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Review

Nature and timing of post-approval manufacturing changes of tumour necrosis factor α inhibitor products: A 20-year follow-up study of originators and biosimilars

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ABSTRACT

The manufacturing of biopharmaceuticals is complex, and minor changes in the process may affect quality attributes (QAs) that may, in turn, impact clinical outcomes. Regulatory documents from the European Medicines Agency were used to characterize two aspects, nature and timing, of post-approval MCs for originators and biosimilars TNF-α inhibitors that were on the European market up to May 2021. The nature of MCs was evaluated in two ways: (1) the type of MCs related to the drug substance (DS) or drug product (DP), classified as manufacturing, quality control, composition, packaging, or stability with various subtypes; and (2) the risk level according to the potential impact of the MCs on QAs, classified as low, medium, or high. Timing was defined as the date of the regulatory decision on the MC in relation to the approval date. We identified 801 post-approval MCs implemented to originators (mean: 137, range: 112–175) and biosimilars (mean: 30, range: 0–133). Most of implemented MCs for originators and biosimilars were classified as low and medium risk (88.1%), and a small fraction were considered high-risk (11.9%). The average incidence rates were comparable for both originators and biosimilars (7.0/year for MCs, 0.8/year for high-risk MCs). In 20% of MCs introduced to biosimilars, the DP manufacturing site was involved (9% for originators). In contrast, 16% of MCs introduced to originators were related to the DS manufacturing processes (only 7% for biosimilars). In conclusion, while the overall MC incidence rate and the risk level of MCs was not substantially different between TNF-α inhibitor products, we observed some differences in a few types of MCs related to DS manufacturing process and DP manufacturing site between originators and biosimilars. As far as our data shows there is no reasons to assume that post-approval MCs will lead to differences between TNF-α-i originators and biosimilars in clinical practice.

1. Introduction

The manufacturing of biopharmaceuticals is a complex process, and every step may influence the quality attributes (QAs) of the drug substance (DS) and/or drug product (DP). Furthermore, an inherent degree of structural heterogeneity occurs in biopharmaceuticals; hence, batch-to-batch variability within certain limits or ranges is acceptable from a regulatory standpoint. Manufacturing changes (MCs) may be implemented after marketing authorization (MA) of a biopharmaceutical, i.e., post-approval MCs. Among others, the reasons for implementing MCs

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include compliance with regulatory commitments and standards, maintaining product quality and consistency between batches, and increasing manufacturing scale, robustness, efficiency, and reliability (Lee et al., 2012; Azevedo et al., 2016; Declerck et al., 2016).

Even minor changes in the manufacturing process can potentially impact clinically relevant QAs (i.e., critical quality attributes), which may, in turn, influence the clinical outcomes of biopharmaceuticals (Schiestl et al., 2011; Planinc et al., 2017). Regulators require therefore the provision of adequate evidence from a comparability exercise to ensure that the quality, safety, and efficacy of DPs are unaffected following post-approval MCs. According to the International Conference on Harmonization (ICH Q5E), the QAs of pre- and post-MC batches must be comparable to minimise the risk that MCs adversely impact clinical performance (ICH, 2004). The cornerstone of assessing comparability is the comparison of QAs based on a risk evaluation of the intended MCs. Sometimes the outcome may warrant (non-)clinical comparative studies. Additional clinical data are, however, rarely required for MC approval and is limited to a very few examples, including Aranesp® (darbepoetin alfa), following a process change to a serum-free bioreactor to reduce the risk of contamination, and Humira® (adalimumab), following a change in formulation and concentration to improve patient convenience (Rojas-Chavarro and de Mora, 2021).

The same scientific and technical principles of comparability apply to the development and regulatory approval of biosimilars. A biosimilar is a biological medicine that is similar to a reference product (i.e., 'originator') with no clinically meaningful differences in terms of quality. A successful demonstration of comparability to the originator at the QA level is the basis of biosimilar approval, but this cannot be achieved without well-designed and quality-driven reverse engineering of the originator production process (Edwards and Bellinvia, 2020). Upon approval, biosimilars are considered standalone products with no need for comparison to the originator if post-approval MCs are introduced.

Previous studies found that a substantial number of post-approval MCs were implemented for originator biopharmaceuticals approved in the European Union (EU) and the USA (Schneider, 2013; Vezér et al., 2016). Most authorized MCs were classified as low (72%) or medium risk (23%), and only a small fraction (5%) as high risk with a potential impact on product quality and clinical outcomes (Vezér et al., 2016). This finding indicates that regulators have extensive experience in assessing post-approval MCs for originator biopharmaceuticals.

TNF-α inhibitor (TNF-α-i) products, including mAbs (infliximab, adalimumab, certolizumab pegol, and golimumab) and a fusion protein (etanercept), provide effective treatment options for several inflammatory diseases (Tracey et al., 2008; Scott and Kingsley, 2006; Lis et al., 2014; Willrich et al., 2015). More than half of the 31 mAbs biosimilars (34 trade names) approved by the European Medicine Agency (EMA) as of 2021 are biosimilars of TNF-α-i products.

