



Do the Outcomes of Clinical Efficacy Trials Matter in Regulatory Decision-Making for Biosimilars?

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Abstract

Background There is an increasing body of evidence supporting a more flexible approach in clinical data requirements for the approval of more complex biosimilar substances such as monoclonal antibodies (mAbs).

Objective The aim of this paper is to further analyse the role of quality/chemistry, manufacturing and controls (CMC) and clinical data for the conclusion on biosimilarity and the decision on marketing authorisation (MA).

Methods In the present study, we analysed the MA applications (MAAs) of all 33 mAbs and three fusion proteins evaluated by the European Medicines Agency (EMA) between July 2012 and November 2022 with special emphasis on all submitted rituximab (four products) and trastuzumab (seven products) biosimilar candidates, including withdrawn applications. For the two withdrawn applications, the comparative efficacy trials suggested biosimilarity, but the quality/CMC package was not accepted by EMA. We therefore investigated whether a negative MAA outcome could have been predicted based on the evidence generated in the quality/CMC packages, regardless of clinical trial data. For this purpose, we reviewed the respective European Public Assessment Reports (EPARs) or withdrawal assessment reports, and the first regulatory assessments for all these 36 MAAs (i.e. day 120 of the centralized procedure), which are not publicly available. During EMA review, where significant issues are identified which would preclude a marketing authorisation, these issues are raised as questions to the applicant and are classified as major objections (MO).

Results In 67% of cases, the outcome of the quality and clinical assessment was the same, i.e. both the quality and clinical assessments either supported approval or did not support approval. In 11% of cases, MO were identified in the quality part of the submission but not in the clinical data. In 22% of cases, MO were raised on the clinical data package but not on the quality data. However, we found no instance where seemingly negative clinical data, including failed efficacy trials, led to a negative overall decision. In each instance, the failure to confirm similar clinical performance in all investigated aspects was eventually viewed as not being related to the biosimilar per se but as being due to imbalances in the trial arms, immaturity of secondary endpoint results, change in the reference product, or even chance findings. Furthermore, when performing an in-depth analysis of the quality and clinical packages of trastuzumab and rituximab biosimilars, we found that in no case were clinical trial data necessary to resolve residual uncertainties regarding the quality part.

Conclusion The results further support the argument that sufficient evidence for biosimilarity can be obtained from a combination of analytical and functional testing and pharmacokinetic studies which may also generate immunogenicity data. This calls into question the usefulness of comparative efficacy studies for the purposes of regulatory decision-making when approving biosimilar mAbs and fusion proteins.

1 Introduction

Biologic medicines are effective treatment options for complex conditions such as cancer and an increasingly important component of health care solutions.

However, patient access to highly effective biological medicines is still unequally distributed across countries, often due to the high cost of these medicines.

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The work contributed by EW-H has been carried out while she was an employee of PEI, member of the Scientific Advice Working Party and chair of the Biosimilar Medicinal Products Working Party.

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Key Points

In the regulatory assessment of 33 mAbs and three fusion proteins evaluated by EMA, we found no instance where seemingly negative clinical data, including failed efficacy trials, led to a negative overall decision.

In the analysis of quality and clinical packages of trastuzumab and rituximab biosimilar candidates, in no case were clinical trial data necessary to resolve residual uncertainties regarding the quality part.

Our analyses suggest that the quality/CMC part of the dossier appears to be predictive for the marketing authorisation of a biosimilar mAb or fusion protein candidate, irrespective of the outcome of the clinical trial.

In the authors' opinion, the findings of this study may allow a reduction of the clinical development program for regulatory review before marketing authorisation.

Biologics represent 35% of medicine spending in Europe at list prices and have been growing at an 11.3% compound annual growth rate over the past 5 years [1]. The expenditure on cancer medicines is growing at rates higher than the growth rates of the patient population and overall health expenditure [2].

Biosimilar competition, i.e. having multiple suppliers of the same active substance, is necessary to curtail overall healthcare costs and to avoid supply shortages. Although the savings from current biosimilar competition in the European Union (EU) market and patient access are improving, a growing disparity is occurring across countries [1].

The past 5 years have shown a maturation of the biosimilars market. However, it is estimated that in the period 2023–2027, 55% of biologics with loss of market exclusivity will be without competitors [1]. Products with low sales value are unattractive to biosimilar manufacturers due to clinical development costs, largely driven by large and lengthy clinical trials and procurement costs of reference product (RP) comparator batches. Cost estimates for developing a biosimilar range from 100 to 300 million US dollars [3], compared with 1–5 million US dollars for a small molecule generic, largely due to clinical development costs [4–6]. This cannot be in the interest of stakeholders, including regulators, and contradicts the strategic priorities of the European Medicines Agency (EMA) [7], which has set out to allow for more rational use of clinical resources.

Recent efforts have resulted in alternatives to costly comparative clinical studies for certain biosimilars, where the

extent of clinical data required can vary depending on the complexity and characterisation of the molecule [8–10]. Also, several initiatives have been launched that could impact regulatory decision making and lead to revised guidelines such as omitting or reducing the size of studies involving human subjects for a larger set of biosimilar products [11, 12].

In a recent publication [13], the degree of analytical similarity and the role of clinical data were analysed for authorised adalimumab and bevacizumab biosimilars. It was argued that clinical trial requirements for monoclonal antibody (mAb)-biosimilars can be further reduced, or such trials even omitted, where a robust and convincing analytical biosimilarity package is available in conjunction with an appropriately powered pharmacokinetic (PK) study that also provides safety and immunogenicity data.

The remaining question is whether product candidates with good or promising quality data could nevertheless translate into poor (i.e. those with high uncertainty) or failed clinical trials, which may prevent approval of the product where otherwise it would have been approved.

The aim of this paper is to further analyse the role of quality/chemistry, manufacturing and controls (CMC) and clinical data for the conclusion on biosimilarity in a broader setting and in more depth, including all classes of approved biosimilar mAbs and refused or withdrawn biosimilar candidates, which likely would have failed marketing authorisation (MA).

We therefore analysed the final outcome of the submitted marketing authorisation applications (MAAs) of all 36 mAbs and fusion protein biosimilar candidates evaluated by EMA up to November 2022, including those for which a withdrawal/refusal assessment report (AR) is available on the EMA website, i.e. one trastuzumab and one rituximab biosimilar candidate, and contextualised these findings by analyses of all approved rituximab and trastuzumab biosimilar products.

We also reviewed the regulatory assessment during the first phase of these MAAs [i.e. the day 120 assessment reports (D120 AR) of the centralised procedure], which are not publicly available, to analyse whether quality data are predictive for clinical outcome and how clinical assessment impacts the decision on MA.

