sedation, sleepiness, dizziness), are grouped together as a unique form of adverse reaction. Similarly, reactions presenting a complex syndrome should usually be grouped under an appropriate name in order to avoid the dissimulation of the full range of the respective symptoms.

VII.8.7. Adverse reactions in clinical trials

Art. 164. – Safety data issued from several trials should be pooled in view of a better accuracy of adverse reaction occurrence rates, as required, without generating distortions (e.g. majore differences in population features or product exposure).

Art. 165. – (1) In case the respective data are available and databases are sufficiently developed in order to provide information, the frequency of adverse reactions should be extracted from pooled placebo-controlled studies.

(2) If the respective data are not available or do not provide sufficient information, data from active control studies or databases from single-arm studies or „add-on" studies (added therapy) may be used in view of frequence estimation.

Art. 166. – The frequency should represent the raw incidence rates (not the relative differences/risks calculated from a placebo or other comparators' viewpoint).

Art. 167. – When a frequent/very frequent/serious adverse reaction (e.g. suicide) also occurrs in a placebo group with a significant frequency, both incident rates may be declared in view of providing a balanced perspective upon the risk (e.g. in subsection *Description of selected adverse reactions*).

VII.8.8. Adverse reactions in safety studies

Art. 168. (1) The option for a frequency category attributed to any adverse reaction is based on a punctual estimation of the raw incidence rate obtained from a study conceived so as to allow the tracking of specific adverse events which occurred in patients during an established observation period, as well as a reasonable attribution of these to the given medicinal product.

(2) In this situation, the punctual estimation of the raw incidence rate may be performed by standard statistical methods.

(3) In case the original information is expressed as incidence density (expressed as person-time denominator), an appropriate transformation into an incidence rate should be performed in order to choose a frequency category.

(4) Usually, in view of obtaining a frequency category, incidence rates should be used during the most representative period of exposure (e.g. 1 week, 3 months, 1 year).

(5) However, this fact may prove to be inadequate as the risk rises in time; in such case, section *Description of selected adverse reactions* shall contain an accurate description of the adverse reaction and its frequency pattern, when relevant from the clinical viewpoint.

Art. 169. – (1) The frequency category to be chosen for each adverse reaction should not be based on the differences reported to a comparator.

(2) However, when data are gathered from a study on a non-exposed group and the rate difference attributable to the product is smaller than the initial value or than the contextual incidence rate, and if the adverse reaction is considered important, contextual incidence may be provided (e.g. in subsection *Description of selected adverse reactions*.

VII.8.9. Adverse reactions from spontaneous reports

Art. 170 – (1) The number of spontaneous reports should not be stated since it can be rapidly overcome.

(2) Frequencies depending on the reporting rates within a spontaneous report system should not be used for the attribution of the frequency category.

(3) In case of an unexpected adverse reaction detected in a spontaneous reporting, in view of choosing a frequency category to assess each each properly designed study.

(4) In case the respective adverse reaction has never been discovered in clinical trials, the upper limit of the interval of trust of 95% does not exceed 3/X, where X represents the total sample size resumed in all clinical/other types of studies (e.g. studies having a sufficiently long follow-up in order to be able to track the adverse reaction).

(5) E.g. If a particular adverse reaction has not been observed in 3600 subjects exposed to the medicinal product in the clinical trials and other types of studies, then the upper limit of the interval of trust of 95% for punctual estimation equals 1/1200 or less, and the frequency category should be „rare", in accordance with the lowest value of punctual estimation; justification of the frequency category of the given adverse reaction may be explained in subsection *Description of selected adverse reactions*.

VII.9 Overdose

Art. 171 - Describe acute symptoms and signs and potential sequelae of different dose levels of the medicinal product based on accidental intake, accidental mistakes and suicide attempts by patients.

Art. 172. – (1) Taking into account all relevant evidence, describe management of overdose in man, e.g. in relation to specific agonists/antagonists or methods to increase elimination of the medicinal product e.g. dialysis.

(2) However, no dosage recommendation should be made for other medicinal products (e.g. antidotes), as a conflict may arise between these and the other medicinal products' SPCs.

(3) If needed, countermeasures based on genetic factors are provided.

