European Medicines Agency
*Inspections*

London, 26 November 2008
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# OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON RADIOPHARMACEUTICALS

Table 1: Organisations that commented on the draft Guideline as released for consultation

| | Name of Organisation or individual | Country |
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| 1 | AIPES (Association of Imaging Producers and Equipment Suppliers) | Belgium |
| 2 | Bayer Schering Pharma AG | Germany |
| 3 | EFPIA (European Federation of Pharmaceutical Industries and Associations) | Belgium |
| 4 | GE Healthcare | United Kingdom |
| 5 | Office of Prescription Medicines, Therapeutic Goods Administration | Australia |

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*Table 2:Discussion of comments*

| **GENERAL COMMENTS - OVERVIEW** | | |
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| The revision of the guideline on radiopharmaceuticals and the inclusion of PET radiopharmaceuticals into this guideline welcomed. | | |
| **SPECIFIC COMMENTS ON TEXT** | | |
| **GUIDELINE SECTION TITLE** | | |
| **Line no.[1] + paragraph no.** | **Comment and Rationale** | **Outcome** |
| Page 3<br>EXECUTIVE SUMMARY,<br>Line 1 | Please replace "additional information" by adjustments to the CMC information:<br>Justification: sometimes information is limited and this should be reflected here. | Not accepted<br>CMC is used in USA but is not used in the EU<br>The word 'specific' was added as a result of this comment to read '… specific additional information…' |
| Page 3<br>1.Introduction, (par. 1)<br>Line 3 | This guideline provides information about the specific requirements for radiopharmaceuticals which have to be provided in the documentation.<br>Justification: This wording reflects better the content of the guideline (see also comment above) | Accepted. |
| Page 3<br>1.Introduction, (par. 2)<br>Line 9 | For clarity, the words 'only once or sometimes on a few occasions' may be replaced by 'infrequently.'<br>Delete '***only once, or sometimes on a few occasions'***<br>Replace with '***They are usually given infrequently…*** | Not accepted.<br>The proposed text would change the meaning of the sentence. |
| Page 3<br>1.Introduction, (par. 2)<br>Line 12 | t should read: "do often not show"<br>Justification: provides more clarity | Accepted. |
| Page 3<br>1.Introduction, (par. 3)<br>Line 19 | This sentence is the first mention of PET radiopharmaceuticals. As the revision of this guideline is specifically intended to include PET radiopharmaceuticals for the first time, it is suggested that this sentence is amended to state that fact. | Not accepted.<br>It is clear in the current text that the scope of the guideline includes PET radiopharmaceuticals. |

[1] Where applicable

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| | Suggested text: ***'This is also the case for positron emitting radiopharmaceuticals for Tomography (PET radiopharmaceuticals), which are included in the scope of this guideline.'*** | |
| Page 3<br>1.Introduction, (par. 3)<br>Line 19 | It should read: this is in particular the case for positron.....<br>Justification: To our understanding PET agents are belonging to radiopharmaceuticals. The original wording could be understood, that they are considered to be separated | Accepted.<br>"Also" is replaced by "in particular" |
| Page 3<br>2. Scope<br>Line 2 | PET radiopharmaceuticals are mentioned in the introduction, it is not necessary to mention PET again here.<br>Delete ' *including certain PET radiopharmaceuticals'* from first bullet point, or delete " certain" : ' *including PET radiopharmaceuticals'*<br>If it is decided to retain the mention of PET radiopharmaceuticals here, then the word ***'certain'*** should be deleted, as this implies that not all PET radiopharmaceuticals are covered by this guideline. This would generate confusion as to whether PET radiopharmaceuticals were included or not.<br>Alternatively, add mention of PET radiopharmaceuticals underneath the bullet points under 'Scope'.<br>***'This guideline includes PET radiopharmaceuticals'*** | Not accepted.<br>It was decided to retain the mention of PET radiopharmaceuticals. It is important that PET radiopharmaceuticals are mentioned under Scope<br>The word 'certain' has been deleted to make clearer that the guideline is applicable to all marketed radiopharmaceuticals. |
| Page 3<br>2. Scope<br>Line 3 | It is suggested that the descriptions of the various types of radiopharmaceuticals listed here are identical to those used in Directive 2001/83/EC (as amended) article 1.6 to 1.9. These articles define the terms radiopharmaceutical, radionuclide generator, kit and radionuclide precursor.<br>Suggested text:<br>***'This guideline covers the following products as defined in Directive 2001/83/EC articles 1.6 to 1.9:***<br>- ***Radiopharmaceuticals***<br>- ***Kits*** | Not accepted.<br>The current text is more descriptive than the proposed one and the guideline does not aim to define terms that are already defined in the legislation. |

