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Research paper

Comparison of consistency and complementarity of reporting biosimilar quality attributes between regulatory and scientific communities: An adalimumab case study

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ABSTRACT

Biosimilar approval relies on the comparability of quality attributes (QAs), for which information can be derived from regulatory or scientific communities. Limited information is known about whether these sources are consistent with or complementary to each other. The consistency and complementarity of QA reporting in biosimilarity assessments for adalimumab biosimilars approved by the European Medicines Agency in European public assessment reports (EPARs) and scientific publications was assessed. A classification of 77 different QAs (53 structural and 24 functional attributes) was used to assess the types of and information on QAs reported. Six adalimumab biosimilars were analyzed, for which the number of QAs reported in EPARs and publications varied (range = 47 [61%]–60 [78%]). The proportion of QAs consistently reported in both sources varied (range = 28%–75%) among biosimilars; functional QAs (mean = 21 QAs [88%]; range = 19–23) were more consistently reported than structural QAs (mean = 33 QAs [62%]; range = 27–34). The EPARs frequently reported biosimilarity interpretation without providing test results (9–57 QAs in EPARs versus 0–8 QAs in publications), whereas publications frequently reported both test results and interpretations (13–40 QAs in publications versus 0–3 QAs in EPARs). Both sources provided information on the biosimilarity of QAs in a complementary manner and the same biosimilarity interpretation of test results for reported QAs (mean = 90%; range = 78%–100%), with a small discrepancy in biosimilarity interpretations of a few clinically relevant QAs related to post-translation modifications and biological activity. Comprehensive reporting of QAs can contribute to an improved understanding of the role of structural and functional attributes in establishing biosimilarity and the mechanism of action of biological substances in general.

1. Introduction

Since 2006, regulatory authorities have approved biosimilars, which are highly similar and clinically equivalent forms of off-patent reference biologicals. The increasing availability of biosimilars contributes to wider patient access to treatments for a variety of diseases due to the low prices of biosimilars. The regulatory assessment of biosimilars primarily relies on data regarding the comparability of quality attributes (QAs), which must remain within the range of variability established by analyzing multiple batches of the reference biological. Quality attributes are measurable structural or functional characteristics that describe specific physical, chemical, biological or microbial properties of a product [1]. Adalimumab (Humira®, AbbVie Inc.) is a fully humanized monoclonal antibody (mAb) that targets tumor necrosis factor-α [2] and

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has the largest number of approved mAb biosimilars and the broadest spectrum of therapeutic indications among TNF-α inhibitors, including infliximab and etanercept [3].

Stakeholders from the pharmaceutical industry, regulators, payers, healthcare professionals and patients can use different information sources to obtain comprehensive knowledge about the QAs of biosimilars. Two main publicly accessible information sources that report biosimilarity assessments are the regulatory community (e.g., European public assessment reports [EPARs]) and the scientific community (e.g., scientific publications) [4]. An EPAR is a regulatory document published by the European Medicine Agency (EMA) that outlines the regulatory procedures of a specific medicinal product and summarizes the evidence submitted by the applicant and the scientific assessment of the Committee for Medicinal Products for Human Use (CHMP) [5]. Scientific publications are published in peer-reviewed journals, by means of which the results from the biosimilarity assessment of QAs are communicated with the scientific community. For both sources, variation in the reporting of QAs has been acknowledged. A previous study from our group showed substantial variation in the reporting of QAs among the EPARs of various adalimumab biosimilars; the regulatory interpretation on biosimilarity was frequently provided for QAs, but the test results of the QAs were less detailed [6]. We have additionally shown that scientific publications on the biosimilarity assessment of QAs are available for only 60% of all biosimilars approved in the European Union (EU) and the United States, and the reporting of the QA types in these publications is highly variable and frequently incomplete [7].

The QA information available in the two publicly accessible sources is derived from biosimilarity or comparability assessments performed to support the development and marketing applications of biosimilars. The publication of information on QAs assessed to establish biosimilarity is likely influenced by the purpose of the information source. The EPARs represent the regulatory process of the registration dossier submitted by industry, whereas the scientific publications reflect the process of data generated and interpreted by researchers affiliated with academia or industry. Only a limited number of studies have assessed whether and how information presented in these two publicly available information sources overlap. These studies focus on assessing the reporting of safety and efficacy data and have found substantial discord between regulatory reports and scientific publications [8–14]. To our knowledge, there are no studies that explore the reporting of QAs in the two sources and whether these QAs are consistent with or complementary to each other. Because the comparison of QAs is a fundamental step in the development and regulatory process of biosimilars and forms the basis for regulatory assessments of biosimilarity, a comprehensive and consistently reported set of QAs is needed to understand the science behind regulatory approval and increase confidence in biosimilars in clinical practice.