VII.9.1. Additional information on special populations

Art. 173. - Information specifically observed in other special populations such as elderly patients, patients with renal insufficiency, patients with hepatic insufficiencies, other concomitant diseases etc.

VII.9.2. Paediatric population

Art. 174. - If there are specific paediatric considerations, there should be a sub-section entitled 'paediatric patients'.

Art. 175. - Special mentioning shall be done for those medicinal products/strengths which can cause a fatal poisoning in the special risk group of young children if just a single tablet is ingested.

CHAPTER VIII
Pharmacological properties

Art. 176. – (1) Sections 5.1 – 5.3 should normally mention information, which is relevant to the prescriber *and* to other health-care professionals, taking into account the approved therapeutic indication(s) and the potential adverse drug reactions.

(2) Statements should be brief and precise.

Art. 177. – Points should be regularly updated each time new information shows up, especially concerning the paediatric population.

VIII.1. Pharmacodynamic properties

Art. 178. – Describe:

- Pharmacotherapeutic group and ATC code:

Inclusion of the therapeutic subgroup (level 2 of WHO classification), along with the 3rd (pharmacological subgroup) or 4th (chemical subgroup).

In case an ATC code is not available yet, this should be stated as „ yet unallocated”.

- Mechanism of action (if known)
- Pharmacodynamic effects
- Clinical efficacy and safety

Art. 179. – (1) It may be appropriate to provide limited information, relevant to the prescriber, such as the main results (statistically compelling and clinically relevant) regarding pre-specified end points or clinical outcomes in the major trials, also giving the main characteristics of the patient population.

(2) Such information on clinical trials should be concise, clear, relevant and balanced and summarise evidence from relevant studies supporting the indication.

(3) The magnitude of the effects shall be described with full numbers. (Relative risks or risk balance should nopt be stated otherwise than in full numbers).

Art. 180. – If, in exceptional situations, clinically relevant issued from a subgroup or post-hoc analysis are provided, this fact should be identified as such, in a balanced manner, reflecting the limited strength of secondary observations, both positive and negative.

Art. 181. – (1) Any relevant pharmacogenetic information issued from clinical trials may be mentioned here.

(2) This fact should include any type of data indicating a risk/benefit difference, depending on a particular genotype/phenotype.

VIII.1.1. Paediatric population

Art. 182. – The results of all (clinically relevant) pharmacodynamic studies or efficacy studies in children should be presented in this section.

Art. 183. - Information should be updated at every occurrence of new relevant information.

Art. 184. – Results should be exposed grouped on ages/relevant subgroups.

Art. 185. – When there is available data but no authorised indication for the paediatric population, data should be presented, always with cross-reference to section 4.2, respectively 4.3.

Art. 186. – When presenting the study results, special attention should be given to the inclusion of relevant safety data.

Art. 187. – As regards exploratory studies, results of the main final criteria are provided, along with the main features of of the respective population and used doses.

Art. 188. – (1) If available, data and results issued from confirmation studies have priority, replacing the results of exploratory studies.

(2) As regards confirmation studies, study objectives are provided, duration, doses employed (and formulation, if different from the one available on the market), main features of the population undergoing clinical trials (age and number of patients included), as well as the main results concerning pre-specified final criteria, regardless of whether they are positive/negative.

(3) If data is considered inconclusive, this should be stated.

Art. 189. – The objective, main results or conclusion of each specific safety clinical trial shall be mentioned.

VIII.2. Pharmacokinetic properties

Art. 190. – (1) Pharmacokinetic properties of the active substance(s) relevant for the advised dose, strength and the pharmaceutical formulation marketed should be given in this section.

(2) If these are not available, results obtained with other administration routes, other pharmaceutical forms or doses can be given as alternative.

Art. 191. – Basic primary pharmacokinetic parameters, for instance bioavailability, clearance and half-life, should be given as mean values with a measure of variability.

Art. 192. - Pharmacokinetics items, which could be included in this section when relevant, are given below.

a) General introduction, information about whether the medicinal product is a pro-drug or whether there are active metabolites, chirality, solubility, information on the population which has provided pharmacokinetic data etc.

b) General characteristics of the active substance(s) after administration of the medicinal product formulation to be marketed.

