

# New CHMP guideline on immunogenicity of monoclonal antibodies

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The importance of monoclonal antibodies as a product class and the challenge of assessing unwanted immunogenicity for these products have prompted the drafting of a new CHMP (Committee for Medicinal Products for Human Use) guideline. The 'Guideline on immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use' is intended as an annex to the existing general immunogenicity guideline. This guidance in conjunction with other relevant CHMP guidelines should assist manufacturers and regulators who are involved with producing or assessing marketing authorization applications for monoclonal antibody products.

**Keywords:** Biosimilar, comparability, quality, risk, safety

Unwanted immunogenicity remains a major concern for biological products including biosimilars. Assessing the immunogenicity of biologicals and the possible clinical consequences of this is a considerable challenge and requires carefully planned, prospective immunogenicity studies, conducted using appropriate patient groups. Regulatory guidance on this has been published by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) (Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins; EMEA/CHMP/BMWP/14327/2006). This guideline, which came into effect in 2008, has been used by manufacturers of biologicals and regulators especially at the marketing authorization stage of regulatory product approval. Although it has been generally well received, one criticism of it is that it is 'too general' and does not provide specific guidance for particular products or classes of products. The latter point is indeed true, as the guideline was intentionally drafted to provide general guidance relating to all biological products. Drafting guidelines dealing with immunogenicity issues for specific products is possible, but has been considered unnecessary or even undesirable. It would be a major task to produce specific guidelines covering the very wide range of biological products now being produced or in development and there would be much overlap in the content of many of the specific guidelines as several aspects of unwanted immunogenicity are common to all biologicals. But, in some cases there are issues that affect some products more than others or are different for different biologicals. Normally, this has to be dealt with on a case-by-case basis. However, in some cases for specific products or product classes, generalities pertaining to their immunogenicity may apply, which may merit the preparation of specific immunogenicity guidelines. One such large class of products is monoclonal antibodies (mAbs). This is clearly a very important class of biotherapeutics and *in vitro* diagnostics, for which there are several approved products in the EU and elsewhere; many more are in development.

In view of this situation, and following internal and external consultation, the decision was taken to draft a mAb specific CHMP

immunogenicity guideline. This guidance, titled 'Guideline on immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use' (EMA/CHMP/BMWP/86289/2010) has now been adopted by CHMP (again following public consultations) and came into effect in December 2012. It is intended as an addendum to the 'Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins' (EMA/CHMP/BMWP/14327/2006), i.e. that it should be read in conjunction with the general guideline. The new guideline includes sections addressing problems experienced with screening and confirmatory assays used in assessing immunogenicity of mAbs (assays for antibody detection, presence of mAb product in samples for analysis, confirmatory assays and controls), assessment of the neutralising capacity of antibodies induced against mAbs and considerations on immunogenicity risk management of mAbs (risk identification, risk management and risk monitoring and mitigation). The guideline concentrates on specific issues, problems and technicalities that relate to mAbs and products that have similarities to mAbs, such as IgFc fusion proteins. However, some parts of the guideline contain useful information that can also apply to other biologicals. The new immunogenicity of mAbs guideline will apply to all mAbs, including biosimilar mAbs, but treats biosimilars as just a subclass of biologicals (which they clearly are) with no specific requirements from the immunogenicity perspective. This follows the approach taken in the 'Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins'.

However, immunogenicity assessment for biosimilars does differ in one important aspect from immunogenicity assessment of stand-alone biologicals, as comparative immunogenicity, which is an essential element of the comparability studies, has to be assessed for the candidate biosimilar and the innovator (reference) product. Non-clinical and clinical issues relating to biosimilar mAbs are addressed in another new guideline, 'Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues' (EMA/CHMP/BMWP/403543/2010); which includes sections that address these aspects of immunogenicity for biosimilar mAbs. This guideline is specific to the mAb

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Submitted: 4 February 2013; Revised: 6 February 2013; Accepted: 7 February 2013; Published online first: 12 February 2013

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product class and therefore needs to be read alongside the 'Guideline on immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use'. Of note, the biosimilar mAb guideline does not reflect on the quality aspects of mAbs as a guideline dealing with this particular aspect is already in place (Guideline on development, production, characterization and specifications for monoclonal antibodies and related products; EMEA/CHMP/BWP/157653/2007) although this does not include any considerations for specific assessment of immunogenicity of biosimilars (this was not thought to be necessary at the time when the guideline was drafted). From the immunogenicity perspective, it is clear that the methodology and strategy for assessment of immunogenicity of biosimilar products including mAbs needs careful evaluation to ensure that this is appropriate for the required comparative assessment. In particular, it is important to ensure that screening procedures identify all patients who develop antibodies against the product that they receive, i.e. the candidate biosimilar or the reference product. This implies that at least screening assays need to be tailored to include the use of the biosimilar and the reference product as antigens (usually conducted as separate assays) and samples from treated patients are screened against the antigen relating to the product that they received. If the trials are double blind (as is normally required for mAbs), then this means that samples will have to be screened against both antigens, as the identity of the product that the patients have received is unlikely to be known at the time of screening. If this strategy is not adopted, it is possible that false negative results may be generated for some patients as one or more epitopes present on the biosimilar and reference products may not be shared. This aspect of immunogenicity assessment strategy is likely to receive considerable attention as more experience is gained with immunogenicity assessment of biosimilar products including mAbs. It is also important to understand the underlying causes of immunogenicity when comparing the incidence of immunogenicity. For example, it may be that differences observed with immunogenicity between a candidate biosimilar and the reference

product are due to differences in impurity profiles due to a change in the expression system.

The new immunogenicity of monoclonal antibodies guideline stresses the importance of risk assessment for immunogenicity management, but emphasises the need to take account of the numerous factors that may contribute to immunogenicity, e.g. the production system used, the patient population treated, the clinical indication(s) selected for treatment and the antigen target of the mAb. It is not possible to assign a single 'risk level' for mAbs as a product class, as each product needs to be assessed on a case-by-case basis, taking account of all the risk factors.

**For patients**

Monoclonal antibody products are potentially very valuable medicines and several are approved for the treatment of a range of clinical problems. Many more such products are in development. Unwanted immunogenicity associated with mAb products can be a problem, occasionally resulting in adverse effects and more often a reduction in clinical efficacy. The new guideline described in this article will help manufacturers of mAb products in assessing unwanted immunogenicity of mAbs and will also aid regulators in their evaluation of mAb products for approval for marketing.

**Competing interests:** None.

**Provenance and peer review:** Commissioned; internally peer reviewed.

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DOI: 10.5639.gabij.2013.0201.007

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