Therefore, the present study aimed to assess the consistency and complementarity of QA reporting in the biosimilarity assessment in EPARs from the regulatory community and in scientific publications from the scientific community using adalimumab biosimilars as a case example.

2. Method

2.1. Study cohort

Data were collected from the two information sources, EPARs and scientific publications, that reported on QAs in biosimilarity or comparability assessments of adalimumab biosimilars that were granted marketing authorization through a centralized procedure of the EMA until May 31, 2020. The EPARs included scientific discussions and technical summaries—after deletion of confidential data—submitted in the registration dossiers by the applicant. The EPARs were updated throughout the product life cycle after regulatory approval; however, only the initial EPARs published at the time of approval were considered for this study. EPARs were retrieved from the official website of the EMA (http://www.ema.europa.eu). Full-text scientific publications in peer-reviewed journals with biosimilarity assessments of adalimumab biosimilars were identified from the PubMed and EMBASE databases according to the search strategy presented in Supplementary Table-S1a–b (search date May 31, 2020). Both scientific publications published before and after biosimilar approval were included. Conference abstracts were not included, as these lack detailed data on QAs. Adalimumab biosimilars for which there were no scientific publications on the biosimilarity or comparability assessment of QAs were excluded.

2.2. Data collection and extraction

Baseline characteristics for each adalimumab biosimilar were collected from each information source, including the company code(s), brand name(s), marketing authorization holder, dates of publication of the initial EPAR and corresponding scientific publications and date of EU marketing authorization. A company code is a specific acronym including letters and numbers assigned by the developer and is used to define the active biological substance produced from the same development program. Certain adalimumab biosimilars are produced by the same manufacturer but marketed under different brand names, for example, Hefiya®, Halimatoz®, Hyrimoz®; however, the company code for these biosimilars is GP2017, for which the registration dossier and corresponding initial EPARs are identical. Thus, the company codes were considered identifiers to confirm that the scientific publications corresponded to the same adalimumab biosimilar described in the EPARs. If multiple brand names were associated with the same company code, only the EPAR of one brand name (e.g., Hefiya® for GP2017) was included in the study for subsequent analysis. The EPARs of brand names with the same company code were cross-checked to ensure that all EPARs presented identical information on biosimilarity assessment. The date of marketing authorization was defined as the calendar month and year when a marketing authorization was granted by the European Commission. The date of publication of the EPAR is generally the same date of the European Commission's decision. The date of publication of a scientific publication was defined as the calendar month and year when a publication first became accessible online.

2.3. Outcomes

The outcomes of this study were (a) the types of QAs and (b) information on the QAs reported in the EPARs or the scientific publications for the included biosimilars.

2.3.1. Types of quality attributes

The QAs reported in the initial EPARs and corresponding scientific publications were mapped according to the classification scheme developed in collaboration with regulators involved in quality assessments of biosimilars [7]. This scheme divided the QAs into structural and functional attributes, including a total of seven types with various subtypes, resulting in a list of 77 (53 structural and 24 functional) QAs identified from publicly available information relevant to a biological drug (Fig. 1).

2.3.2. Information on quality attributes

Information on QAs reported in EPARs and scientific publications was investigated by assessing the extent of the information reported as well as the biosimilarity interpretation of the test result of QAs. The extent of information on QAs reported in each EPAR and corresponding scientific publication was classified into four categories (Table 1). The extent of information on QAs was defined based on the reporting of the test results and biosimilarity interpretation for reported QAs. The test results are presented in terms of the quantitative or qualitative acceptance criteria of a given QA, which included numerical limits, range and distribution, as shown in the examples in Table 1, or other suitable visual assessment measures such as spectra for higher-order structures and