- **Absorption:** complete or incomplete absorption; absolute and/or relative bioavailability; first pass effect; Tmax; the influence of food; in case of locally applied medicinal product the systemic bioavailability; involvement of transport proteins; if any, information on the absorption at the absorption site in the gastrointestinal tract shall be provided (this information might be important in view of the administration via the gastrointestinal tract).

- **Distribution:** plasma protein binding; apparent volume of distribution per kg/bodyweight (1/kg); tissue and/or plasma concentrations; pronounced multi-compartment behaviour; involvement of transport proteins.

- **Biotransformation:** degree of metabolism; which metabolites; activity of metabolites; enzymes involved in metabolism; site of metabolism; results from in vitro interaction studies that indicate whether the new compound can induce/inhibit metabolic enzymes.

- **Elimination:** elimination half-lives, the total clearance; inter and/or intra-subject variability in total clearance; excretion routes of the unchanged substance and the metabolites, including the relative portion of hepatic and renal elimination and the involvement of transport proteins.

- **Linearity/non-linearity:** linearity/non-linearity of the pharmacokinetics of the new compound with respect to dose and/or time; if the pharmacokinetics are nonlinear with respect to dose and/or time, the underlying reason for the non-linearity should be presented.

Additional relevant information should be included here.

c) Characteristics in patients

- Variations with respect to factors such as age, gender, smoking status, polymorphic metabolism and concomitant pathological situations such as renal failure, hepatic insufficiency, including degree of impairment; f this influence on the pharmacokinetics is considered to be clinically relevant, it should be described here in quantitative terms (cross-referral to 4.2 when applicable).

d) Pharmacokinetic/pharmacodynamic relationship(s)

- Relationship between dose/concentration/pharmacokinetic parameter and effect (either true endpoint, validated surrogate endpoint or a side effect).

- The established population should be described.

VII.2.1. Paediatric population

Art. 193. – (1) The results of pharmacokinetic studies in different groups of children and teenagers should be briefly described, along with a comparison with the adults group, if any.

(2) If required, the dose creating exposure to the medicinal product (similar to the one recommended for adults) may be stated.

(3) The pharmaceutical form(s) used should be stated for pharmacokinetic studies in children.

(4) Uncertainties determined by limited experience should be stated.

VIII.3. Preclinical safety data

Art. 194. - Information should be given on any findings in the preclinical testing which could be of relevance for the prescriber, in recognising the safety profile of the medicinal product used for the authorised indication(s), and which is not already included in other relevant sections of the SPC.

Art. 195. - If the results of the non-clinical studies do not add to the information needed by the prescriber, then the results (either positive or negative) need not be repeated in the SPC.

Art. 196. - The findings of the non-clinical testing should be described in brief and qualitative statements as outlined in the following example statements:

- Non-clinical data reveal no special hazard for humans based on conventional studies of safety
pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

- Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

- Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows.

Art. 197. – Results from non-clinical trials, appropriate for use in children and teenagers, including those carried out on young animals and perinatal/postnatal studies should be exposed along with a comment on their clinical relevance, in a separate subtitle, if deemed necessary.

VIII.3.1. <Environmental Risk Assessment (ERA)>

Art. 198. - Conclusions on the environmental risk assessment on the product should be included where relevant, with reference to section 6.6.

CHAPTER IX
Pharmacokinetic properties

IX.1. List of excipients

Art. 199. – (1) A list should be given of the excipients, expressed qualitatively only.

(2) All excipients, which are present in the product, should be included, even those present in small amounts, such as printing inks.

(3) Further details on the excipients to be declared may be found in the section on definitions and examples in the Scientific Council Decision No. 29/14.07.2006.

(4) For transdermal patches, all ingredients of the patch (including the adhesive, release liner and backing film) should be mentioned.

Art. 200. - The active substance itself, residues of substances used during manufacture of the finished product (for example, solvents, head-space gases or antibiotics in vaccine manufacture), lubricants for prefilled syringes and constituents of capsule shells for inhalation powders not intended to be taken should not be included.

Art. 201. - However, certain residues such as residues of antibiotic or other antimicrobial agents used in production that are known allergens with a potential for inducing undesirable effects should be mentioned in section 4.3 or 4.4, as required.

Art. 202. – (1) Excipients should be referred to by their recommended INN if existing, accompanied by the salt or hydrate form if relevant or by their European Pharmacopoeia name.