2 Methods

2.1 Analysis of MAA Outcome

We analysed the outcome of the MAAs, as well as the available regulatory ARs of all biosimilar mAbs and fusion proteins, i.e. adalimumab, bevacizumab, etanercept, infliximab, ranibizumab, rituximab, and trastuzumab, which included 33 mAbs

and three fusion proteins evaluated by the EMA between July 2012 and November 2022. This included biosimilar candidates, which received a MA or a negative opinion by the Committee for Medicinal Products for Human Use (CHMP) or which were withdrawn by applicants prior to a CHMP opinion; a European Public Assessment Report (EPAR) or a withdrawal AR for these candidates is available on the EMA website [14–49]. Concerns regarding quality/CMC (biosimilarity, general quality) or clinical aspects [PK/pharmacodynamic (PD), efficacy (E)/safety (S)/immunogenicity (I)], as indicated in the EPAR or withdrawal AR, were analysed. We categorised the 36 mAbs and fusion protein biosimilar candidates according to five possible scenarios (Fig. 1) indicating whether the quality/CMC, PK and clinical aspects of the biosimilar MAA dossier were acceptable to the EMA (shown in green/no pattern) or not acceptable (shown as horizontal red stripes). Vertical green stripes indicate some remaining uncertainties that were discussed within the EMA scientific committees and working parties, but not severe enough to prevent MA. Furthermore, the outcome of the MAA is indicated as well as the active substance and the IgG class.

2.2 Analysis of First Regulatory Assessment Reports

We analysed the list of questions (LoQ) raised by the CHMP in the D120 ARs of all above-mentioned 36 mAbs and fusion protein biosimilar candidates. D120 ARs are discussed and agreed by the CHMP during the first phase of the centralised MA procedure. They are shared with the applicant but are usually not publicly available [50].

They include formal regulatory aspects (Table 1) and the scientific evaluation of all quality/CMC, non-clinical and clinical data and the risk management plan that led to a LoQ regarding concerns and uncertainties that must be addressed by applicants before MA [51]. These questions are classified as major objections (MO) and other concerns (OC). MO are defined as critical issues that will preclude authorisation if not resolved [52], while OC should be resolved but are not severe enough to preclude authorisation per se.

We counted the number of MO and OC and classified those as either related to quality or clinical aspects, in the same manner as for the MAA outcome analyses (Fig. 2). Formal regulatory aspects were not included in the analysis because these are not of direct scientific concern in the context of this study.

2.3 Evaluation of Analytical and Clinical Biosimilarity for Rituximab and Trastuzumab Biosimilars

We analysed the quality/CMC and clinical data packages for all submitted rituximab and trastuzumab biosimilars to contextualise the results observed for the two withdrawn

products [43, 44]. The analysis included four rituximab biosimilars [26–28, 43, 53, 54] and seven trastuzumab biosimilars [36–39, 44, 48, 49]. The data lock point for the analysis was February 2023.

Comparison of analytical biosimilarity [quality attributes (QA)] for approved biosimilars was performed using the methodology of our previous paper. Briefly, we extracted raw data from the biosimilar product dossiers, anonymised and colour-categorised them depending on the percentage of analysed biosimilar batches with values within the similarity range of the RP (Online Resource 1). For cases where less than 100% of batches were within the reference range it was analysed how the resulting uncertainty was resolved (Table 2).

For full details, see Guillen et al. [13].

For withdrawn applications, we also looked at quality issues of the biosimilar itself affecting performance and consistency of the manufacturing process, which must be ensured in line with current guidance [55]. Therefore, we constructed a figure (Fig. 3) that covers all these aspects, following the key quality/CMC requirements from Bielsky et al. as a reference [56]. Analytical data were extracted from the withdrawal ARs, which contain public information that can be found on the EMA website and therefore anonymisation is not necessary [57].

Comparison of clinical biosimilarity is presented in Online Resources 2–5 and employs the same methodology as Guillen et al. [13]. For cases where discrepancies were observed in clinical attributes, it was analysed how the resulting uncertainty was resolved (Table 3).

3 Results

3.1 MAA Evidence and Results

For 36 mAbs and fusion protein biosimilar candidates (mostly IgG1), the quality/CMC (i.e. general quality aspects and analytical comparability exercise), clinical PK/PD and clinical efficacy, safety and immunogenicity (E/S/I) aspects were analysed based on the information provided in the EPAR. Results are shown in Fig. 1 according to five possible scenarios.

For more than 80% of the biosimilar candidates analysed (29/36), the quality/CMC part of the dossier, the clinical PK/PD as well as the E/S/I results all unambiguously supported biosimilarity (Fig. 1, Scenario 1). For two biosimilar candidates, differences in some QAs and functional assays were observed [14, 15], but these differences were not seen in PK/PD and clinical E/S/I studies. One candidate had higher immunogenicity [15], later deemed irrelevant (see Discussion). All these biosimilar candidates listed for Scenario 1 obtained a MA.

Cases	IgG type	Date of MA	Quality		Clinical		Reference	
			biosimilarity	general Q	PK/PD	E/S/I		
SCENARIO 1			+	+	+	+		
1	Infliximab 1	IgG1	10-09-2013					[14]
2	Infliximab 2	IgG1	26-05-2016					[15]
3	Infliximab 3	IgG1	18-05-2018					[16]
4	Etanercept 1	Mod. IgG1	13-01-2016					[17]
5	Etanercept 2	Mod. IgG1	23-06-2017					[18]
6	Adalimumab 1	IgG1	21-03-2017					[19]
7	Adalimumab 2	IgG1	24-08-2017					[20]
8	Adalimumab 3	IgG1	17-09-2018					[21]
9	Adalimumab 4	IgG1	02-04-2019					[22]
10	Adalimumab 5	IgG1	13-02-2020					[23]
11	Adalimumab 6	IgG1	11-02-2021					[24]
12	Adalimumab 7	IgG1	15-11-2021					[25]
13	Rituximab 1	IgG1	15-06-2017					[26]
14	Rituximab 2	IgG1	13-07-2017					[27]
15	Rituximab 3	IgG1	01-04-2020					[28]
16	Bevacizumab 1	IgG1	15-01-2018					[29]
17	Bevacizumab 2	IgG1	14-02-2019					[30]
18	Bevacizumab 3	IgG1	19-08-2020					[31]
19	Bevacizumab 4	IgG1	24-09-2020					[32]
20	Bevacizumab 5	IgG1	26-03-2021					[33]
21	Bevacizumab 6	IgG1	21-04-2021					[34]
22	Bevacizumab 7	IgG1	17-08-2022					[35]
23	Trastuzumab 1	IgG1	09-02-2018					[36]
24	Trastuzumab 2	IgG1	26-07-2018					[37]
25	Trastuzumab 3	IgG1	12-12-2018					[38]
26	Trastuzumab 4	IgG1	27-07-2020					[39]
27	Ranibizumab 1	IgG1	18-08-2021					[40]
28	Ranibizumab 2	IgG1	25-08-2022					[41]
29	Ranibizumab 3	IgG1	09-11-2022					[42]
SCENARIO 2			-	-	+	+		
30	Rituximab 4	IgG1	not approved					[43]
31	Trastuzumab 5	IgG1	not approved					[44]
SCENARIO 3			+	+	-	+		
32	Adalimumab 8	IgG1	10-11-2017					[45]
33	Adalimumab 9	IgG1	26-07-2018					[46]
34	Etanercept 3	Mod. IgG1	20-05-2020					[47]
SCENARIO 4			+	+	+	-		
35	Trastuzumab 6	IgG1	15-11-2017					[48]
36	Trastuzumab 7	IgG1	16-05-2018					[49]
SCENARIO 5			-	-	-	-		
<i>Does not apply to any of the biosimilars analyzed</i>								