Structural quality attributes (n=53 ,70%)							Functional quality attributes (n=24, 30%)	
Physiochemical properties	Primary structures	Higher order structures	Post transaltions modifications		Purity & Impurities		Biological activity	Immunochemical activity
			Enzymatic PTMs	Non-Enzymatic PTMs	Size variants	Charge variants		
Molecular Mass	Amino acid sequence	Secondary structure	Glycosylation	Glycation	Aggregates	Main forms	Binding activity	Binding to C1q
Protein concentration	C-terminal variants	Tertiary strucutre	Glycosylation site	Oxidation	Sub-micron Particles	Acidic forms	Binding affinity	Binding to FcRn
Isoelectric point	N-terminal variants	Quaternary strucutre	Glycosylation site occupancy	Deamidation	Monomer	Basic forms	Binding specificity	Binding to Fcγ-RI
Visible Particles	Trisulfide variants	Thermodynamics properties	Glycoforms	Truncation	Dimer		Binding to s-TNF	Binding to Fcγ-RIa
Subvisible Particles	Disulfide bridges		Galactosylated glycans	Amidation	Isoforms		Binding to tm-TNF	Binding to Fcγ-RIIa
Hydropphobcity	Thloether Bonds		High mannose glycans	Isomerization	LMWs		Neutralization of TNF	Binding to Fcγ-RIIIa
	Free-thiol SH		Fucosylated glycans	Cysteinylation	MMWs		Inhibition of apoptosis	Binding to Fcγ-RIIb
			Afucosylated glycans	Acetylation	Non-glycosylated heavy chain		Induction of apoptosis	Binding to Fcγ-RIIIb
			Total afucosylated glycans	Formylation			Inhibition of proliferation	Binding to TNF-β
			Sialylated glycans	Methylation			Induction of regulatory macrophages	
			Neuraminic N-acetyl acid (NANA)	Hydroxylation			Inhibition of cytokine release	
			Neuraminic N-glycolyl acid (NGNA)	Phosphorylation			Inhibition of adhesion molecule expression	
			Galactose alpha-1,3-galactose				ADCC activity	
							CDC activity	
							ADCP activity	

Fig. 1. A classification scheme of 77 common quality attributes or a biological drug.

chromatograms for purity and impurities. The biosimilarity interpretation was defined as the interpretation of the test result in terms of biosimilarity for a given QA provided by regulators in the EPARs and independent researchers in the scientific publications. The reporting of the biosimilarity interpretation of the test result of QAs was divided into two types: similar or different. The biosimilarity interpretation was defined as similar when the assessment included wording such as "identical", "same", "match", "(highly) similar", "comparable" and "consistent". The biosimilarity interpretation was defined as different when the assessment included wording such as "(minor) difference(s)" or "not similar".

2.4. Data analysis

The reported QAs identified in EPARs and the corresponding scientific publications of adalimumab biosimilars were coded according to the classification scheme of QAs presented in Fig. 1. The reporting of QAs (yes/no) was identified in each source; then the consistency and complementarity of the two sources in the QA reporting were assessed. A QA was considered consistently reported if it was reported at least once in both EPAR and scientific publications. A QA was considered complementarily reported if it was reported at least once in either EPAR or scientific publications. The same analysis was applied to assess the reporting of the extent of information on QAs for each biosimilar according to the above-mentioned four categories (see Table 1). The proportion of consistently reported QAs and complementarily reported QAs was calculated. For adalimumab biosimilars where the biosimilarity interpretation (with or without the test results being presented) was reported in both EPAR and scientific publication, an assessment of whether both sources had the same interpretation was conducted. The same interpretation was considered if regulators in the EPAR and researchers in the scientific publication came up with the same biosimilarity interpretation of the test result for a given QA in both information sources (i.e. both reported "similar" or both reported "different").

3. Results

3.1. Characteristics of initial European public assessment reports and scientific publications

As of May 31, 2020, the EMA had approved 11 adalimumab biosimilars. These products were developed from seven unique biosimilars since several were marketed under different brand names. Although the marketing authorization holders had voluntarily withdrawn Solymbic®, Cyltezo® and Kromeya® from the EU market for commercial purposes, these were considered in the present study since the study aimed to assess the consistency and complementarity of information on QAs reported in biosimilarity assessments at the time of regulatory approval. For six of the seven unique biosimilars (85%), the biosimilarity assessment of QAs was reported in at least one corresponding scientific publication; one unique biosimilar—BI695501 [15]—was excluded as it had no corresponding scientific publications. Thus, the following unique biosimilars were included for subsequent analysis: ABP501 [16–19], SB5 [20–22], GP2017 [23–26], FKB327 [27,28], MSB11022 [29–31] and PF06410293 [32,33]. The biosimilarity assessments of QAs were available through scientific publications before the publication of the initial EPAR for ABP502, GP2017, MSB11022 and PF06410293. The relevant scientific publications were published, on average, one month (range = 1–29 months, standard deviation = 17 months) before the initial EPARs were available (Table 2).

3.2. Types of reported quality attributes

The number of QAs reported in the EPARs and scientific publications varied among adalimumab biosimilars and ranged from 47 (61%) QAs for PF06410293 to 60 (78%) QAs for FKB327 (Table 3). Overall, the proportion of QAs consistently reported in both the EPARs and scientific publications further varied among biosimilars and ranged from 28% for PF06410293 to 75% for SB5 and FKB327 (Fig. 2). More QAs were presented in the EPARs (range = 36–57 QAs) than in the scientific publications (range = 14–49 QAs). For all biosimilars, both sources provided complementary information on a greater number of QAs than the total QAs reported in each information source individually (e.g., for FKB327, EPAR = 57 QAs, publications = 47 QAs, both sources = 60 QAs; Fig. 2). With respect to the type of QAs, functional QAs were reported more frequently (23/24; 96%) and consistently (mean = 21 QAs (88%); range

Table 1
Definitions of the four reporting categories for the quality attributes (QAs) assessed to establish biosimilarity and reported in the European public assessment reports (EPARs) and corresponding scientific publications.