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| | - ***Radionuclide generators***<br>***Radionuclide precursors'*** | |
| Page 4<br>4.1 Drug substance (3.2.S)<br>Lines 1 and 4 | Regarding the label: this guideline does not provide any recommendation concerning packaging and labelling (although included in the current guideline).<br>Indications on primary packaging should be appropriate and take specificities of radiopharmaceuticals into consideration (i.e. small size of vials and labels, protection of users' eyes from radiation). | Not accepted.<br>Labelling is outside the scope of this quality guideline. |
| Page 4<br>4.1 Drug substance (3.2.S)<br>Line 3 | It is conventional to use the word 'active substance' rather than 'active ingredient' when referring to pharmaceuticals.<br>See ref in the link below:<br>Compilation of QRD decisions on the use of terms<br>For clarity, we suggest that 'Radiopharmaceutical kit' is expanded as shown.<br>Use the word ***'active substance'*** in place of ***'active ingredient'*** throughout the document.<br>Suggested text:<br>***'For radiopharmaceutical kits for reconstitution, the active substance is considered to be …..'*** | Accepted.<br>The words 'active ingredient' have been replaced with 'active substance' throughout the guideline text. |
| Page 4<br>4.1 Drug substance (3.2.S)<br>Line 6 | It is suggested that this paragraph is clarified to state that data requirements on chemical precursors use in the production of PET radiopharmaceuticals are the same as those expected for the non-labelled active substance of a radiopharmaceutical kit.<br>Suggested text:<br>***'The active substance of a radiopharmaceutical kit should satisfy the Note for Guidance on Summary of Requirements for Active Substances in Part II of the Dossier (CHMP/QWP/297/97 ). Data requirements for chemical precursors used in the production of PET radiopharmaceuticals are the same as those expected for the non-labelled active substance of a radiopharmaceutical kit.'*** | Not accepted.<br>The proposed text would be more than a rewording and would substantially change the meaning of the text, which is considered to be right as it is. |

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| Page 4<br>4.1 Drug substance (3.2.S)<br>Line 9 | As before, page 3, PET radiopharmaceuticals are mentioned in the introduction and there should be no need to specifically mention them here.<br>Delete '***including those for synthesis of PET radiopharmaceuticals***'<br>It is clearer to say 'subsection' rather than 'separate section'<br>Proposed text:<br>*' Information on chemical precursors may be presented in a subsection of 3.2.S.'* | Not accepted.<br>The current text is considered to be clearer than the proposed text.<br>Not accepted.<br>Separate 3.2.S sections are possible and preferable to follow the expected CTD format. |
| Page 4<br>4.1 Drug substance (3.2.S)<br>Line 11 – 16 (par. 4 and 5) | For clarity we would suggest rewording of the text in lines 11 – 16. We believe that the intention here is to state that for some radiopharmaceuticals it is more logical to present data in sections of the CTD format which are not strictly in line with the guidance notes. This is because some active substances are not isolated (ready to use radiopharmaceuticals) and because for kits data should also be presented on the reconstituted solution. The CTD format was not designed with radiopharmaceuticals in mind.<br>Suggested text:<br>***'For ready-to-use radiopharmaceuticals, radioactive drug substances are, as a rule, not isolated; they are usually prepared as solutions in a continuous production process. Radiopharmaceutical kits are reconstituted before use by the end user. Hence for both of these types of products, data may be presented in sections of the CTD format which are not strictly in line with the guidance notes. It should, however, be ensured that all information necessary to evaluate the active substance specification is available.'*** | Not accepted.<br>The current text is considered to be clearer than the proposed text.<br>The CTD format may be used as it is and where necessary a reference is given to the 3.2.P section. |
| Page 4<br>4.1 Drug substance (3.2.S)<br>Line 15 (par. 5) | Please comment, whether this has to be justified in the overview summary. | This guideline will not describe the content of the overview summary. |
| Page 4<br>4.1 Drug substance (3.2.S) | It is not practical to express the amount of radioactivity in product labelling only in terms of Becquerels. Because of the small market size for Radiopharmaceuticals, products are often marketed in packaging which is common to many markets, including countries outside the European Union. | Not accepted.<br>Curies should not be used any more. Becquerels are the International Units and should be the only units used to express |