Fig. 1 Analysis of MAA outcome. Fulfilment of EMA requirements and outcome of marketing authorisation applications (MAAs) for monoclonal antibody and fusion protein biosimilar candidates based on information provided in the European Public Assessment Reports or Withdrawal Assessment Reports. Green (no pattern) indicates fulfilment of EMA requirements. Vertical green stripes indicate some

remaining uncertainties not precluding marketing authorisation (MA). Horizontal red stripes indicate failure to meet EMA requirements. *EMA* European Medicines Agency, *E/S/I* efficacy, safety and immunogenicity, *IgG* Immunoglobulin G, *MA* marketing authorisation, *PD* pharmacodynamics, *PK* pharmacokinetics, *Q* quality

Table 1 Most frequent major objections

	MO regarding	Most frequent questions for MO
Quality	Formal aspects	GMP certificate missing EU GMP inspection pending Provision of a risk evaluation concerning the presence of nitrosamine impurities (EMA/369136/2020, EMA/409815/2020)
	Biosimilarity	Difference in critical quality attributes Insufficiency of ADCC assays used to conclude on biosimilarity Insufficient number of batches used for biosimilarity exercise, testing panel incomplete
	General quality	Manufacturing process In-process controls Comparability of clinical versus commercial batches of the biosimilar candidate Consistency of the manufacturing process Missing information or data to assess quality and comparability of the biosimilar candidate
Clinical	PK/PD	Investigation of observed PK differences/difference in biosimilarity regarding PK Clinical justification of the pre-specified margins of PK comparability PD analysis in second therapeutic area in case of extrapolation to all indications of RP Submission of individual patient data
	E/S/I—formal aspects	Confirmation of compliance with ethical requirements (directive 2001/20/EC) or with the principles of GCP and of the Declaration of Helsinki Pending GCP inspections 1-year safety and immunogenicity data not yet submitted at timepoint of initial submission in line with EMA Guideline (EMEA/CHMP/BMWP/42832/2005 Rev. 1)
	E	Failed primary endpoint analysis Differences observed for RP compared to published data
	S/I	Additional safety and immunogenicity data in case of observed ADAs Insufficient submitted data with respect to i.e. ADA and occurrence of neutralizing antibodies Justification for observed differences in safety profile

Major objections (MO) of the day 120 assessment reports were classified in same manner as for the MAA outcome analyses and examples for frequent questions regarding quality and clinical are given

ADA anti-drug antibodies, *ADCC* antibody dependent cellular cytotoxicity, *E* efficacy, *EMA* European Medicines Agency, *EU* European Union, *GCP* good clinical practice, *GMP* good manufacturing practice, *I* immunogenicity, *MAA* marketing authorization application, *MO* major objections, *PD* pharmacodynamics, *PK* pharmacokinetics, *RP* reference product, *S* safety

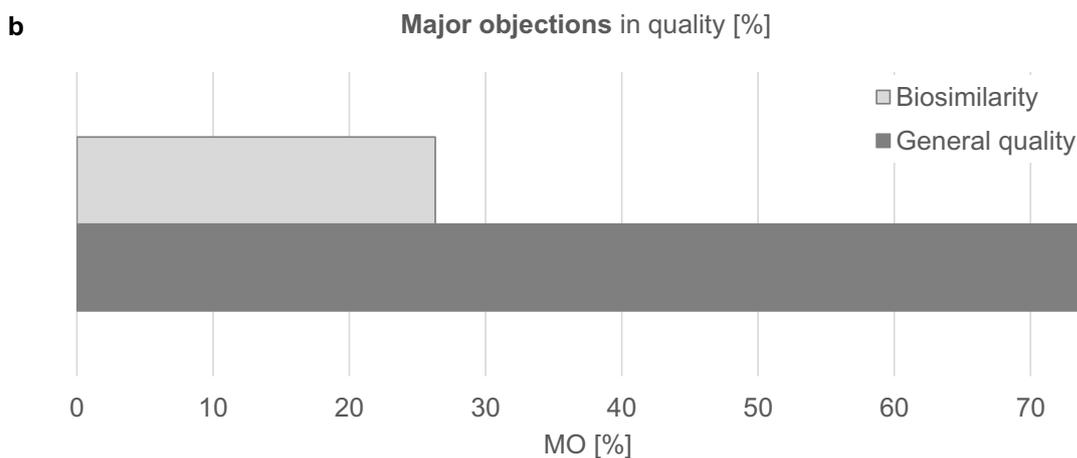
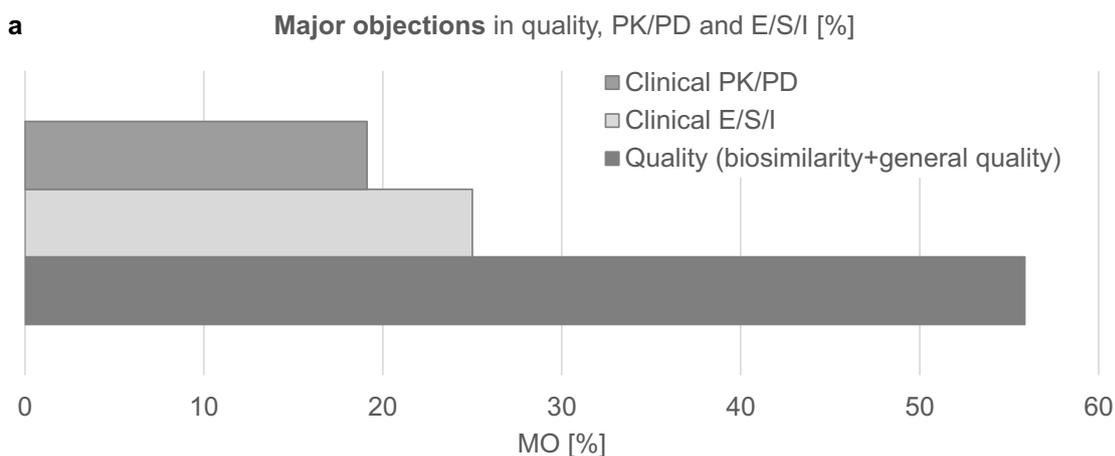
Scenario 2 applies to two cases with an unsatisfactory quality/CMC package but with overall acceptable clinical trial results (Fig. 1, Scenario 2). In these two cases [43, 44], major concerns were raised regarding the biosimilarity exercise as well as regarding the comparability of the clinical batches and the commercial batches of the biosimilar. The clinical PK and efficacy trials formally met their primary endpoints. However, uncertainties remained for the clinical efficacy trial regarding secondary and subgroup analyses for the rituximab biosimilar candidate [43]. Both applications were withdrawn by the companies owing to major remaining uncertainties expressed in unresolved quality MO.