(2) If an excipient has neither an INN nor European Pharmacopoeia name, it should be described by its usual common name.

(3) References to the pharmacopoeial quality should not be included.

(4) E numbers should be given where they exist for correct use, along with the common name of the excipient, e.g. in case the excipient is mentioned in SCD No. 29/14.07.2006 (as having a known action/effect).

Art. 203. – (1) The ingredients in excipient mixtures should be listed individually.

(2) In cases where the full composition of a flavour or fragrance is not known to the applicant, they may be declared in general terms (e.g. ‘orange flavour’, ‘citrus perfume’). However, any of the components, which are known, or which have a recognised action or effect must be included.

Art. 204. - Ingredients that may or may not be added for the pH adjustment should be followed by the parenthesis ‘(for pH-adjustment)’.

Art. 205. - Invented names or general descriptive names such as ‘printing ink’ should not be used in place of the common name of an ingredient or of a mixture of ingredients but may be used in conjunction with the name(s) of the ingredient(s), so long as it is clear which ingredients are described by the name.

Art. 206. - Chemically modified excipients should be declared in such a way as to avoid confusion with the unmodified excipients, e.g. ‘pregelatinised starch’.

Art. 207. – In case of a medicinal product containing a hidden marker in view of tracking, follow up and authentification, on the list of ecipients, a general term should be included in the excipient’s place, such as „authentification factor”; exception: in case the excipient has a known action or effect.

Art. 208. – (1) For clarity, it is recommended that each excipient be listed on a separate line.

(2) It can be useful to list excipients according to the different parts of the product, e.g. tablet core/coat, capsule contents/shells, etc.

(3) For medicinal products that are presented in more than one container or in dual-chamber containers, the excipients should be listed per container or per chamber.

Art. 209. – (1) Abbreviations for excipients should not be used.

(2) However, where justified for space considerations, abbreviations for excipient names may appear on the labelling, on condition that these abbreviations are designated in section 6.1.

IX.2. Incompatibilities

Art. 210. – (1) Information on physical and chemical incompatibilities of the medicinal product with other products with which it is likely to be mixed or co-administered should be stated.

(2) This is particularly important for medicinal products to be reconstituted and/or diluted before parenteral administration.

(3) Significant interaction problems, e.g. sorption of products or product components to syringes, large volume parenteral containers, tubing, administration sets, etc. should be stated.

Art. 211. – (1) Statements concerning compatibility of the product with other medicinal products or devices should not be included in this section but in section 6.6.

(2) Statements concerning pharmacological incompatibilities with food should be included in section 4.5.

(3) If appropriate, the standard statement, 'Not applicable', should be included.

Art. 212. - For certain pharmaceutical forms, e.g. parenterals, either of the following standard statements should be included as appropriate:

- *'In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.'*
- *'This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.'*

IX.3. Shelf life

Art. 213. - The shelf life should be given for the medicinal product as packaged for sale and after dilution or reconstitution or after first opening if appropriate.

Art. 214. - A clear statement of the shelf life should be given, in an appropriate unit of time.

Art. 215. – (1) For statements to be included regarding in-use shelf lives of sterile products, consult the *Note for Guidance on maximum shelf life for sterile products for human use after first opening or following reconstitution*

approved by CPMP (Committee for Proprietary Medicinal Products, precursor of CHMP).

(2) An in-use shelf life may need to be stated for other medicinal products if development studies have found it to be necessary.

Art. 216. - Moreover, if different strengths should be manufactured, e.g. for use in children, the physicochemical stability should be mentioned throughout the entire strength interval, e.g. „*Stability has been assessed between x mg/ml and y mg/ml for t hours/days at 25° C and between 2-8° C* ".

Art. 217. – In case of poisoning in the paediatric population, in case there is no adequate formulation for use in children, and in case an extraporaneous formulation may be derived from an existing formulation, relevant physicochemical data on storage and stability shall be hereby included, with cross-reference to section 6.4 „Special cautions for storage" (further mentioned in this Guideline, section 6.4) and 6.6.

Art. 218. – (1) In case it is mandatory that healthcare professionals or patients are required specific temporary conditions for storage, e.g. for ambulatory use (e.g. an availability period of 24 months at temperatures of 2-8°C, of which 3 months below 25°C), additional specific recommendations should be provided, as required.