		Reporting of biosimilarity interpretation of the QAs	
		No	Yes
Reporting of test results for the QAs	No	QAs reported include **no test results and no biosimilarity interpretation of the reported QAs**, for example, - The amino acid sequence and N-glycosylation site were compared. - Protein concentration was determined. - Binding to FcRn and Fcγ-RIIIa was studied, and a comparison of ADCC activity was performed. - Neutralization of TNFα, binding to s-TNFα and binding to tm-TNFα were addressed.	QAs reported include **the biosimilarity interpretation but not test results of the reported QAs**, for example, - The amino acid sequence and N-glycosylation site of the biosimilar were identical to those of the reference. - The protein concentration was similar to that of the reference. - Minor differences with no clinical relevance were observed in glycation, galactosylated N-glycans, high mannose N-glycans, fucosylated N-glycans and sialylated glycans. - The FcRn, C1q binding, CDC, ADCC and neutralization of TNFα were comparable with those of the reference.
	Yes	QAs reported include **the test results but not the biosimilarity interpretation of reported QAs**, for example, - The levels of high mannose N-glycans (biosimilar: 1.9–2.5%; reference: 5.3–12.0%). - The K_D ranges for Fcγ-RIIIa binding (biosimilar: 6.2–10.1 nM; reference: 3.8–8.0 nM) - The EC_{50} values for inhibition of cytokine release (204 pM, 294 pM and 200 pM for the three batches of biosimilars tested and 177 pM, 168 pM and 222 pM for the three batches of reference tested). - The ADCC activity (biosimilar: 89–107%; reference: 84–115%)	QAs reported **include the test results and biosimilarity interpretation of the reported QAs**, for example, - Minor differences with no clinical relevance were observed in the levels of high mannose N-glycans (biosimilar: 1.9–2.5%; reference: 5.3–12.0%). - The ADCC activity (biosimilar: 89–107%; reference: 84–115%) was comparable/similar between the two products.

ADCC, antibody-dependent cellular cytotoxicity; CDC, complement dependent cytotoxicity; EC50, half-maximal effective concentration; TNFα, tumor necrosis factor-alpha; s-TNFα, surface tumor necrosis factor-alpha; tm-TNFα, transmembrane tumor necrosis factor-alpha; Fc, Fragment crystallizable; FcR, Fc receptor; KD, equilibrium dissociation constant; nM, nanomoles; pM, picomoles.

= 19–23) than structural QAs (47/53; 89%; mean = 33 QAs [62%]; range = 27–34) in the EPARs and scientific publications (Table 3). For example, the binding to soluble-TNFα is a functional attribute directly related to the mode of action, which was reported in both information sources for all adalimumab biosimilars (data shown in the supplementary Figure S1). A list of QAs, the type and extent of information on each QA described in the EPARs and corresponding scientific publications for the same biosimilar are presented in Figure S1.

3.3. Information on reported quality attributes

The reporting of biosimilarity interpretation without providing the test results was more frequent in EPARs (range = 9–57 QAs) than scientific publications (range = 0–8 QAs). Conversely, the reporting of test results and biosimilarity interpretations was more common in scientific publications (range = 13–40 QAs) than EPARs (range = 0–3 QAs). The consistency of reporting the extent of information on QAs (as defined in Table 1) between the EPARs and scientific publications of included biosimilars was low and ranged from 0%, which mainly applied to the reporting categories "test results without biosimilarity interpretation" and "test results with biosimilarity interpretation", to 10% for the category "no test results but with biosimilarity interpretation" for FKB327. The EPARs and scientific publications of three biosimilars (ABP501, SB5 and GP2017) lacked test result reporting and biosimilarity interpretation for several of the reported QAs (Fig. 2).