Scenario 3 was defined as those product candidates having an acceptable quality/CMC package but indicating differences in the clinical PK/PD profile or remaining questions regarding representativeness of test material used in the PK study, while all other clinical data demonstrated comparability (Fig. 1, Scenario 3). Two of the biosimilar candidates analysed [45, 46] had an initially failed PK study. In both instances, it was argued that the observed differences in glycan structures known to affect PK (high mannose content)

were too small to explain the initially observed PK differences [58]. The conduct of a second PK trial with improved design features was requested and led to successful demonstration of similar PK profiles [59]. For a third biosimilar candidate, PK results were not accepted because the test product was not deemed representative of the commercial product [47].

Scenario 4 lists those cases with an acceptable quality/CMC package and successful PK trial but with issues regarding the clinical E/S/I package (Fig. 1, Scenario 4). For both affected trastuzumabs [48, 49] the primary efficacy endpoint was formally not met as the upper limit of the confidence interval (CI) was not contained within the pre-defined equivalence margin. For both trastuzumabs, a MA was granted based on the convincing quality/CMC, PK, safety and immunogenicity data packages, despite a failed primary endpoint.

The last hypothetical scenario would be unconvincing quality/CMC data and failed clinical trials (PK and efficacy trial), which was not observed in any of the 36 cases (Fig. 1, Scenario 5).



c

Case	Quality MO	Clinical MO		% of biosimilar candidates applicable to each case*
		PK/PD	E/S/I	
1	Green	Green	Green	42
2	Red/striped	Green	Green	11
3	Green	Red/striped	Green	22
	Green	Red/striped	Red/striped	
4	Red/striped	Green	Red/striped	25
	Red/striped	Red/striped	Green	
	Red/striped	Red/striped	Red/striped	

*green/no pattern indicates no MO in the respective area (quality/CMC, PK/PD, E/S/I); red/striped indicates at least one MO in the respective area

3.2 Analysis of First Regulatory Assessment Reports

For the majority of biosimilar candidates analysed (34/36), the LoQ raised by the CHMP in the D120 AR was adequately addressed by the applicants and thus led to the final approval.

Analysing the number of MO for the 36 biosimilar candidates concerning scientific issues indicates that 56% of MO were related to quality/CMC, 19% to clinical PK/PD and 25% to clinical E/S/I issues, respectively (Fig. 2a). Within the quality/CMC part, the majority of MO dealt with general

Fig. 2 Analysis of questions raised in the first assessment report of the MAA procedure. MO are classified in same manner as for the MAA outcome analyses. In case of MO within multidisciplinary aspects, the specific itemised questions were analysed and distributed according to their content to the quality/CMC or clinical (PK/PD, E/S/I) categories. MO regarding formal aspects were not included in the analysis because these are not of direct scientific concern. **a** For the comparison of the percentage of MO raised with regard to quality/CMC or clinical aspects of the MAAs, the sum of MO (quality/CMC, clinical PK/PD and clinical E/S/I) was calculated and normalised to the number of all MO. **b** MO related to the quality/CMC of the biosimilar candidate were analysed in more detail. Here the number of MO with regard to general quality/CMC or biosimilarity aspects was divided by the sum of all quality/CMC MO. **c** Based on the D120 AR, biosimilar candidates were categorised to four different cases with no MO (green/no pattern) or at least one MO (horizontal red stripes) in the respective area. The percentage of candidates represented by the different cases is indicated. CMC chemistry manufacturing and control, D120 AR day 120 assessment report, E/S/I efficacy, safety, immunogenicity, MAA marketing authorisation application, MO major objections, PD pharmacodynamics, PK pharmacokinetics

pharmaceutical issues rather than biosimilarity aspects (Fig. 2b).

Analysis of OC revealed a similar distribution with 64% of OC pertaining to the quality of the biosimilar candidates, 12% to PK/PD and 24% to E/S/I (data not shown).

When categorising the 36 biosimilar candidates based on where MO were raised, i.e. quality versus PK/PD versus E/S/I, we differentiated four cases, depending on whether MO were identified and knowing that any unresolved MO would prevent approval. We differentiated case 1 when assessment of quality and clinical parts of the dossier led to no MO (positive alignment) in 42% (15/36) of the MAAs analysed, thus supporting biosimilarity. Case 2 was when the quality assessment led to MO that, if not resolved, would lead to rejection of the filing. This applies to 11% (4/36) of MAAs analysed. For case 3, when quality assessment supported biosimilarity but clinical queries challenged the validity of the package, 22% (8/36) of cases were identified (8% of cases with MO regarding PK/PD, 11% with MO regarding E/S/I and 3% regarding both PK/PD and E/S/I). And finally, case 4, when both quality and clinical packages raised concerns (negative alignment), with 25% (9/36) of MAAs analysed (Fig. 2c).

The main reasons for MO are summarised in Table 1.

3.3 Evaluation of Analytical Biosimilarity and Clinical Comparability for Rituximab and Trastuzumab Biosimilars

Rituximab and trastuzumab biosimilar products were selected for further in-depth analysis of quality/CMC (Online Resource 1, Table 2; Fig. 3) and clinical data (Online Resource 2–5, Table 3) as these included withdrawn applications.

3.3.1 Comparison of Analytical Biosimilarity Across Products

The number of biosimilar batches analysed per product varied between 3 and 40, for most QAs. The analytical comparability packages of the rituximab and trastuzumab biosimilars comprised between 35 and 85 individual assays per product. For most of the QAs, orthogonal analytical methods were used.

Rituximab is an IgG1 kappa type mAb directed against CD20 expressed on the surface of pre-B and mature B lymphocytes, but not on hematopoietic stem cells and terminally differentiated antibody-producing plasma cells or other tissues. Upon binding to CD20, rituximab mediates B cell lysis (leading to B cell depletion) by three distinct mechanisms of action (MoAs): complement dependent cytotoxicity (CDC), antibody dependent cellular cytotoxicity (ADCC) and apoptosis [60]. Therefore, the biological activity of rituximab is determined by a combination of CD20 binding assay and an apoptosis induction assay, together with fragment crystallisable (Fc) functionality. Besides activating the pathways of CDC and ADCC, binding of rituximab to its target (CD20 expressed on B cells) also triggers apoptosis via the caspase signalling pathway [61]. Antibody-dependent cellular phagocytosis (ADCP) has been further implicated as plausible MoA of rituximab in its killing of chronic lymphocytic leukaemia cells [60, 62].

Trastuzumab is an IgG1 mAb which binds to human epidermal growth factor receptor 2 (HER2), a transmembrane oncoprotein overexpressed in approximately 20–25% of invasive breast cancers [63]. Binding of trastuzumab to HER2 inhibits ligand-independent HER2 signalling and prevents the proteolytic cleavage of its extracellular domain, an activation mechanism of HER2. As a result, trastuzumab inhibits the proliferation of human tumour cells that overexpress HER2. Therefore, the biological activity of trastuzumab is determined by the combination of HER2 binding assay and an inhibition of cellular proliferation assay, together with Fc functionality. However, in contrast to rituximab, CDC activation is not thought of as a MoA of trastuzumab [64].