(2) Such information should be based upon stability data.

(3) Particularly, the recommended temperature interval and maximum duration of temporary storage should be stated.

(4) These recommendations may also refer to the measures imposed after the storage of the medicinal product under temporary conditions (e.g. „throw away immediately").

Art. 219. – Statements such as „This information does not represent storage recommendations" shall not be used.

Art. 220. – (1) No reference should be made to the container unless there are different shelf lives for different containers.

(2) Storage conditions should not be included, except for the storage conditions after opening (see the corresponding guideline).

(3) Statements such as 'Do not use after the expiry date' should not be included.

Art. 221. - In case a device is provided with the medicinal product, the in-use shelf life is to be stated, if required.

IX.4. Special precautions for storage

Art. 222. – (1) Storage warnings should use one or more of the standard statements from the *Note for Guidance on declaration of storage conditions in the product information of medicinal products approved by the CHMP*.

(2) When such a standard statement is used, an explanation should be added, mentioning whether the medicinal product is sensitive to light and/or moisture.

Art. 223. - As regards the storage of sterile products which have been opened, diluted or reconstituted, a cross-reference shall be made to section 6.3 "Shelf life" (further mentioned in this Guideline, section 6.3).

Art. 224. - It should be observed that, in case there is a need for a specific warning concerning the storage, it should be done in accordance with the SPC, labelling and leaflet.

Art. 225. – The SPC does not provide a warning stating that the medicinal product should be kept away from children.

IX.5. Nature and contents of container

Art. 226. – (1) Reference should be made to the immediate container using the European Pharmacopoeia standard term; the material of construction of the immediate container should be stated ('Type I glass vials', 'PVC/Aluminium blisters', 'HDPE bottles'); likewise, and any other component of the product should be listed, e.g. needles, swabs, measuring spoons, inhaler devices, desiccant.

(2) Dosing device gradations should be specified.

(3) The container of any solvent provided with the medicinal product should also be described.

(4) Excessive detail, e.g., concerning the colour of the stopper, the nature of the heat-seal lacquer, should usually not be included.

(5) In parenteral preparations, in case the colour of the primary packaging closure system is used in order to make the difference between the formulations of a medicinal product, this fact should be hereby stated.

Art. 227. – If needed, it should be indicated whether the primary packaging closure system is secured for children.

Art. 228. - Examples on the text in this section:

'<Volume> ml suspension in a pre-filled syringe (type I glass) with plunger stopper (chlorobutyl rubber) with or without needle in pack sizes of 5 or 10.'

'HDPE bottle with a child-resistant closure and a silica gel desiccant. Pack-sizes of 30, 60 or 90 film-coated tablets .'

Art. 229. – (1) All pack sizes should be listed.

(2) Pack sizes mentioned should include the number of units, number of doses (for e.g. multi-dose vaccines, inhalers, etc.), total weight or volume of the immediate container, as appropriate, and the number of containers present in any outer carton.

(3) If appropriate, a standard statement, ‘Not all pack sizes may be marketed’, should be included, in order to alert health professionals to the fact that not all listed pack sizes may be available for prescribing or dispensing.

Art. 230. - Multiple unit packs for distribution purposes only do not constitute new pack sizes for marketing of the medicinal product and should therefore not be included in this section.

IX.6. Special precautions for disposal of used medicinal products or waste materials derived from such medicinal products and other handling of the products[2]

Art. 231. - Instructions for disposal should be included here, if appropriate for the respective product.

Art. 232. – (1) Where special precautions for the disposal of certain medicinal products such as cytotoxics and some biological products or waste material derived from it are advised, e.g. in the case of products containing live organisms, these should be stated in this section, as should, where relevant, the disposal of items which come into contact with the product, such as spoons used to administer oral vaccines.

(2) If applicable, a cross-reference may be included to the conclusions of the assessment concerning the risk on the medicinal product described in section 5.3.

Art. 233. - If applicable, e.g. for cytotoxics, the following standard statement should be included, ‘Any unused product or waste material should be disposed of in accordance with local requirements.’

Art. 234. - If there are no special use or handling instructions for the pharmacist or other healthcare professionals, the standard statement, ‘No special requirements.’ should be included.