The biosimilarity interpretation for reported QAs (with or without the test result of QAs being presented) was, in general, identical for a majority of reported QAs in the two information sources for included biosimilars. The QAs with same biosimilarity interpretation in both sources ranged from seven out of nine (78%) for ABP501 to 25 out of 25 (100%) for FKB327 and 13 out of 13 (100%) for PF06410293, whereas the QAs with different biosimilarity interpretations in both sources ranged from two out of 45 QAs (4%) for FKB327 to 6 out of 35 (17%) QAs for SB5. The proportion of QAs reported with the same biosimilarity interpretation in both sources was, on average, 90% (range = 78%–100%) for included biosimilars (Table 3). The types of QAs with the same biosimilarity interpretation in both sources were frequently related to biological and immunochemical activity. Different biosimilarity interpretations of the test results between the two sources, where one source indicated similarity while the other indicated (minor) differences for the same QA, was observed for a few QAs among the included biosimilars. The types of QAs with different biosimilarity interpretations in both sources were frequently related to post-translation modifications and biological activity. For example, the biosimilarity interpretation of the test result of glycoforms was "minor differences" for a majority of EPAR and scientific publication pairs, except for the biosimilar SB5, where "minor differences" were reported in the EPAR and "similar" in the publication. Another example is the biosimilarity interpretation of the test result of antibody-dependent cellular cytotoxicity (ADCC activity), which was "similar" for a majority of EPAR and scientific publication pairs, except for the biosimilar GP2017, where "minor differences" were reported in the EPAR and "similar" in the publication. Although the test results of ADCC activity for biosimilars (ABP501, SB5, GP2017, and FKB327) was interpreted as "similar" in pertinent scientific publications, this same biosimilarity interpretation of ADCC activity for ABP501 (60–120%), SB5 (95–142%), GP2017 (85–183%) and FKB327 (69.5–130.9%) was based on different acceptance ranges presented in pertinent publications.

The test results and their biosimilarity interpretations were reported in the EPAR as well as the scientific publications for only two QAs of ABP501 (protein concentration and FcγRIIIa binding) and one QA for MSB11022 (FcγRIIIa binding). For both biosimilars, the same biosimilarity interpretation of the test result of reported QAs ("similar") was reported in both sources, although the numerical value of the test result differed between the two sources with the use of a strict range of acceptance criteria in the scientific publications (Table S2).

4. Discussion

The present study assessed the consistency and complementarity of

Table 2
Characteristics of included European public assessment reports (EPARs) and scientific publications of adalimumab biosimilars.

Company code	Brand name	Marketing authorization holder	EU Marketing authorization date (mm/yy)	Initial EPAR publication date mm/yy (ref.)	Scientific publication date mm/yy (ref.)
ABP501	Amgevita® Solymbic®[a]	Amgen Europe B.V.	03–2017	04-2017 [16,17]	07-2016 [18,19]
SB5	Imraldi®	Samsung Bioepis NL B.V.	08–2017	08-2017 [20]	10-2018 [21,22]
BI695501	Cyltezo®[a]	Boehringer Ingelheim International GmbH	11–2017	11-2017 [15]	None
GP2017	Hefiya® Halimatoz® Hyrimoz®	Sandoz GmbH	07–2018	08-2018 [23–25]	07-2018 [26]
FKB327	Hulio®	Mylan S.A.S.	09–2018	09-2018 [27]	05-2020 [28]
MSB11022	Idacio® Kromeya®[a]	Fresenius Kabi Deutschland GmbH	04–2019	04-2019 [29,30]	11-2016 [31]
PF06410293	Amsparity®	Pfizer Europe MA EEIG	02–2020	02-2020 [23]	01-2020 [33]

[a] Solymbic®, Cyltezo® and Kromeya® were approved by the European Medicines Agency but voluntarily withdrawn by the applicant for commercial reasons.

Table 3
Reporting of types of quality attributes stratified by the company code of adalimumab biosimilars in the European public assessment reports (EPARs) and scientific publications.

	All QAs (n = 77, %)	Types of QAs		QAs with biosimilarity interpretation in both sources (n = QAs with same interpretation, %)
		Structural (n = 53, %)	Functional (n = 24, %)	
All biosimilars	70 (91%)	47 (89%)	23 (96%)	[a]
ABP501	53 (69%)	32 (60%)	21 (88%)	9 (7, 78%)
SB5	56 (73%)	33 (62%)	23 (96%)	35 (29, 83%)
GP2017	53 (69%)	34 (64%)	19 (79%)	16 (13, 81%)
FKB327	60 (78%)	40 (75%)	20 (83%)	45 (43, 96%)
MSB11022	53 (69%)	31 (58%)	22 (92%)	25 (25, 100%)
PF06410293	47 (61%)	27 (51%)	20 (83%)	13 (13, 100%)

[a] No single QA was reported with interpretation in both information sources for all included biosimilars.

the types of and information on QAs reported by regulators in the EPARs and researchers in the scientific publications of adalimumab biosimilars. Overall, the proportion of QAs consistently reported in both sources ranged from 28% for PF06410293 to 75% for SB5 and FKB327. Combining the information on QAs presented in both sources provided a more complete reporting of the biosimilarity assessment. Functional QAs were more frequently and consistently reported than structural QAs, which might be explained by their direct relation to clinical relevance. With respect to the extent of information on QAs, the EPARs more frequently reported biosimilarity interpretation without providing the test results, while the reporting of both test results and biosimilarity interpretation was more common in scientific publications. In general, both sources frequently reported the same biosimilarity interpretation of the test result for reported QAs, while a small discrepancy in reporting the biosimilarity interpretation or the acceptance criteria was detected for a few clinically relevant number of QAs (e.g. glycoforms and ADCC activity).