For other fragment antigen binding (Fab) mediated assays, glycan and purity profile and charge variants we followed a similar categorisation as in our previous paper [13]. Additional assays include, for example, ADCP for both rituximab and trastuzumab, and inhibition of vascular endothelial growth factor (VEGF) secretion for trastuzumab.

Online Resource 1 provides a summary of the analytical biosimilarity results for approved rituximab (products A–C) and trastuzumab (D–I) biosimilars, and Table 2 provides a summary of the instances where less than 100% of batches were within the reference range and how the resulting uncertainty was resolved.

Table 2 QAs with < 100% of batches meeting similarity ranges and how the resulting uncertainty during MAA was resolved

	QA	Percentage of batches within the similarity range	How resolved
Rituximab			
Product B	Cell based CD20 binding assay	≥ 90% of batches	Minor difference not expected to affect the clinical performance of the product Slight differences explained and justified by the method variability
Products B and C	Binding to several Fcγ-Receptors (FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa-158 f/f and FcγRIIIb)	Variable, see Online Resource 1	Minor differences in binding results, similarity confirmed in cell-based functional assays
Product B	Binding to FcγRIIIa 158 v/v	80–50% of batches	Viewed as sufficient based on ADCC assay results
Product C	Binding to FcRn	≥ 90% of batches	Based on regulatory experience and the results from the comparative PK study, the minor difference was seen as negligible
Product A–C (all)	Glycosylation (6 attributes)	Variable, often < 90%, see Online Resource 1	Similarity confirmed in cell-based functional assays No clinically significant difference in PK profile
Product A–C (all)	Purity testing	Variable, often < 90%, see Online Resource 1	Based on regulatory experience, the small difference was seen as negligible. In most cases, purity of biosimilar was marginally increased
Product A–C (all)	Charge variants	Variable, often < 90%, see Online Resource 1	Acceptable based on product understanding
Trastuzumab			
Product D and F	Protein content	≥ 90% of batches	The small difference in protein content was concluded to be of no clinical relevance. Batch-to-batch variability of the biosimilar within the expected range
Product I	Inhibition of cellular proliferation	80–50% of batches	Slight differences explained and justified by the method variability
Product I	Binding to FcRn	80–50% of batches	Based on regulatory experience and the results from the comparative PK study, the minor difference was seen as negligible
Product D, E, I	Binding to several Fcγ-Receptors (FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa-158 f/f and FcγRIIIb)	Variable, see Online Resource 1	Minor differences in binding results, similarity confirmed in cell-based functional assays
Product I	Binding to FcγRIIIa 158 v/v	≥ 90% of batches	Minor differences viewed as irrelevant based on ADCC assay results
Product D–I (all)	Glycosylation (6 attributes)	Variable, often < 90%, see Online Resource 1	Similarity confirmed in cell-based functional assays No clinically significant difference in PK profile
Products D–I (all)	Purity testing	Variable, often < 90%, see Online Resource 1	Based on regulatory experience, the small difference was seen as negligible
Products D, E, F, H, I (all except G)	Charge variants	Variable, often < 90%, see Online Resource 1	Acceptable based on product understanding
Products G, I	ADCP	< 50% of batches or not done	Acceptable based on FcγRIIIa assay results, considered surrogate for ADCP function
Products D, G, H, I	Inhibition of VEGF secretion	< 50% of batches or not done	The assays are not considered as critical, differences accepted based on the totality of evidence presented for similarity

ADCC antibody dependent cellular cytotoxicity, ADCP antibody dependent cellular phagocytosis, FcRn neonatal Fc receptor, QAs quality attributes, MAA marketing authorisation application, PK pharmacokinetics, VEGF vascular endothelial growth factor

Key quality requirements	Withdrawn rituximab biosimilar candidate	Withdrawn trastuzumab biosimilar candidate
In-depth knowledge of the RP		
The main MoA is known and demonstrable	✓	✓
CQA are known	✓	✓
Sufficient (representative) batches of the RP are analysed	✗	✗
Adequately established QTPP	✗	✗
Attributes of the biosimilar candidate		
The manufacturing process is well controlled. Release and stability specification limits are appropriate	✗	✓
The quality profile of the batches used to generate clinical biosimilarity data is representative of the quality profile of the proposed commercial batches	✗	✗
Suitable and appropriately qualified analytical methods used for analytical and functional similarity assessment	✓	✗
Biosimilarity exercise		
Adequate overall approach for demonstrating biosimilarity	✓	✗

Fig. 3 Analysis of quality requirements for biosimilars withdrawn by the applicant during the review process. For the withdrawn biosimilar applications key relevant quality requirements (and if they were met) were analysed (applications withdrawn for commercial reasons

not included). *BS* biosimilar candidate, *CQA* critical quality attributes, *MoA* mechanism of action, *QTPP* quality target product profile, *RP* reference product

High similarity [$\geq 90\%$ of batches within range (solid dark and light-green horizontal stripes)] was found for protein content, biological activity (CD20 binding and apoptosis induction for rituximab, and HER2 binding and inhibition of cellular proliferation assay for trastuzumab), Fc γ RIIIa binding, neonatal Fc Receptor (FcRn) and C1q binding, ADCC and CDC for almost all rituximab and trastuzumab biosimilars. Exceptions included inhibition of cellular proliferation for one trastuzumab (product I), FcRn for one rituximab (product C) and one trastuzumab (product I) biosimilar and the high affinity Fc γ RIIIa v/v genotype for one rituximab (product B). However, as seen in Table 2, in most cases these differences were considered within the method variability or viewed as sufficiently justified based on high similarity found in other critical QAs (CQA) (i.e., ADCC for Fc γ RIIIa v/v), the results from PK comparability studies and regulatory experience. None of the authorised trastuzumab biosimilars displayed CDC activity (represented as dark-green vertical stripes in Online Resource 1), which is expected.

More variability was found for binding to other Fc γ receptors, purity and glycosylation profile, charged variants

and additional assays (Online Resource 1). Again, as seen in Table 2 the observed differences in Fc binding assays and the glycan profiles were accepted because similarity was confirmed in biological assays. Moreover, afucosylation was 100% within range for all except one trastuzumab biosimilar (product G). Differences in purity and charge variants were seen as negligible based on regulatory experience and product understanding, and differences in additional assays were accepted based on the totality of the evidence presented for similarity.

3.3.2 Comparison of Analytical Biosimilarity for Withdrawn Products

Figure 3 represents the key quality/CMC requirements and whether these were met for the two withdrawn biosimilar applications [43, 44]. These key requirements were categorised following the classification from Bielsky et al. [56].