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| Line 18 (par. 6) | Hence, radioactivity expressed in Becquerels (followed by Curies in brackets) in product labelling is the commonly accepted format across many countries. It would not be cost effective to require labelling for radioactivity only in Becquerels.<br>Suggest delete the word 'only' and insert additional text as follows:<br>***'Radioactivity should be expressed in Becquerels at a given date, and time if appropriate. Curies may be added as a secondary unit if desired. If a calibration time ……'*** | radioactivity. The use of curie is considered confusing. |
| Page 4 Structure (3.2.S.1.2) Line 1 | In cases, where this is not possible, this might be a major hurdle. On the other hand, it might always be good to know, where the drug substance is labelled and therefore, we propose to indicate the position of the label in any case where this is possible. | Accepted. |
| Page 4 Structure (3.2.S.1.2) Line 1 | Replace 'relevant' with 'possible' | Accepted. |
| Page 5 Manufacturer(s) (3.2.S.2.1) Line 1 | The source of target material is commercial information and should not be relevant, as the target material will be controlled as specified in the MA application<br>Suggest delete the words '***source of any irradiation target materials and'***<br>Suggested text to read:<br>***'For radionuclides this should include the site(s) at which irradiation occurs.'*** | Not accepted.<br>It is expected that the source material is described in the dossier, as this information is essential for assessment. |
| Page 5 Description of manufacturing process and process controls (3.2.S.2.2) Line 1 | This sentence is unclear because of the double negative 'Except for non radioactive….'.<br>Suggest rephrase as follows:<br>***'For radioactive components*** *a full description of the production process to produce the radionuclide (including isolation or manufacture) is required.'* | Accepted. |

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| Page 5<br>Control of material (3.2.S.2.3)<br>Line 1 | There is no need to use the word 'methods' here. Also the words 'when applicable' should be removed, they are superfluous.<br>Suggest replace the word ***'methods'*** with ***'controls'***. Delete the words '***when applicable'*** as follows:<br>***' Requirements for the target material (specifications and controls) should be described here.'*** | Accepted to delete the words 'when applicable'.<br>Not accepted to replace the word 'methods' with 'controls'. The use of 'control methods', as in the current text is considered appropriate. |
| Page 5<br>Manufacturing process development (3.2.S.2.6)<br>Line 3-4 | It should not be necessary to include data on effect of variations on nuclear reactions in the dossier as the specifications of the materials produced after the irradiation process has been completed will be sufficient to control the material produced as an outcome of the reaction. In addition, the material of the target chamber (last word of this section) is unnecessary detail for a dossier.<br>Delete '*including effect of variations on nuclear reactions'* and '*and its material*'.<br>Suggested text:<br>***'For radionuclides this should include nuclear transformation, including unwanted transformations that may occur under the irradiation conditions used due to isotopic impurities present in the target material; irradiation conditions; description and validation of separation processes; influence of geometry of the target chamber.'*** | Not accepted.<br>The requested information may be essential for the evaluation of the quality and is a parallel to requirements for chemical drug substances.. |
| Page 5<br>Elucidation of Structure and other characteristics (3.2.S.3.1) | Since the structure of radiolabelled kits often follows known complex chemistry, we would suggest replacing 'elucidated' by 'described'. Otherwise, a full structural elucidation of the radiolabelled molecule can be very cost intensive and time consuming.<br>Suggested text:<br>'***For radiopharmaceutical kits the structure of the radiolabelled compound should be described where possible'***. | Accepted. |
| Page 5<br>Impurities (3.2.S.3.2)<br>Line 3 | For radiopharmaceuticals there are many drug substances that are not isolated during production, where the production process is a continuous operation. In these circumstances it would be logical for data on impurities to be presented in the section on drug product. We suggest that this paragraph be expanded to include this option for drug substance impurity | Accepted. |