Art. 235. - Any directions necessary for the accurate preparation of certain products such as cytotoxics and some biological products and/or necessary for the protection of persons preparing or handling the product should be stated.

Art. 236. – (1) In section 4.2, instructions on handling of the product by the doctor, other health personnel or patient should be included, as well as general information concerning the administration of the medicinal product (whether administered by the patient or the health personnel).

(2) If instructions for use/handling are needed where the medicinal product has to be prepared before use, e.g. where it must be suspended or diluted, this information has to be given here.

Art. 237. - For clarity, a cross-reference in section 4.2 to the relevant information in section 6.6 could be included, e.g. ‘For instructions on dilution of the product before administration, see section 6.6.’

Art. 238. - It is recommended that only information necessary for the pharmacist or other health personnel to prepare the medicinal product for administration to the patient should be included here.

Art. 239. – (1) Information on the preparation (e.g. the suspension of a powder for injection, or preparing a dilution) of medicinal products should be included in section 6.6, regardless of who prepares the product (e.g. pharmacist, doctor, other healthcare personnel, patient, parents or caregivers).

(2) In the case of products for reconstitution, the appearance of the product after reconstitution should be stated.

Art. 240. - Statements concerning compatibility of the medicinal product with other medicinal products or devices can be given here provided the data have been provided in the dossier.

Art. 241. – (1) In exceptional cases where the medicinal product is indicated in children and adequate paediatric formulations cannot be developed (based on adequately justified scientific considerations), the information on the extemporaneous formulation should appear under the title *„Use in children and adolescents”*, with cross-reference to section 4.2.

(2) Detailed instructions for the preparation and quality control of the extemporaneous formulation from the appropriate “adult” dosage form and additional information on extemporaneous formulations for use in children shall be provided and, where appropriate, the maximum storage time during which such preparation will conform to its specifications.

(3) When deemed necessary, the packaging material and storage conditions are hereby declared.

Art. 242. – Any specific warnings for the handling of the medicinal product should be included in section 4.4.

Art. 243. - Information on the risks caused by occupational exposure are provided in this section, with reference to section 4.4 or 4.8, if the respective sections contain such information.

CHAPTER X

Marketing Authorisation Holder

Art. 244. - Name and permanent address or registered place of business of the Marketing Authorisation Holder.

Art. 245. - Telephone, fax numbers or e-mail addresses may be included (no websites or emails linking to websites).

CHAPTER XI

Marketing Authorisation Number(s)

Art. 246. – (1) Item to be completed by the National Medicines Agency or by the Marketing Authorisation Holder once the Marketing Authorisation has been released/renewed.

(2) For medicinal products authorised through centralised procedure, the number to be included in this section is the number in the Community Register.

CHAPTER XII
Date of first authorisation/renewal of the authorisation

Art. 247. – (1) Item to be completed by the National Medicines Agency or by the Marketing Authorisation Holder once the Marketing Authorisation has been granted or renewed.

(2) Both the date of first authorisation and, if the authorisation has been renewed, the date of the (last) renewal should be stated in the format given in the following example:

Date of first authorisation: 3 April 1985

Date of last renewal: 3 April 2000

CHAPTER XIII
Date of revision of the text

Art. 248. - Leave blank in case of a first Marketing Authorisation.

Art. 249. - For medicinal products authorised through centralised procedure: date of approval of latest variation or transfer, e.g. the latest Commission Decision amending the SPC, implementation date of the Urgent Safety Restriction or date of (EMEA) notification amending the annexes to the Marketing Authorisation.

Art. 250. - For medicinal products for which Member States are the Competent Authorities: date of approval of latest variation or implementation date of the Urgent Safety Restriction resulting in a revision of the SPC.

Art. 251. - Item to be completed by the National Medicines Agency or by the Marketing Authorisation Holder at time of printing the SPC.

CHAPTER XIV
Dosimetry (if applicable)

Art. 252. – Full details of internal radiation dosimetry should be included in this section for radiopharmaceuticals.

Art. 253. - For all other medicinal products, this section should be excluded.

CHAPTER XV
Instriuctions for preparation of pharmaceuticals (if applicable)

Art. 254. - As far as radiopharmaceuticals are concerned, additional detailed instructions for extemporaneous preparation and quality control of such preparation and, where appropriate, maximum storage time during which any intermediate preparation such as an eluate or the ready-to-use medicinal product will conform to its specifications.