Along with the surge of biosimilars introduced to the European market over the last decade, the need for comprehensive and reliable information among decision makers (e.g., clinicians, pharmacists, payers and regulators) about the justification of biosimilarity has become pertinent. Data supporting the claim of biosimilarity, particularly those related to QAs, is reported by the EMA in EPARs and has increasingly been reported by industry in scientific publications [7]. The present study identified information for 70 (91%) of the 77 pre-defined QAs in the EPARs and scientific publications of adalimumab biosimilars. As expected, reporting on QAs varied between the two sources among the included biosimilars. This variation was in part due to the different aims of the two sources and was consistent with previous findings of substantial differences in reporting safety and efficacy information in regulatory reports and scientific publications [8–14]. Therefore, both sources should be systematically consulted to obtain comprehensive information on QAs for an improved understanding of how biosimilarity was established at the molecular level.

Functional QAs were more frequently described in EPARs and scientific publications than structural attributes (88% versus 62%). For adalimumab, the binding to and neutralizing of both the soluble and membrane-bound TNF-α were functional QAs relevant to the mechanism(s) of action (MoA), which was consistently reported in both sources for all included biosimilars. By the binding to Fc gamma receptors (FcγRs), and component 1q (C1q), adalimumab can additionally mediate effector functions such as ADCC and CDC activity [34], which were additionally described in both sources for at least five adalimumab biosimilars (Figure S1). The relevance of ADCC or CDC activity to the efficacy of adalimumab is not well established but may be important, particularly in inflammatory bowel disease [3]. The underlying reason for functional attributes to be more comprehensively and consistently reported could relate to the fact that they reflect the clinically relevant MoA and provide useful information in predicting the outcomes of clinical studies [35–37]. Moreover, functional attributes provide not only the final insight into (dis)similarity at the quality level but also the basis for supporting the extrapolation of biosimilars across all indications authorized for the reference product [38–41].

Although we were not able to study the clinical relevance of our findings, it is known that (minor) differences in QAs (e.g., post-translational modifications and size and charge variants) may directly or indirectly impact functional attributes and clinical profiles [42–44]. The clinical profiles of biologicals, including biosimilars, are influenced by structural and functional attributes. Subsets of these attributes are likely related to clinical profiles and are frequently referred to as critical quality attributes (CQAs). Although there is no consensus on which attributes are CQAs, these need to be identified and controlled to ensure that clinical effects and product safety are not impacted by (minor) differences. In practice, (minor) differences in QAs between a biosimilar and reference biological are expected due to different production processes. This further applies to batch-to-batch variability during the life