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| | data.<br>Add to the end of line 3.<br>***'Where an active substance is not isolated during the production process, information on impurities may be presented in section 3.2.P.5.5., Characterisation of impurities.'*** | |
| Page 5<br>Specification (3.2.S.4.1)<br>Line 2 | For radiopharmaceuticals there are many drug substances that are not isolated during production, where the production process is a continuous operation. In these circumstances it would be logical for data on specification to be presented in the section on drug product. We suggest that this paragraph be expanded to include this option for drug substance specification.<br>Add to the end of line 2.<br>***'Where a active substance is not isolated during the production process, information on specification may be presented in section 3.2.P.5.1 Drug Product Specification(s)'*** | Accepted. |
| Page 5<br>Justification of specification (3.2.S.4.5) | If the specification deviates, it should be specified here, what has to be done. Is it necessary to discuss this in the overview summary, to provide a scientific justification, or to discuss this with authorities? | Not accepted.<br>The applicant should justify the specification. It was considered that it is not appropriate to give too many details here. |
| Page 6<br>Reference Standards or Materials (3.2.S.5) | Radioactivity calibration standards should be provided with the content of impurity radionuclides and the uncertainty of the standard. | Not accepted.<br>It was considered that it is not appropriate to give too many details here. |
| Page 6<br>Reference Standards or Materials (3.2.S.5) | For some short-lived isotopes a calibration standard is not feasible and factors are empirically derived. To cover these situations it should be allowable to describe and justify an alternative method of calibration.<br>Suggested text:<br>***'Information on calibration of the radioactivity measurement system should be provided. If an appropriate traceable standard of the isotope is not available, justification for the use of another method of calibration should be included.'*** | First part of the sentence retained as it was, because considered clearer.<br>Accepted to add the sentence 'If an appropriate traceable standard of the isotope is not available, justification for the use of another method of calibration should be included.' At the end of the paragraph. |
| Page 6 | Delete the word 'lead' as the shielding may not necessarily be lead. | Accepted. |

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| Container closure system (3.2.S.6) | Delete '***lead shielding'*** replace with ***'shielding container'***<br><br>Proposed text:<br><br>***'The shielding container is secondary packaging and should only be briefly described.'*** | |
| Page 6<br>Stability (3.2.S.7) | For clarification it is suggested that this paragraph addresses active substances first and that chemical precursors for PET radiopharmaceuticals are addressed at the end of the paragraph.<br><br>Suggested text;<br>***'The shelf life and storage conditions for the active substance should be specified and justified. The general stability guidelines are fully applicable to the non-labelled active ingredient of radiopharmaceutical kits. The stability guidelines are not fully applicable for drug substances of ready-for-use radiopharmaceuticals, radionuclide generators and radioactive precursors due to the radioactive nature of these substances. Stress testing of radioactive substances is often not feasible. In some cases simulated stress testing may be performed on the non-radioactive chemical form. The shelf life of chemical precursors used in the manufacture of PET radiopharmaceuticals should be justified.'*** | Not accepted.<br><br>The proposed text suggests that the shelf life of chemical precursors used in the manufacture of PET radiopharmaceuticals can be justified, while it was considered that full application of the general stability guidelines is necessary. |
| Page 6<br>Stability (3.2.S.7)<br>Line 6 | Is it always a requirement to demonstrate that this is not feasible? From my understanding all non-radioactive substances, which are stable enough, could undergo a stress testing. Are these cases meant here? Then this sentence might be reworded as proposed.<br><br>Proposed text:<br><br>***Where feasible, simulated stress testing should be performed on the non radioactive chemical form.*** | Not accepted.<br><br>In certain cases it is acceptable to perform simulated stress testing. |
| Page 6<br>Description and composition of the drug product (3.2.P.1)<br>Line 4 (par. 2) | As this section of the Dossier addresses drug product, we are unclear as to whether the author intended to specify that the chemical amounts of the constituents of a radiopharmaceutical kit should be specified (rather than only the chemical amount of active substance).<br><br>Suggested text:<br><br>***'For radiopharmaceutical kits, the chemical amounts of all ingredients should be specified'*** | Partially accepted.<br><br>The comment was not entirely accepted, but it was agreed to delete the sentence in question and not to replace it at all, because it was considered redundant (the chemical amount of ingredients needs to be specified in the Marketing Authorisation dossier for any product, this is not specific for radiopharmaceutical kits). |