Of the quality/CMC requirements included, less than half were met for either of the products. Regarding the RP characterisation, both applicants failed to demonstrate two out of four of the prerequisites, demonstrating in both cases an

Table 3 Discrepancies in clinical attributes and how the resulting uncertainty during MAA was resolved

	Clinical attribute	Observation	How resolved
Rituximab			
Rixathon/Riximyo	PK	C _{max} 1 slightly exceeded the upper limit (i.e. 126%)	<ol style="list-style-type: none"> 1. Primary endpoint (AUC) met 2. C_{max}2 was within the standard acceptance limits and therefore, the criterion of bioequivalence was met
Truxima/Blitzima/Ritemvia	PK	AUC _{t-inf} outside of acceptance limits	<ol style="list-style-type: none"> 1. Primary endpoints (AUC_{0-last}, AUC_{0-inf}, C_{max}) met 2. Deviation seen as minor; all other secondary endpoints met standard acceptance limits
Rixathon/Riximyo	PFS	HR of 1.33 (0.98, 1.80)	<ol style="list-style-type: none"> 1. Primary endpoint (ORR) met 2. Study not designed to demonstrate equivalence for PFS 3. Conclusion of biosimilarity based on overall biosimilarity assessment
Rixathon/Riximyo	OS	HR of 1.03 (0.59, 1.80)	<ol style="list-style-type: none"> 1. Primary endpoint (ORR) met 2. Study not designed to demonstrate equivalence for PFS 3. Conclusion of biosimilarity based on the overall biosimilarity assessment
Trastuzumab			
Ontruzant	bpCR (RD)	95% CI not fully contained within prespecified equivalence margin	<ol style="list-style-type: none"> 1. Justified by confounding effect of ADCC shift in reference lots 2. Conclusion of biosimilarity based on the overall biosimilarity assessment
Kanjinti	pCR in breast tissue and axillary lymph nodes (RD and RR)	95% CI not fully contained within prespecified equivalence margin	<ol style="list-style-type: none"> 1. Justified by confounding effect of ADCC shift in reference lots 2. Additional functional analysis for ADCC performed 3. Additional analysis adjusting for subjects exposed to IMP with low ADCC 4. Conclusion of biosimilarity based on overall biosimilarity assessment
Kanjinti	pCR (only breast) (RD and RR)-except RD in PP	95% CI not fully contained within prespecified equivalence margin	<ol style="list-style-type: none"> 1. Justified by confounding effect of ADCC shift in reference lots 2. Additional functional analysis for ADCC performed 3. Additional analysis adjusting for subjects exposed to IMP with low ADCC 4. Conclusion of biosimilarity based on overall biosimilarity assessment
Zercepac	DOR, PFS, OS	Seemingly better efficacy (HR < 1)	<ol style="list-style-type: none"> 1. Study not designed to demonstrate equivalence for PFS 2. No significant differences found in second interim analysis 3. Conclusion of biosimilarity based overall biosimilarity assessment
Withdrawn rituximab biosimilar candidate	Deaths	Eight patients died in the product arm versus none in the reference arm	<ol style="list-style-type: none"> 1. Chance finding likely 2. Study not designed to evaluate hard clinical endpoints

ADCC antibody dependent cell-mediated cytotoxicity, AUC area under the curve, AUC-inf AUC to infinity, C_{max} maximum concentration, pCR pathologic complete response, bpCR breast pathologic complete response, CI confidence interval, C_{max} peak concentration, DOR duration of response, HV healthy volunteers, HR hazard ratio, IMP investigational medicinal product, MAA marketing authorisation application, ORR overall response rate, OS overall survival, PFS progression-free survival, PK pharmacokinetic, PP per protocol, RA rheumatoid arthritis, RD risk difference, RR risk ratio

in-depth knowledge of MoA and CQA of the RP but failing to analyse enough representative RP batches or to adequately establish the quality target product profile (QTTP). Regarding the biosimilar candidate attributes, out of the three prerequisites, only one was met for each product. The quality/CMC package included suitable and qualified analytical methods for the withdrawn rituximab and an adequate manufacturing process for the trastuzumab. However, none of the other requirements were met, including the representativeness of clinical and commercial batches or the use of additional orthogonal assays. Finally, only the withdrawn rituximab included an adequate overall approach for demonstrating biosimilarity.

3.4 Results of Clinical Comparability Studies

Clinical data are presented as raw data in Online Resource 2–5 (the product rows are not in the same order as Online Resource 1 to maintain anonymity). Table 3 provides a summary on all the uncertainties in clinical data, and how these were resolved.

3.4.1 PK Studies

3.4.1.1 Rituximab For all rituximab biosimilars, PK studies were performed in patients with rheumatoid arthritis (RA) with supportive PK data from oncology patients as part of the efficacy studies. With regard to the withdrawn rituximab application, a comparative efficacy study (in RA) that included PK similarity as a secondary objective was conducted prior to a dedicated comparative PK study [in non-Hodgkin's lymphoma (NHL)] [43]. Length of follow-up ranged from 24 to 25 weeks (26 weeks in case of the withdrawn application). Primary endpoints [area under the curve to infinity (AUC_{inf}), maximum concentration (C_{max}) and AUC from time of administration up to the time of the last quantifiable concentration (AUC_{last}) were contained within the pre-specified acceptance range for all approved biosimilars and secondary endpoints supported biosimilarity. Although for the withdrawn rituximab the pre-defined equivalence margin was 70–143% in the PK comparability study, the 90% CIs of the primary endpoints also met the standard equivalence margin of 0.8–1.25. As seen in Table 3, in two cases [26, 27, 53, 54, 65], results of a secondary endpoint were found outside of the standard acceptance limits, but deviations were seen as minor and not clinically relevant. Detailed information on the PK studies is available in Online Resource 2.

3.4.1.2 Trastuzumab For all trastuzumab biosimilar candidates, PK studies were performed in healthy subjects with supportive PK data obtained in clinical trials in oncology patients. For the withdrawn trastuzumab application, an

additional PK similarity study in healthy subjects was submitted. Length of follow-up of the PK studies ranged from 56 to 99 days (53 days in case of the withdrawn application). In all cases, the primary endpoints (AUC_{inf}, C_{max} and AUC_{last}) were contained within the pre-specified acceptance range and secondary endpoints supported biosimilarity. Detailed information on the PK studies is available in Online Resource 4.

3.4.1.3 Population PK Population PK (PopPK) was performed for some products, using different approaches [28, 37–39, 49]. Absence of PopPK analysis was accepted where PK similarity had been demonstrated in the dedicated PK study and PopPK was seen as supportive in the other cases.

3.4.2 Clinical Efficacy Studies

3.4.2.1 Rituximab Rituximab is currently approved in seven indications, both autoimmune and oncological [66]. Two applicants, including the one for the withdrawn rituximab MAA [27, 43, 53, 65], chose to compare efficacy in RA subjects as a model indication and the remaining two [26, 28, 54] chose follicular lymphoma (FL). Length of follow-up was up to 3 years. Overall response rate (ORR) was chosen as primary endpoint in FL and disease activity score using 28 joint counts (DAS28) or American College of Rheumatology Response (ACR 20) for RA. Detailed information on the efficacy studies is available in Online Resource 3.