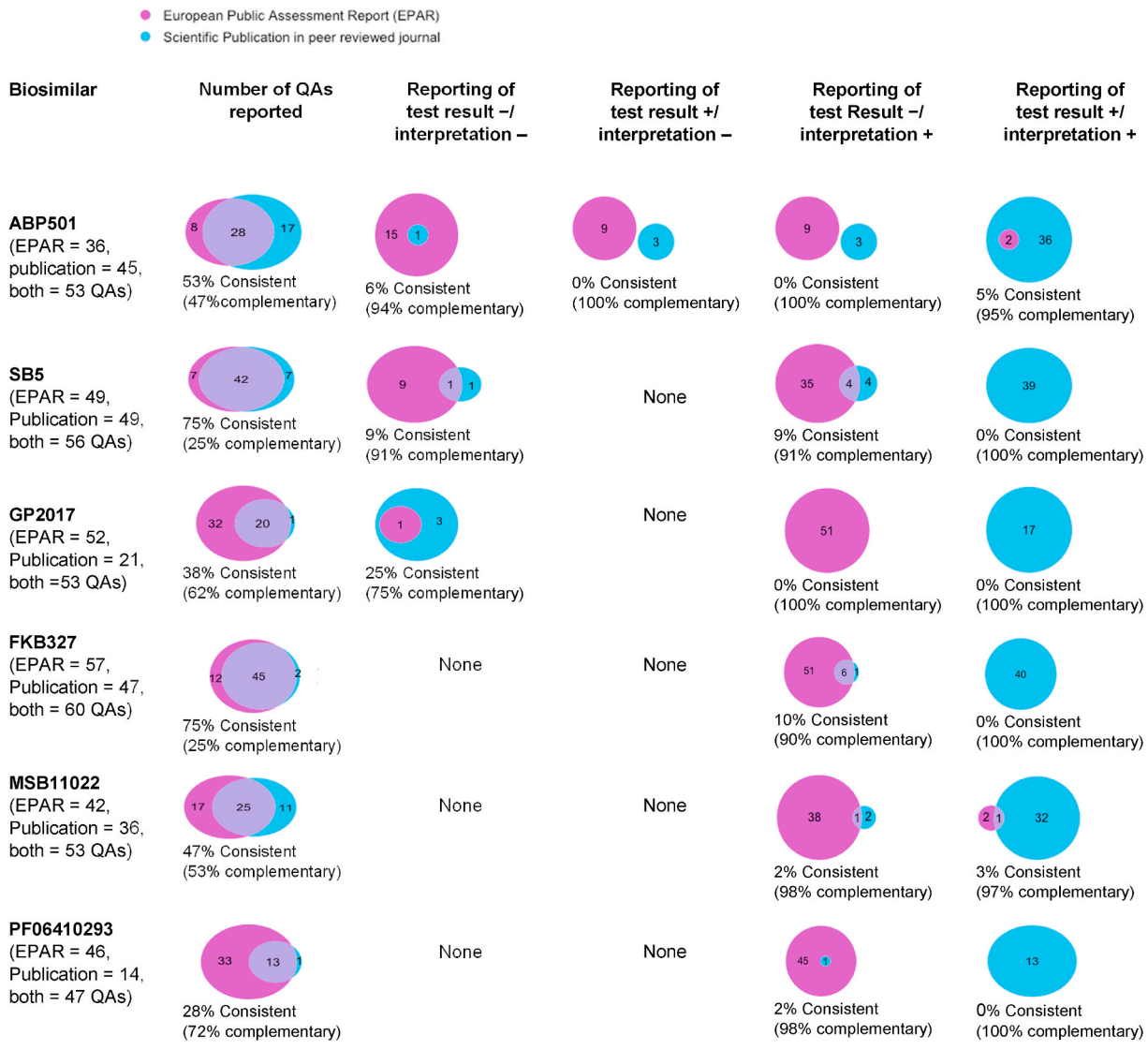

Fig. 2. Proportional Venn diagrams presenting the number of quality attributes (QAs) described in the European public assessment reports (EPARs) and corresponding scientific publications for the adalimumab biosimilars approved in the EU.

cycle of the reference biological due to introducing changes to enhance the production process [45]. The biosimilar only has to show biosimilarity to the reference product as part of the initial approval. After approval, the biosimilar is considered a standalone product and can undergo changes to the production process without the need to show biosimilarity to the reference biological. Examples of the potential clinical impact of structural differences in biologicals include increased immunogenicity due to increased aggregates; a decrease in antibody specificity and affinity due to increased deamidation in the complementarity-region (CDR) and a decrease in neonatal Fc receptor (FcRn) binding leading to an increase in drug clearance due to increased oxidation. It is additionally known that differences in glycoforms can have a significant impact on functional attributes. An increase in afucosylated glycans can positively impact FcγRIIIa binding, leading to increased ADCC activity, while an increase in sialylated glycans negatively impacts FcγRIIIa binding, hence decreasing ADCC activity. Furthermore, an increase in galactosylated glycans leads to increased C1q binding and hence increased CDC, while an increase in high mannose glycans can lead to increased drug clearance.

For the majority of adalimumab biosimilars included in the present study, the reporting of the extent of information on QAs in the two sources was inconsistent but reasonably complementary. For example, biosimilarity interpretation without providing the test results of QAs was frequently reported in the EPARs (range = 9–57 QAs in EPARs versus 0–8 QAs in publications), whereas a combination of the test results and biosimilarity interpretation was frequently present in the scientific publications (range = 13–40 QAs in publications versus 0–3 QAs in EPARs). Although the scientific publications were available before the EPARs for most included biosimilars, both sources provided the same biosimilarity interpretation for a majority of reported QAs. This alignment in biosimilarity interpretation between the two sources is reassuring for the biosimilar system. There was only a small discrepancy in reporting biosimilarity interpretation for the glycoforms and ADCC activity of SB5 and GP2017, respectively. For both examples, the test results were interpreted as having "(minor) differences" in EPARs and being "similar" in publications. The EPARs stated that these (minor) differences were appropriately justified in the dossier and considered clinically meaningless. Nonetheless, the scientific justifications underlying these (minor) differences and the test results were frequently not presented in the EPARs, which did not allow for further insight into the extent of (minor) differences.