Art. 255. - Special instructions relating to the disposal of containers and unused contents should also be included.

ANNEX 1

The medical dictionary for regulatory activities terminology (MedDRA)

All ADRs should be grouped according to the MedDRA system organ classes (SOC). As a general rule, MedDRA terms should be classified according to the most relevant SOC related to the target organ.

A pragmatic approach to the location of terms should be taken in order to make the identification of adverse reactions simpler and clinically appropriate for the reader. For example, it may be helpful on some occasions – solely in the context of the SPC - to use secondary SOC locations of some MedDRA Preferred Terms (PT), or sometimes to use locations that do not strictly accord with the MedDRA architecture. For example, if the terms 'Liver function test abnormal', 'Hepatitis' and 'Hepatic encephalopathy' are to be included in an SPC, it would be acceptable to include them all under the 'Hepato-biliary SOC' instead of distributing the reactions among the 'Hepato-biliary disorders', 'Nervous system disorders' and 'Investigations System Organ Classes' as dictated by their primary location in MedDRA.

SOC List

- Infections and infestations
- Neoplasms benign, malignant and nonspecified (including cysts and polyps)
- Blood and the lymphatic system disorders
- Immune system disorders
- Endocrine disorders
- Metabolism and nutrition disorders
- Psychiatric disorders
- Nervous system disorders

- Eye disorders
- Ear and labyrinth disorders
- Cardiac disorders
- Vascular disorders
- Respiratory, thoracic and mediastinal disorders
- Gastrointestinal disorders
- Hepato-biliary disorders
- Skin and subcutaneous tissue disorders
- Musculoskeletal, connective tissue and bone disorders
- Renal and urinary disorders
- Pregnancy, puerperium and perinatal conditions
- Reproductive system and breast disorders
- Congenital and familial/genetic disorders
- General disorders and administration site conditions
- Investigations
- Injury and poisoning
- Surgical and medical procedures
- Social circumstances

ADR descriptions should be based on the most suitable representation within the MedDRA terminology. This will usually be at the PT level, although there may be instances where the use of Lowest Level Terms (LLT) or group terms, such as high-level terms (HLT) may be appropriate.

It is acceptable to adapt the names of the MedDRA group terms if this makes their meaning more transparent to the reader of the SPC; e.g. the use of the suffixes NEC and NOS are not appropriate for inclusion in the SPC. The adverse reaction term should be expressed in natural word order, e.g. 'Interstitial pneumonia' in preference to 'Pneumonia interstitial'. It may be appropriate to modify MedDRA terms in other ways in the interests of comprehensibility. The most widely recognised term for a particular condition should be used, e.g. the LLT 'Churg Strauss syndrome' might be more appropriate than the PT 'Allergic granulomatous angiitis'.

Within each MedDRA SOC, ADRs should be classified according to their frequency of occurrence. Prior to estimating frequency of occurrence of adverse events from systematic studies (clinical trials or other sources), appropriate levels of the MedDRA hierarchy should be used in order to group together clinically related conditions in a meaningful way. For example, if 'postural dizziness', 'exertional dizziness' and 'unspecified dizziness' were each reported by 2% of patients, this might reasonably be represented in the SPC as 'Dizziness' occurring in 4% of patients (assuming that only one report of dizziness applied to each patient). It may also be appropriate to use *ad hoc* groupings of terms, or to adapt MedDRA group terms if the established

MedDRA group terms are not completely suitable, e.g. reports of adverse reactions represented as the MedDRA PT ‘Diarrhoea’, ‘Diarrhoea aggravated’, ‘Loose stools’, ‘Stools watery’, and ‘Intestinal hypermotility’ are present in MedDRA under 3 separate HLT – ‘Diarrhoea (excl infective)’, ‘Gastrointestinal spastic and hypermotility disorders’ and ‘Faeces abnormal’. These HLTs may not be useful for representing the findings in the SPC. In the interests of making the SPC relevant and comprehensible to clinicians, these might all reasonably be represented as the single term ‘Diarrhoea’. The total number of cases with the respective MedDRA PT counted together should be used in order to estimate frequency of occurrence.