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Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
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<Date of submission>

Submission of comments on Guideline on quality of radiopharmaceuticals

(EMA/CHMP/QWP/363827/2025)

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.
When completed, this form should be sent to the European Medicines Agency via the EU survey, in Excel format (not PDF).
Columns A to D should mandatorily be filled in prior to completing the columns "Comment and rationale" and/or "Proposed changes / recommendation". The "Outcome" column should not be completed.
For more details on how to use this template please refer to the tab "Manual for commenter".

Name of organisation or individual*	General or Specific comment*	Line from* (line nr. or 0 for general comment)	Line to* (line nr. or 0 for general comment)2	Comment and rationale (to go to next line within the same cell use Alt + Enter)	Proposed changes / recommendation (if applicable - to be used if you want to propose specific text changes)	Outcome (To be completed by the Agency)
European Association of Nuclear Medicine (EANM)	General			The EMA guideline on quality of radiopharmaceuticals addresses the needs for quality documentation for radiopharmaceuticals "in the context of applications for marketing authorisations or variations to authorized medicinal products". The activities of EANM and its members are not related to the marketing authorisation of radiopharmaceuticals; however, we are supporting the development of new clinically useful radiopharmaceuticals and their clinical implementation. However, in the past, it has been the experience of EANM members, that this guideline is also applied in the context of clinical development of novel radiopharmaceuticals, as it is the only official reference document available specifically for radiopharmaceuticals. This is further reinforced by the precision of scope establishing that "principles of this guideline are also applicable for radiopharmaceuticals intended to be used in the conduct of clinical trials allowing flexible and phase appropriate interpretation". It is appreciated that such a flexible interpretation is facilitated, but experience showed that the principles are applied in a quite strict way. Our comments must be read in particular in this respect.		
EANM		39	45	The EANM welcomes that radiopharmaceuticals are recognised as "*a special type of medicinal products*" . However, we would like to highlight some additional particularities in addition to the ones already mentioned including: small batch size, specific logistics and distribution pathways and the fact that radiopharmaceuticals doses are exclusively handled by the designated professionals (i.e., nuclear medicine physician) and never by the patients.		
EANM		53		The EANM would like to kindly request a clarification of what is meant by "*measurement of biodistribution*". Our community interpret this as radiopharmaceuticals being used to measure e.g. radioactivity in tissue, blood or urine for diagnostic purposed without generating an image (such as I-131 sodium iodide uptake in thyroid). However, we would like to highlight that this could also be misinterpreted as pharmacokinetic studies in research applications. We would therefore like to suggest rewording the "*measurement of biodistribution*" into "**non image-based measurement of biodistribution"**.		
EANM		60		The EANM would like to highlight that, for kit-based radiopharmaceuticals, administration to the patients does not always have to be done shortly after final preparation.	Therefore, we would like to suggest rewording "*in these cases*" into "***in certain cases."***	
EANM		63		We have well noted that *"according to Directive 2001/83/EC radiopharmaceuticals are considered medicinal products and, as such, cannot be placed on the market unless they hold a valid marketing authorisation"*. However, it is important to note that there are some exemptions to this general rule, notably for products prepared in the hospital Radiopharmacy and more generally for all products falling under the in-house, non-industrial preparation category. These exemptions, related to the particular nature of radiopharmaceuticals, should be mentioned here.		
EANM		64		The EANM would like to clarify that it is not only the "*short physical half-life of most radionuclides in radiopharmaceuticals"* which has led to define *"three additional special types of substances/preparations"* . It is rather the particular nature of radiopharmaceuticals (indeed including the short half-life but also other particularities including radioactivity), which has		
EANM		70	73		*"On the other hand, when a substance/preparation covered by the definition ofradionuclide generator, radionuclide precursor or kit is used as starting material, active substance or intermediate in the manufacture of a radiopharmaceutical subject of a marketing authorisation application* ***or based on national or clinical trials authorizations*** *, they do not need to hold a marketing authorisation"*	
EANM		93		The EANM has noted that while the other products and substances are well defined either in this guideline or the EU Pharmaceutical Directive, *"active substances in kits"* is not defined. We urge EMA to provide an appropriate definition to avoid unclarity when implementing. Also, we would like to highlight that the radionuclide precursors are defined in two different ways throughout the guideline. Similarly, we would like to strongly suggest using another term than *"radionuclide precursor (used as a starting material)"* as it makes the distinction with the "*radionuclide precursors"* complex. Overall, we would like to hihglight a discrepancy with the definition of radionuclide precursor given in the general monographc 0125 - radiopharmaceutical preparation.		
EANM		96		The EANM believes it is crucial to flag that it is not possible to isolate the active substance, and that this point should be clarified to avoid legal uncertainties when it comes to implementation. It is not *per se* the active substance, but what is considered as active substance.	We would therefore invite to reword "*the main body of the guideline clarifies what are the substances/medicinal products that should be the subject of modules 3.2.S and 3.2.P and the specific requirements for their content"* into *"the main body of the guideline clarifies* ***what is considered from a regulatory point of view as active*** *substances /medicinal products that should be the subject of modules 3.2.S and 3.2.P and the specific requirements for their content"*	
EANM		102	106	We would kindly invite EMA to remove the specification about investigational or auxiliary investigational medicinal products (IMPs), or to request clarification on the principles of the guideline (only the formal/structural principles or not). Indeed, a number of requirements of this guideline should not be applicable to IMPs, e.g. the extended validation of analytical methods. Instead, flexible and phase appropriate interpretation should be facilitated, in line with the intention of the Clinical Trials Regulation.		