3.4.2.2 Trastuzumab Trastuzumab is currently approved in three indications [67]. For three biosimilars [37–39] metastatic breast cancer (MBC) was chosen as model indication in the pivotal clinical trial and for the remaining four, including the withdrawn MAA [36, 44, 48, 49], early breast cancer (EBC) was used. Length of follow-up was up to 3 years.

Three applicants chose ORR and the remaining four pathologic complete response (pCR) as the primary endpoint. Pre-specified equivalence margins for risk difference (RD) varied even though patient populations were the same as different reference studies were used for clinical and statistical justifications [37, 39, 48, 49]. Detailed information on the efficacy studies is available in Online Resource 5.

Table 3 shows those instances where some differences were found and how the remaining uncertainties were resolved. For two products [48, 49], the 95% CI of the difference in the pCR rates between treatments was not fully contained within the pre-defined equivalence margin, thus superiority of the biosimilar cannot be excluded.

3.4.2.3 Safety and Immunogenicity The overall safety and immunogenicity profiles were compared descriptively and

appeared similar between the biosimilars and the RP, as reviewed in detail by Kurki et al. [68].

With regard to the withdrawn rituximab biosimilar candidate application [43], the overall safety profile appeared to be similar in patients with RA but imbalances in adverse events (AEs), serious adverse events (SAEs), severity and deaths were observed in the comparative PK study in patients with NHL. Eight patients died in the product arm versus none in the reference arm; investigators assessed the causal relationship as not (6/8) or unlikely (2/8) related to study drug for all fatal SAEs.

4 Discussion

When considering any change in the current requirements for comparative efficacy studies for biosimilar mAb and fusion protein developments, a fundamental concern of stakeholders including patients, physicians and regulators is that biosimilar product candidates with demonstrated analytical/functional comparability could nevertheless translate into failed clinical comparability. The concern is that in the absence of such clinical trial data, a biosimilar might be inappropriately approved based on quality data only.

Our study shows that this concern is not supported by data and that regulatory decision-making follows a totality-of-the-evidence approach with the main focus on the pharmaceutical quality/CMC (biosimilarity, general quality) and PK similarity aspects. In our opinion, a clinical efficacy study may not need to be routinely requested. In the following parts, we discuss evidence obtained from different analyses performed and its implications.

4.1 Discussion of MAA Evidence and Results

We analysed the MAA reviews of biosimilar mAbs and fusion proteins performed by the EMA CHMP and found that in most cases (29/36 cases) good quality/CMC packages were matched with successful clinical trials leading to MA. Interestingly, good quality/CMC packages could also be paired with formally failed efficacy studies, which were evaluated to be due to reasons not related to the biosimilar candidate, thus permitting MA (see discussion of analysis of clinical comparability for rituximab and trastuzumab biosimilars including withdrawn biosimilar candidates below).

On the contrary, unconvincing quality/CMC data paired with successful clinical trials precluded MA, primarily due to the lack of demonstration of sufficient pharmaceutical quality and/or analytical/functional similarity with the RP [43, 44].

In our analysis, there was only one case where clinical data analysis led to a MO with a divergent position published by the CHMP [15] (Annex) which nevertheless received

MA. The issue was later resolved by more mature follow-up data, which did not confirm the objections regarding potentially increased immunogenicity of the biosimilar [69].

For three of the biosimilar candidates analysed [45–47] PK studies were deemed insufficient, which led to the conduct of a new, acceptable PK trial. The reasons for repeating the PK trials were due to methodological issues and differences in the formulation buffer [59] or because of representativeness of the test product used [47]. For two biosimilar candidates the PK data submitted in the initial MAA raised major questions regarding biosimilarity. However, re-analysis of the data, which was already pre-specified in the statistical analysis plan, led to the conclusion that PK similarity was shown [18, 21]. Taking this into account, our analysis indicates that, where biosimilarity was shown at the quality/CMC level, this always translated into PK similarity of the biosimilar candidates with the RP.

4.2 Discussion of Analysis of First Regulatory Assessment Reports

We investigated whether the MAA outcome could have been predicted based on the evidence generated solely in the quality dossier. We found that the quality and clinical assessments aligned in 67% of cases, i.e. both quality and clinical data packages, were considered sufficient to support a MA, or both the quality and clinical data packages were not accepted. In 11% of cases, MO were identified in quality parts of the submission, whereas the clinical data supported biosimilarity.

Of particular interest are those 22% of cases (11% E/S/I only) where no MO were observed in the quality part, but MO were raised on the clinical data. Without further regulatory deliberation and additional justifications from the applicants, these cases could have resulted in false negative conclusions, i.e. a true biosimilar being rejected due to issues with clinical studies. However, even in those cases where the efficacy trials formally failed, biosimilarity was ultimately accepted by EMA based on the demonstration of analytical/functional comparability and comparable PK profiles. In each instance, identified issues in the clinical package were eventually accepted as the result of unanticipated problems such as imbalances in trial arms, immaturity of secondary endpoint data at the time of MAA submission, changes in the QA of the RP or even chance findings. In some cases, a further in-depth sensitivity analysis improved the understanding of the clinical data and facilitated a positive conclusion. These cases highlight that for biosimilar mAbs and fusion proteins, the analytical and functional characterisation data are the most critical for decision making and regulatory approval.

In summary, our analyses of MAAs and first regulatory assessment reports show that the quality/CMC part of the dossier is predictive for the MA of a biosimilar candidate.

4.3 Discussion of Analysis of Analytical Biosimilarity for Rituximab and Trastuzumab Biosimilars

Since our analyses included the two withdrawn MAs, we reviewed to what degree thorough analysis of the quality/CMC package could have been predictive for the clinical outcome. These two substance classes are particularly interesting, as the two originator mAbs are used in oncology (rituximab, trastuzumab) and/or in autoimmune indications (rituximab). Based on information provided in the MAA, and following the scientific evaluation carried out by EMA CHMP, for approved rituximab and trastuzumab biosimilars, we found that over 90% (and in most cases 100%) of the biosimilar batches met the EU reference product similarity range for CQAs such as protein content, biological activity (CD20 binding and apoptosis induction for rituximab and HER2-binding and inhibition of cellular proliferation assay for trastuzumab), Fc γ RIIIa binding, FcRn and C1q binding, ADCC and CDC.

A lower percentage of biosimilar batches were within the similarity range for QAs which are considered less critical (glycosylation profile, charge variants or additional assays). Furthermore, as seen in Table 2, in all instances where uncertainties were raised, these were resolved considering the close similarity demonstrated in CQAs, the results of PK studies and overall, the totality of the evidence.

In no case were clinical trial data necessary to resolve residual uncertainties regarding the quality part. As seen in Fig. 1 (Scenario 4), for the withdrawn MAs, clinical data was also not sufficient to justify the differences in the quality/CMC package. This is in line with previous findings [13, 56] and further demonstrates that the array of orthogonal methods that are submitted in the quality/CMC package are robust and predictive of clinical outcome.