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| Page 6<br>Description and composition of the drug product (3.2.P.1)<br>Line 5 (par. 3) | - Typo. ***'radioactive'*** | Accepted. |
| | - The phrase 'volumic activity' is clearer if it is replaced by '(Bq/ml)'<br>Delete '***(volumic activity')*** replace with ***'(Bq/ml)***'<br>Suggested text: ***'Only one radioactive concentration (Bq/ml) may be included in the application ……..'*** | Partly accepted. It was decided to add in Bq/ml after volumic activity. |
| | - For oral forms (like I-131 capsules), one marketing authorisation application can include a range of radioactive concentrations (for example: from 37 to 3700 MBq per capsule). Moreover, radioactive colloid suspensions (like Y-90 citrate colloid for intra-articular injection) are difficult to produce and cannot be obtained with a fixed radioactive concentration. In this case, it is necessary to include a range of radioactive concentrations in one application.<br>Exceptions should be allowed to the 'one radioactive concentration' limitation. | Diagnostic capsules and therapeutic capsules should be in separate applications.<br>Exemption may be accepted, if they are justified. |
| | - In some cases, the same product can be used for therapy as well as diagnostic (with lower doses), which might justify exemption to separate applications.<br>Suggested text:<br>'**Although diagnostic and therapeutic products should be in separate applications, exemption might be considered if appropriate'**. | Not accepted.<br>Even for the same products, applications for diagnostic and therapeutic use should be submitted through separate applications. |
| Page 6<br>Drug substance (3.2.P.2.1.1) | As discussed below, we think that this section should cover drug substance (not excipients), and hence suggest text<br>Suggested text:<br>***'In the manufacture of radiopharmaceuticals the drug substance is rarely isolated and stored. In many situations manufacture is a continuous process until the drug product is available for dispensing. The influence of radioactivity on the purity and stability of the drug product should be discussed.'*** | Not accepted. This section should cover drug substance (e.g. radioactivity) influence on excipients<br>The current text is clearer. |
| Page 6<br>Drug substance (3.2.P.2.1.1) | We think that data on excipients should be placed in section 3.2.P.2.1.2. (not 3.2.P.2.1.1)<br>It is not necessary to provide information on excipients normally used in | The current text is in accordance with the CTD format. However it does not specify anything about excipients in section P.2.1.2 as it is not special for radiopharmaceuticals. |

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| | radiopharmaceutical products, only on novel excipients.<br>Add the word ***'novel'***<br>We also suggest that choice of pH, use of stabilizers etc. should be addressed.<br>Proposed text:<br>***' Choice of pH and use of any stabilizers should be discussed. Influence of radioactivity on novel excipients should be discussed.'*** | Not accepted.<br>Interactions should be described in the dossier also for known excipients.<br>Not accepted.<br>The choice and function of excipients should be discussed here as for other pharmaceuticals. |
| Page 6<br>Formulation development (3.2.P.2.2.1) | Suggest add 'as appropriate'<br>Proposed text:<br>***' Data on stability of particles after reconstitution (e.g. colloid size) should be presented, as appropriate.'*** | Accepted. |
| Page 6<br>Manufacturing process development (3.2.P.2.3)<br>Line 9 | Minor rewording for clarity<br>Existing text:<br>'Reproducibility and robustness must be demonstrated. Moreover, the quality control method used by the end-user should be cross-validated against the quality control method applied for batch release by the manufacturer.'<br>Proposed text:<br>***'Reproducibility and robustness must be demonstrated. Moreover, the quality control method <u>as recommended by the manufacturer for use by the end-user</u> should be cross-validated against the quality control method used for batch release by the manufacturer.'*** | Accepted. |
| Page 7<br>Manufacturing process development (3.2.P.2.3)<br>Line 15 | The pharmaceutical development studies performed on a generator should include a demonstration that the generator eluate is suitable for use after the generator has been subject to the limits of recommended storage and elution schedule. We believe this is intended by the text on lines 15 and 16 of this paragraph. We suggest alternative text for clarity<br>Proposed to delete ***'Measures to take to avoid malfunctioning due to misuse (e.g. during transportation or drying) should be discussed.'***<br>Suggested text:<br>***'Development studies performed on a generator should include a demonstration that the generator eluate is suitable for use after the generator has been subject to the limits of recommended storage and*** | Not accepted.<br>Reference to transportation and drying are necessary. |