This means that for an improved understanding of the science behind the regulatory approval of biosimilars, there is a need to know both the test results and the interpretations. It may be not as important to report

the test results for all QAs but important to place more emphasis on CQAs. The discrepancy in reporting the biosimilarity interpretation of the test results in terms of biosimilarity between the two sources could be explained by the following. (1) The wording chosen to describe the biosimilarity interpretation may differ between the EPAR and publication and be subjective; for example (minor) difference might mean the same as (highly) similar. (2) The test result of QAs presented in publications may differ from those submitted in the dossier for regulatory decision. (3) The acceptance criteria for defining the biosimilarity limit or range of a given QA may differ between the two sources as well as across publications. The acceptance criteria might be influenced by the number and age of batches of the reference product at the time of analysis [46]. Based on our analysis, a more strict biosimilarity range of reported QAs was present in publications when compared to EPARs (Table S2). The publications additionally used different acceptance criteria for biosimilarity, for example, the ranges of ADCC activity for ABP501 (60–120%), SB5 (95–142%), GP2017 (85–183%) and FKB327 (69.5–130.9%), although all the included biosimilars were compared to the same reference product. These differences in the ranges of ADCC activity between publications could be related to the variability between batches of the reference product, which may additionally raise questions on what the range considered by regulators to be acceptable for biosimilarity is.

The differences in QA reporting between the EPARs and scientific publications reflect the different purposes of the two sources (i.e. information affecting regulatory decisions versus information focusing on study and data). Regulators, who have access to a complete quality, nonclinical and clinical data of biosimilars during the regulatory process, may be more concerned with the consistency and accountability of decisions. Researchers, frequently affiliated with biosimilar companies, might be more focused on presenting positive news, that is QAs with favorable results in terms of biosimilarity, such as highly similar attributes. The present study could not detect any signatures of bias, although selective reporting on QAs in both sources could not be excluded and would need further study. For instance, the biosimilarity assessment for functional attributes of GP2017 was only reported in a single scientific publication [26]. The dissemination of a comprehensive biosimilarity assessment of all relevant and critical QAs in the public domain contributes to an enhanced understanding of the relationship between structural and functional attributes and provides insight into MoA and clinically relevant attributes. For example, drifts in FcγRIIIa binding and ADCC activity due to changes in the level of afucosylated glycans, which occurred transiently for multiple batches with different expiry dates of the reference trastuzumab product [47], were associated with a reduced event-free survival (EFS) rate [48]. These drifts would likely not have been discovered without the analysis of multiple batches of the reference biological by the biosimilar company.

The present study was not without caveats. Only adalimumab biosimilars were examined in this study, raising a concern about generalizability. The data extraction of QAs may have been affected by the various terminologies used to describe the same QAs, particularly in scientific publications, because no consensus classification was available. We attempted to minimize this drawback by using a classification of QAs of a biological drug, which may not have reflected all QAs required by regulators to establish biosimilarity. As the study only relied on published QA data in the selected information sources, it was difficult to determine whether or not the unreported QAs were tested by the authors or assessed by the regulators.

Reporting the types of QAs and information on QAs may differ between scientific publications and EPARs as well as across biosimilars, but both sources provide information on the biosimilarity assessment of QAs in a complementary fashion. Functional attributes are consistently reported in comparison to structural attributes in the two sources, suggesting that MoA and clinically relevant QAs are reported in both sources, whereas less clinically relevant QAs are reported in one of the two sources. The EPARs are comprehensive regarding reporting the regulatory interpretation of QA biosimilarity, whereas scientific publications are focused on presenting both the test results and biosimilarity interpretation of QAs. There were no essential differences between the two sources' biosimilarity interpretations of the QA test results, which is reassuring the robustness of biosimilar regulation system as it has evolved in Europe over the last decade. Greater transparency and consistency in reporting QAs could lead to an improved understanding of the science behind biosimilar approval, which heavily relies on a comprehensive assessment of structural and functional attributes. The comprehensive reporting of QAs can contribute to improving the understanding of the role of QAs in establishing biosimilarity and the MoA of biological substances in general, which is essential for not only marketing authorization decisions but also informed decision making once a product is approved.

Author contributions

AMA, TJG, TCE, HGL, and HG contributed to the study conception and design; or participated in the data acquisition. AMA performed data collection; statistical analysis and drafted the manuscript for important intellectual content. AMA, TJG, TCE, HGL and HG contributed to interpretation of data. TJG, TCE, HGL, and HG critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript submitted for publication.

Compliance with Ethical Standards

Not applicable.

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Availability of data and materials

The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest

AMA, TJG, TCE, HGL, and HG declare that they have no conflict of interest.Consent for publicationNot applicable.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.biologicals.2020.12.003.

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