4.4 Discussion of Analysis of Clinical Comparability for Rituximab and Trastuzumab Biosimilars Including Withdrawn Biosimilar Candidates

For all rituximab and trastuzumab biosimilar candidates studied, a comprehensive clinical program was submitted according to the relevant EMA guidelines, i.e. consisting of at least one PK study and a clinical efficacy study, which confirmed biosimilarity in all but two instances [36–39, 44, 48, 49].

For all rituximab biosimilars included in the analysis, PK results were obtained in one therapeutic area and confirmed in a subset of patients in the second therapeutic indication either by supportive PK analysis [26, 27, 43, 53, 54, 65] or by PopPK analyses [28]. In no instance were deviating results observed. One applicant [26] removed PopPK in a protocol amendment which was acceptable to the regulators. In our opinion, this redundancy of PK evaluations should no longer be necessary, as besides CD20 no other antigen or target is involved in rituximab's binding and MoA. This has been demonstrated by the tissue specificity in several human tissue cross reactivity studies [66, 70].

In our study, in all cases except for the withdrawn applications, remaining uncertainties regarding clinical data were resolved based on a strong quality/CMC package, together with demonstrated PK similarity and considering that the studies were not powered to demonstrate similarity with regard to secondary endpoints. Moreover, regarding safety, it should be noted that clinical trials are not powered for safety endpoints, since this is considered unnecessary according to EMA guidelines and would usually require several thousand study participants.

Therefore, the value of extensive analyses of secondary endpoints in efficacy trials remains questionable, as they were either viewed as inconclusive [27, 53, 65], or immature [26, 54].

For both trastuzumab cases [48, 49], EMA concluded that it was likely that the apparent difference was caused by a noted downward “shift” in ADCC activity in some of the RP batches and did not preclude approval. These findings have been discussed in the literature [56, 71, 72] and also demonstrate that physicochemical methods and functional assays are able to detect differences in functional attributes with predictive character. With regards to the withdrawn trastuzumab biosimilar [44], a conclusion on biosimilarity from a safety point of view was precluded as the clinical batches were not considered representative for the commercial product.

Several authors [56, 59, 73–75] pointed out limitations of indiscriminate clinical efficacy studies in light of technical advances in analytical methods, which provide more discriminative research tools sparing patients from entering unnecessary and redundant clinical trials.

It is known from the literature that the recommended doses of many mAbs are in the flat part of the dose-response curve, e.g. half of the administered dose of rituximab would result in the same clinical outcome, suggesting the overall equivalence of 2×500 mg with the licensed dose of 2×1000 mg for clinical efficacy outcomes [76], thus rendering clinical trials insensitive tools to assess biosimilarity. Some authors argue that treatment response to rituximab in RA is only determined by the level of B cell depletion, regardless of how it is achieved [76–79], yet it is important

to measure binding and all functional activity. In our analysis we found that rituximab binding to the CD20 receptor plus all four important MoAs of rituximab [60] were adequately measured by appropriate analytical testing and that for the successful quality/CMC dossiers > 90% of batches met the required similarity ranges.

4.5 General Discussion on Current Flexibility in Clinical Trial Requirements

Our analysis revealed that there is regulatory flexibility in the acceptability of clinical data packages. This is, for example, evidenced by the acceptance of different primary endpoints such as DAS28 versus ACR20 in RA trials, different methods of analyses such as RD versus risk ratio (RR), or different equivalence margins for the same study population depending on the reference study chosen, provided appropriate scientific justification is given [29, 37, 38, 48].

Currently, most mAb developers are planning to evaluate S/I over one year, as advised by guidelines. However, the primary efficacy analysis is usually performed at a much earlier timepoint [26–28, 37–39]. Based on our analyses of the submitted clinical trial data, as well as on the raw data analysis of Kurki et al. [68], it is clear that most dossiers are submitted with preliminary 4–6 months S/I data, depending on the timepoint of primary efficacy analysis, while the full one-year dataset is submitted later during the evaluation period. In no instance have the conclusions reached after the initial data submission changed after completion of the study after 12 months, suggesting that such long trials are unnecessary. Other authors have concluded that pertinent comparative safety and immunogenicity data will be obtained from the PK trials, which in all instances were shown to support results of the E/S study [68].

We conclude that a sufficiently robust analytical/functional similarity package, together with a PK trial capturing data on safety and immunogenicity would be sufficient for the purpose of regulatory decision making for biosimilar mAbs and fusion proteins. In some case, if it were deemed necessary (e.g. when the MoA of the biologic is poorly understood), a shorter efficacy trial ending at or near the timepoint of primary efficacy analysis could provide additional safety and immunogenicity information.

4.6 Limitation of the Study

Since our study was limited to mAb and fusion protein biosimilars of IgG class, our conclusions may not be applicable to more complex biologics. Furthermore, our analysis is restricted to products that have undergone regulatory assessment and appraisal. Whether there have been biosimilars that failed quality/CMC and/or clinical development and were therefore never submitted for regulatory evaluation

or publication has not been scrutinised in our study. Also, overall, the sample size of 36 was limited by the available submissions to EMA in the previous 10 years. However, to our knowledge this is the largest set of biosimilar MAs analysed to date.

5 Conclusions of Our Study

The results of our analysis show that a comprehensive and convincing quality/CMC package demonstrating high analytical/functional similarity of the biosimilar with the RP is essential for MA. Since the first approval of less complex biosimilars, the analytical techniques have advanced markedly resulting in very sensitive assays for the structural and functional characterisation of even complex mAb molecules.

The concern, that in the absence of comparative efficacy and safety results, a biosimilar candidate might be inappropriately approved based on quality data only, is not supported by our findings. The analytical and biological results can be considered predictive for the clinical performance of the biosimilar candidates.

Based on the combination of modern analytics, control and pharmacovigilance systems in place, as well as requirements on comparability assessment in case of manufacturing changes, clinical performance of IgG biopharmaceuticals is ensured throughout the lifecycle of the product. As shown in our analysis, the CQA that are known to impact clinical efficacy and safety, including immunogenicity, must be closely monitored.

In the authors' opinion, these findings allow a reduction of the clinical development program for regulatory review before MA. This conclusion is further supported by the positive experience in the market gained for biosimilar mAbs approved in the last ten years. Consequently, a revision of the respective regulatory biosimilars guidelines in Europe should be considered, to allow a more rational use of clinical resources and improve the access to innovative and affordable medicines for patients.

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Consent to participate Consent to participate is not applicable to this article as no human or animal subjects were analysed.

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Availability of data and material The datasets analysed for clinical comparability during the current study are available in the EMA repository, which are publicly available at: https://www.ema.europa.eu/en/medicines/field_ema_web_categories%253Aname_field/Human. The datasets generated and/or analysed during the current study for analytical biosimilarity, marketing authorization applications and regulatory assessment reports are not publicly available due to confidentiality issues.

Code availability Not applicable.

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