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| | ***elution schedule.'*** | |
| Page 7<br>Batch formula (3.2.P.3.2)<br>Line 2 | In some circumstances for single dose radiopharmaceuticals it may not be possible to state the maximum batch size. This is dependent on customer orders. It would be helpful if the requirement to state maximum batch size could be flexible if justified in the dossier.<br><br>Proposed text:<br><br>***'Generally, the minimum and maximum batch size that can be applied in commercial manufacturing ….'***<br><br>In addition, for PET radiopharmaceuticals, significant variation in overall yield are observed, consideration should be given to defining batch size based on the starting amount of radioactivity, to avoid very high yielding reactions producing a batch size that is greater that the registered maximum batch size.<br><br>Additional text:<br><br>***'For PET radiopharmaceuticals batch size may be based on the starting amount of radioactivity if justified in the dossier.'*** | Not accepted.<br><br>It is not possible to accept a flexible batch size in a dossier. The maximum possible batch size should be subject to validation.<br><br>Not accepted.<br><br>The yield may be varying, but as long as the maximum batch size is within a validated range there should be no problems. |
| Page 7<br>Description of Manufacturing Process and Process Control (3.2.P.3.3)<br>Par 5 | This information could be provided in 3.2.A.1. | Not accepted.<br><br>This information is more relevant in this section. |
| Page 7<br>Description of Manufacturing Process and Process Control (3.2.P.3.3)<br>Par 6 | Does this requirement refer to the radioactive or non-radioactive suspension? | It refers to both as appropriate. |
| Page 8<br>Controls of critical steps | Suggest minor rewording of first sentence and specific mention of aseptic processes in second sentence in relation to filter integrity testing.<br>Suggested text: | First addition 'need to' accepted. |

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| and intermediates (3.2.P.3.4) | ***'For radiopharmaceuticals containing radionuclides of short physical half-life (e.g. PET radiopharmaceuticals), that need to be released before all results on finished product testing are available, special attention should be devoted to in-process controls for critical parameters of the production process. For aseptic processes the filter used in final filtration should be tested for integrity before release of the product in accordance with Ph.Eur. requirements (5.1.1 Methods of Preparation of Sterile Products - Filtration).'*** | Second addition 'For aseptic processe' not accepted. The reference to the relevant chapter of the Ph.Eur. clarifies when the filter used in final filtration should be tested for integrity before release. |
| Page 8 Process validation and/or evaluation (3.2.P.3.5) Line 1 | Need to refer to PET radiopharmaceuticals as an example for when radiopharmaceuticals are manufactured in situ for direct administration to the patient. This sentence will also apply to other short lived non PET radiopharmaceuticals.<br>Proposed text:<br>*' When radiopharmaceuticals are manufactured in situ for direct administration to the patient (e.g.PET radiopharmaceuticals with physical half life of the radionuclide ≤ 20 min), the consistency of the production process has a particularly great importance.'* | Accepted. |
| Page 8 Control of drug product Specification(s) (3.2.P.5.1) Line 7 | It should be acceptable for the acceptance limits for therapeutic radiopharmaceuticals to be 90 to 110%, (as are diagnostic radiopharmaceuticals), rather than 95 to 105% as included in the draft text. The acceptance limits are composed of the measurement inaccuracy and the manufacturing tolerances. Assuming a measurement inaccuracy of ± 3 % (a common value for ion chambers) only a manufacturing tolerance of ± 2 % remains. For a single dose preparation of capsules this is not achievable.<br>The generally accepted range for activity measurements is +/- 10% (see European Pharmacopoeia). The radioactivity measurement equipment used in the nuclear medicine departments do not show a +/- 5% accuracy.<br>This tight acceptance limit is also not necessary from a medical point of view: so for example the inaccuracy in determining the weight of the thyroid in thyroid therapy is at least ± 30 %.<br>Proposed text:<br>***'Acceptance limits for the radioactive concentration for radiopharmaceuticals (diagnostic and therapeutic) should be within 90 to 110% of the label claim.'*** | Not accepted.<br>95-105 % is the normal limits applied to medicinal products. It is already in the text that wider limits can be accepted if justified. No need to change the current text. |