EANM		140	144	The EANM would like to highlight that, in line with the Clinical Trials Regulation, it is important that IMPs are explicitly excluded from GMP requirements.		
EANM		145	149	The EANM has a semantic concern with regards to section 4.1 on radionuclide precursors. The definition of radionuclide precursors and the status of active substances is not very clear and might be misleading for national regulators. The EANM encourages EMA to change the terminology for radionuclide precursors. Especially, the EANM has concerns with regards to the statement made in line 147 about isolation of pure substances. We would like to suggest rewording into "radioactive substances cannot usually be isolated as pure substances". Similarly, further clarification is needed on the parent-daughter relationship, i.e., the parent nuclide being the radionuclide precursor. We also suggest EMA to include practical examples to allow the readers to better understand what they mean.		
EANM		167 (same for 176 and 277)		The EANM appreciates the widening of production methods for radionuclides to include not only accelerator and cyclotrons but also mass separation techniques. We, however, believe that the description should even be widened, e.g. several novel radionuclides, in particular alpha emitters, are extracted from long lived sources of certain radionuclides. This technique should not be considered as radionuclide generator based techniques, as in this context, this would imply that the parent radionuclide would be in the focus of quality considerations (which is in certain cases not possible in a traditional pharmaceutical quality version: e.g. Ac-225 is mainly extracted from Th-229 sources, which only are available in highly specialized nuclear research centres and cannot be controlled in a usual way). Therefore, we would suggest to add the term "*extraction*" as another production processes where manufacturing of radionuclides is described.		
EANM		230		(highest radioactivity)" might not be flexible enough. Highest radioactivity may not always be the "*worst-case scenario*": for some technical reasons, the highest specific radioactivity or molar radioactivity may be a worse-case scenario than the highest radioactivity.	We would therefore suggest changing to *"worst-case scenario (**e.g** . highest radioactivity **to be used, concentration)** "*.	
EANM		241			"*For kits, **what is considered as** active substance **from a regulatory point of view** is considered to be that part of the formulation that is intended to carry or bind the radionuclide".* See rationale line 96.	
EANM		244		Even though the EANM supports the concept that chemical precursors should undergo rigorous quality tests (as being the most closely related compound that can be isolated), we believe that chemical precursors should not only be viewed in a way that all requirements for active substances should be applied. The current wording line 249 seems to state indeed that all requirements for active substances would apply to chemical precursors. Considering the special nature of radiopharmaceuticals (non-pharmacological masses, separation of precursors) and the great variation in production and application, a differentiated, risk-based approach on quality considerations should be applied, as described in the Ph. Eur. General monograph "Chemical precursors for radiopharmaceutical preparations (2902)".	This should be clearly stated in line 257: ***"In the absence of a specific Ph. Eur, monograph, the principles of the Ph. Eur. General monograph "Chemical precursors for radiopharmaceutical preparations (2902)" should be applied and limits should be based on batch and stability data and consider the principles outlined in the currently available guidelines and compendial texts pertaining to the control of impurities in chemical precursors, active substances and drug products, as applicable. An overall safety evaluation of the levels of impurities delivered with each dose to the target patient population should be taken into account (e.g. whether the manufacturing/preparation process includes or not a purification step)."***	
