EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2023
EMA/CHMP/BWP/245588/2023
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the revision of the Guideline on Radiopharmaceuticals Based on Monoclonal Antibodies

Agreed by Biologics Working Party	12 July 2023
Adopted by CHMP for release for consultation	20 July 2023
Start of public consultation	21 July 2023
End of consultation (deadline for comments)	31 October 2023

The proposed guideline will replace "Guideline on Radiopharmaceuticals Based on Monoclonal Antibodies" (3AQ21a).

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	guideline, radiopharmaceuticals, monoclonal antibodies, radionuclides

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

1. Introduction

The current Guideline on Radiopharmaceuticals Based on Monoclonal Antibodies (Eudralex 3AQ21a) was last revised in May 1991. An in-depth revision is now considered necessary to update the guideline to the current state-of-the-art, addressing novel developments and regulatory requirements.

2. Problem statement

Since 1991, numerous developments have been made in the field of radiopharmaceuticals, i.a. various new antibody formats, new conjugation technologies. At the same time, new manufacturing technologies and analytical methods have evolved concomitant with new regulatory expectations, which are partially reflected in current regulatory documents. These developments need to be addressed in a revised guideline.

The revision of the Guideline on Radiopharmaceuticals Based on Monoclonal Antibodies will be prepared in parallel with the revision of the quality Guideline on radiopharmaceuticals (EMEA/CHMP/QWP/306970/2007) and with the development of a clinical Guideline for the development of therapeutic radiopharmaceuticals. This specific document will not address the same areas, but complement the links between quality, non-clinical and clinical modules to be included in the dossier.

3. Discussion (on the problem statement)

Monoclonal antibodies may form the basis of radiopharmaceuticals for *in vivo* diagnosis or therapy. The antibody or antibody fragment is thus only one component of the medicinal product and in the evaluation of quality and safety of this group of products, the radiopharmaceutical and radiation protection aspects must be considered in addition to those of the antibody component. Principles as outlined in this guideline might also be applicable for other types of biotechnology-derived proteins which might be conjugated to radionuclides.

The revision of the guideline will reflect the latest developments of radiopharmaceuticals based on monoclonal antibodies and will provide recommendations regarding quality and non-clinical aspects of these products. This will include, but not be limited to, the following topics and other related issues, as appropriate, based on feedback and discussions in the drafting group:

- A clear terminology identifying starting materials, intermediates, linkers, active substance and finished product stages
- Structure of CTD quality and non-clinical modules for intermediates, active substance and finished product
- Making reference to the dossier of an already authorised medicinal product (e.g., monoclonal antibodies, radionuclide intermediates) and use of an ASMF procedure for radiopharmaceutical precursors
- Specification requirements for radionuclide, e.g., radionuclide characteristics, radionuclide concentration, radionuclide purity, radiochemical purity, specific activity, chemical composition, chemical impurities, chemical stability
- State-of–the-art radiolabelling method (to generate stable conjugate) requirements and description (either carried out by the manufacturer or by the user)
- Specification requirements for active substance and finished product, e.g., identity, purity, potency, sterility

- Shelf-life assignment, labelling and packaging of the finished product
- Non-clinical testing, e.g., mechanism of action (MoA), stability of conjugate in plasma, free radionuclide, free antibody, reproductive function, foetal toxicity, mutagenic potential, carcinogenic potential
- Guidance for calculation of the absorbed dose to target tissues/organs, e.g. milliGrays per unit of activity administered considering decay rates

4. Recommendation

The Biologics Working Party (BWP) recommends revising the Guideline on Radiopharmaceuticals Based on Monoclonal Antibodies (3AQ21A) taking into account the issues identified above.

The revision of the Guideline on Radiopharmaceuticals Based on Monoclonal Antibodies will primarily focus on quality aspects for radiopharmaceuticals based on monoclonal antibody active substance and finished product and will be done to ensure consistency and complementarity with other existing guidelines on monoclonal antibodies and on radiopharmaceuticals.

It will be emphasised that the non-clinical program needs to cover the mode of action, e.g. whether the antibody functions solely as carrier to bring the radiation dose to the target site or whether action also relies on target binding and Fc-mediated effector functions of the monoclonal antibody. Additionally, guidance will be provided on what type of data is needed for addressing stability of the conjugate and the individual compounds (free nuclide and free antibody), including their distribution.

For the clinical documentation, guidance will be provided in terms of the effective dose equivalents.

5. Proposed timetable

This concept paper will be published for a three-month public consultation period.

BWP will take account of all comments received during the public consultation on the concept paper when preparing the draft guideline. The draft guideline will be published for a six-month public consultation period.

The BWP will take account of all comments received during the public consultation on the draft guideline when preparing the final guideline text. It is expected that the final guideline will come into operation six months after publication following adoption by CHMP.

6. Resource requirements for preparation

The development of the revised guideline will be carried out by BWP, in close co-operation with the Quality Working Party (QWP), the Non-clinical Working Party (NcWP), Oncology Working Party (ONCWP) and the Working Group on Quality Review of Documents (QRD), as necessary.

7. Impact assessment (anticipated)

The revision of the guideline will support a uniform approach in the EU for both the development and the assessment of medicinal products containing radiopharmaceuticals based on monoclonal antibodies and will benefit industry through harmonisation of data requirements and making the acceptance by regulators of state-of-the-art approaches easier. It is observed that outside stakeholders have requested this revision and expect a positive impact.

It will also benefit regulators by bringing the guidance up–to-date and easing the assessment of related applications.

No adverse impact on industry with respect to either resources or costs is foreseen.

The guideline will not introduce new requirements on medicinal products already authorised and on the market.

8. Interested parties

EFPIA (European Federation of Pharmaceutical Industries and Associations), NMEU (Nuclear Medicine Europe), EANM (European Association of Nuclear Medicine), EU Competent Authorities, GMP/GDP Inspectors Working Group.

9. References to literature, guidelines, etc.

Directive 2001/83/EC, as amended

European Pharmacopoeia (Ph. Eur.) monograph 2031 on Monoclonal antibodies for human use, current edition

Guideline on Development, Production, Characterisation and Specifications for Monoclonal Antibodies and Related Products (EMA/CHMP/BWP/532517/2008)

ICH Q5A-Q5E Guidelines on Quality of Biotechnological Products

ICH Q8-12 Guideline on Pharmaceutical Development

Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission (EMA/CHMP/BWP/187338/2014)

Guideline on Radiopharmaceuticals (EMEA/CHMP/QWP/306970/2007)

Eudralex Volume 4 EU Guidelines on Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, Annex 3 Manufacture of Radiopharmaceuticals

Guideline on core SmPC and Package Leaflet for Radiopharmaceuticals (EMA/CHMP/167834/2011)

Other general texts and monographs of the Ph. Eur. and other guidelines not specific for radiopharmaceuticals and/or monoclonal antibodies but also applicable, should be considered.