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| Page 8<br>Control of drug product Specification(s)<br>(3.2.P.5.1)<br>Line 7 | What is the reason for this narrower limit? | See above. |
| Page 8<br>Control of drug product Specification(s)<br>(3.2.P.5.1)<br>Line 7<br>Par 3 | Which performance is meant here? | Accepted.<br>'Performance' replaced with 'quality'. |
| Page 9<br>Justification of Specification(s)<br>(3.2.P.5.6) | The specifications should apply throughout the shelf-life of the product. Where radionuclidic impurities are specified at the calibration time it needs to be demonstrated that this is the case. Where a radionuclidic impurity has a shorter radioactive half-life than the drug product radionuclide it needs to be shown that the specification will not be exceeded where the product is available for administration prior to the calibration date and time.<br><br>Batch release specifications should be such as to demonstrate that the product specifications will apply throughout the shelf-life at the recommended storage conditions. | Not accepted.<br>Radioactivity follows well known physical laws, so radioactivity at the end of shelf-life can be predicted by the radioactivity level measured at release. Batch release specifications should be set to ensure that end of shelf-life specifications are met. |
| Page 9<br>Reference Standards or Materials<br>(3.2.P.6) | For some short-lived isotopes a calibration standard is not feasible and factors are empirically derived. To cover these situations it should be allowable to describe and justify an alternative method of calibration. Suggested text:<br>***'Information on calibration of the radioactivity measurement system should be provided. If an appropriate traceable standard of the isotope is not available, justification for the use of another method of calibration should be included.'*** | Accepted. |
| Page 9<br>Container closure system<br>(3.2.P.7) | Delete the word 'lead' as the shielding may not necessarily be lead. Add testing for suitability of container.<br>Delete '***lead shielding'*** replace with ***'shielding container'*** | Accepted. |

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| Page 9<br>Stability<br>(3.2.P.8)<br>Line 5 (par. 3) | The current text specifically indicates PET radiopharmaceuticals; this is superfluous information as these radiopharmaceuticals are by definition ready-to-use. Either remove specific reference to PET, or provide this as an example.<br><br>It is believed this statement is trying to express the need to take into account the effect of radiolysis during stability testing by examining the full range of available radioactive concentration (RAC). Ideally this should be explained more clearly in the text.<br><br>Replace paragraph with:<br><br>***'-In stability testing of ready-to-use radiopharmaceuticals, for example PET radiopharmaceuticals, radiolysis effects should be taken into account by performing stability testing at both the minimum and maximum radioactive concentration available at the time of manufacture.'*** | Not accepted.<br><br>The comment focus on PET radiopharmaceuticals, but the sentence is also applicable to other ready-to-use radiopharmaceuticals. Moreover, the sentence under consideration does not only address radiolysis, but also other effects on concentration of radioactivity. |
| Page 9<br>Stability<br>(3.2.P.8)<br>Line 18-19<br>(par. 6) | Stating that stability studies require at least 5 test points is not appropriate for products with a short shelf life. It should be acceptable to provide data on less points e.g. initial, reference and expiry.<br><br>In these situations, the testing frequency should be adapted according to the specifics of the isotope.<br><br>Delete '***so that data on at least 5 test points (including the initial one)'***<br><br>Proposed text;<br><br>*- ' The minimum time periods covered at submission defined in the stability guidelines (12 months long term testing, 6 months accelerated testing, etc.) cannot be applied for radiopharmaceuticals with a proposed shelf life of less than one year. In these situations, the testing frequency should be adapted and justified, based on shelf life, and presented in the submission.'* | Accepted with minor rewording of the proposed additional text. |
| Page 10<br>Stability<br>(3.2.P.8)<br>Line 28 (par. | The term 'vacuous vials' should be replaced with 'evacuated vials'<br><br>Proposed text; | Accepted. |

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| 9) | ***'(e.g. eluent and evacuated vials)'*** | |
| Page 10<br>Stability<br>(3.2.P.8)<br>Line 36 | It would be appropriate to include a statement that an end of life specification may be considered.<br>Add:<br>***'An end of shelf life specification may be justified if appropriate.'*** | Not accepted. There is no need to deviate from the general stability specifications (release and shelf-life).<br>It was considered that adding a statement on end of shelf-life specifications was not appropriate, because it might be confusing. |
| Page 10<br>Stability<br>(3.2.P.8)<br>Line 41 (par. 13) | Shelf life in terms of one working day is not clear<br>Delete ***maximum shelf life should be one working day after first use or following reconstitution***<br>Replace with: ***'Shelf life must be adequately justified after first use or following reconstitution.'*** | Accepted partially.<br>It is recognised that the current text was not adequate, but the proposed text was also not agreed. An alternative text was adopted: 'maximum shelf-life should usually be 8 hours after first use or following reconstitution, unless adequately justified by data'. |
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