



1 20 July 2023
2 EMA/CHMP/BWP/245588/2023
3 Committee for Medicinal Products for Human Use (CHMP)

4 **Concept paper on the revision of the Guideline on**
5 **Radiopharmaceuticals Based on Monoclonal Antibodies**

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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

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

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12 Comments should be provided using this EUSurvey [form](#). For any technical issues, please contact
the [EUSurvey Support](#).

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Keywords	guideline, radiopharmaceuticals, monoclonal antibodies, radionuclides
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15 **1. Introduction**

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

19 **2. Problem statement**

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

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

30 **3. Discussion (on the problem statement)**

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

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

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

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

61 **4. Recommendation**

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

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

68 It will be emphasised that the non-clinical program needs to cover the mode of action, e.g. whether
69 the antibody functions solely as carrier to bring the radiation dose to the target site or whether action
70 also relies on target binding and Fc-mediated effector functions of the monoclonal antibody.

71 Additionally, guidance will be provided on what type of data is needed for addressing stability of the
72 conjugate and the individual compounds (free nuclide and free antibody), including their distribution.

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

74 **5. Proposed timetable**

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

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

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

82 **6. Resource requirements for preparation**

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

86 **7. Impact assessment (anticipated)**

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

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

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

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

97 **8. Interested parties**

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

101 **9. References to literature, guidelines, etc.**

102 Directive 2001/83/EC, as amended

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

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

107 ICH Q5A-Q5E Guidelines on Quality of Biotechnological Products

108 ICH Q8-12 Guideline on Pharmaceutical Development

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

111 Guideline on Radiopharmaceuticals (EMA/CHMP/QWP/306970/2007)

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

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

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