EANM		313		When it comes to the description of drug product (section 5.1), the draft guideline states that "*in most cases, a range of strengths for the finished product is not acceptable* ". While the EANM agrees with this statement for a marketed product, it is not the case for clinical trials products. This issue is a typical example of how developments can be hindered if the scope of the guideline is not fully clarified. Specifically, in the clinical development, different strengths (in terms of radioactivity per volume) should be applied, especially for products with very short shelf life (e.g. C-11) and technically challenging processes, but also for therapeutic radiopharmaceuticals.		
EANM		315	317		*"For radiopharmaceuticals containing a radionuclide with a physical half-life shorter than two hours and presented as a solution or **investigational medicines products (IMPs**), a range of strengths for the finished product could be acceptable".*	
EANM		330		As part of the pharmaceutical development, the guideline states that "osmolarity of the preparation should be addressed". The EANM would like to clarify that osmolarity test is no longer required by Eur. Ph. monographs for radiopharmaceuticals due to the small volumes typically administered to the patients. In the case of radiopharmaceuticals, osmolarity is of low relevance and not a safety concern.		
EANM		342	345	The EANM supports the exemption to fil "*the final container by piercing the stopper of closed pre-sterilised containers* " in the case of "*radiopharmaceuticals containing a radionuclide with a shelf-life shorter than 24 hours".* Such a small approach would benefit the development for small scale production.	In this context, we would like to suggest rewording for "*radiopharmaceuticals containing a radionuclide with a shelf-life shorter than 24 hours"* (line 344) into *"radiopharmaceuticals containing a radionuclide with a shelf-life shorter than 24 hours **and IMPs.** "*	
EANM		367	370	The EANM would like to request further clarification on the manufacture requirements for the drug product. Especially, it would be helpful to provide some description how the limits for bioburden in raw materials should be set to "*ensure a consistent bioburden of NMT 10 CFU/100ml before sterile filtration"*.		
EANM		396	400	The EANM would like to request again clarification on the scope of the guideline and ask whether regulatory bodies are considering requiring marketing authorisation for "ready for use radiopharmaceuticals are manufactured in situ for direct administration to the patients". Should the draft guideline be interpreted in that way, the delivery of ready for use radiopharmaceuticals would become close to impossible. Therefore, we trust that clarification of what is covered by the guideline is crucial to avoid a situation in the future where marketing authorisations would be required for products with a half-life of less than 20minutes.		
EANM		425	426	The EANM would like to flag a semantic concern with the "*the suitability of the monograph should in all cases be demonstrated".* We understand this statement as the request to demonstrate not the suitability of the monograph, but rather that the monograph is also applicable for the proposed production process. Should our understanding be correct, we trust that leaving the text as it might create further confusion.		
EANM		434			*"Radioactivity detectors should be appropriately **calibrated** with respect to sensitivity"*	
EANM		588	589		*generator to permit elution (e.g. eluent and evacuated vials). The eluent is expected to be sterile **if intended to be used for parental application without further processing".***	
EANM		730			*"Radioactivity detectors used in the analytical procedures should be appropriately **calibrated"***	

EANM		756	757	From a user's perspective reading an SmPC, the term "immediately" should be specified. EANM would suggest not more than 30min).		
EANM		808			Replace *specific activity* by ***molar (radio)activity*** & replace *Teribility* by ***Sterility***	
EANM	General	0	0	In addition to its own comments, the EANM endorses the comments submitted by the subcommittee on Contrast Agents, Radiotracers and Theranostics of the European Society of Radiology, which is committed to support the development and use of as well as patients access to novel diagnostic radiopharmaceuticals by a suitable regulatory framework.		