Previous studies have reflected on the number and risk level of post-approval MCs of originator mAbs from the MA date up to 2014 (Schneider, 2013; Vezér et al., 2016). Information on the nature and timing of post-approval MCs of biosimilars is scarce. In this study we aim to complement the current evidence with a description and characterization of post-approval MCs of both originators and biosimilars of TNF-α-i -products in Europe (most recent observation date, May 2021).

2. Method

2.1. Setting and study design

A retrospective descriptive analysis was conducted for TNF-α-i products (originators and corresponding biosimilars) with data sourced from publicly available regulatory documents retrieved from the EMA's official website (www.ema.europa.eu; access date 31 May 2021). The study included the mAbs infliximab and adalimumab and the fusion protein etanercept, which were centrally authorized in the EU between January 1999 and May 2020. TNF-α-i products for which only the originators have been approved (i.e., certolizumab pegol, and golimumab) were excluded. Baseline characteristics of TNF-α-i products were obtained from the initial European Public Assessment Reports (EPARs) and included the trade name(s), company code of the development programme, and MA date in the EU. The company code of the development programme only applies to biosimilars because these are marketed under different trade names that originated from the same development programme. The biosimilars were ordered according to the MA date (i.e., Remsima® and Inflectra® were considered as the first biosimilars of infliximab [BS1] and Flixabi® the second [BS2], etc.).

2.2. Post-approval manufacturing changes

The scope and dates for the regulatory decisions on post-approval MCs for the included TNF-α-i products were obtained from the EPARs, which contain information regarding the procedural steps and scientific information after authorization. This information is posted in the section "assessment history" on the EMA website (www.ema.europa.eu; access date 31 May 2021) and includes a detailed description of the nature of post-approval MCs. Since one assessment procedure may include more than one post-approval MC, every MC was considered and included as an independent MC. Each post-approval MC was evaluated on two aspects: (1) the nature of the MC, including type and risk level; and (2) the timing of regulatory approval of MCs in relation to the MA date.

The classification of MC types was developed based on types of post-approval changes for MA of human medicines available in the European Commission regulation (No. 1234/2008) (European-Commission 2013). This classification includes four types of MCs related to the DS and six related to the DP, with various subtypes (Box 1). Post-approval MCs not related to quality or manufacturing (i.e., changes made to update the regulatory dossier and related to regional administrative information, safety, and efficacy of the products) were not considered in this study, and those made to update documentation of the quality dossier (e.g., changes to approved management protocol; submission of a new, updated, or deleted certificate of suitability to the European Pharmacopoeia) were outside the scope of this study.

The risk level of each post-approval MC was classified as low, medium, or high, based on definitions proposed by Lee et al. (2012) and applied by Vezér et al. (2016). Lee et al. (2012) used the risk-level definitions as per the ICH Q5E (ICH, 2004).

MCs that are not expected to adversely impact the QAs of the DS and DP and for which additional (non-)clinical data are not required for regulatory approval were classified as low risk (e.g., changes in the DP

Box 1
Classification of the type of manufacturing changes (MCs) according to European Commission regulation 1234/2008.

Drug substance (DS)	Drug product (DP)
DS manufacturing	***DP Composition***
Manufacturing site	Strength
Manufacturing process	Formulation
Batch size	***DP manufacturing***
In-process test or limits	Manufacturing site
DS quality control	Manufacturing process
Specification parameters or limits	Batch size
Analytical test procedures	In-process test or limits
DS packaging system	***Excipient quality control***
Primary (immediate) packaging	Specification parameters or limits
DS stability	Analytical test procedures
Shelf life	***DP quality control***
Storage conditions	Specification parameters or limits
Stability protocol	Analytical test procedures
	DP packaging system
	Primary (immediate) packaging
	Secondary packaging
	DP stability
	Shelf life
	Storage conditions
	Stability protocol

stability protocol). MCs that may result in minor differences in clinically not-relevant QAs and do not require additional (non-)clinical data for regulatory approval were classified as moderate risk (e.g., changes to in-process tests or limits applied during DS manufacture). MCs that may result in differences in clinically relevant QAs that potentially warrant additional (non-)clinical data for regulatory approval were classified as high risk (e.g., changes in DS purification or DP formulation).

Each post-approval MC was assessed and allocated to a specific risk level. The first assessment was performed by the author (AMA) and thereafter validated by an expert in the quality and manufacturing of biopharmaceuticals (ED). In the event of discrepancies regarding the risk-level allocation, a decision was made by team consensus. The overall inter-rater reliability was 93.5% (kappa = 0.867).

The dates of regulatory approval of MCs were used to assess the timing of the implementation of post-approval MCs relative to the date of MA.

2.3. Data analysis

Descriptive statistics were performed to evaluate the nature, including type and risk level, and timing of the post-approval MCs. Timing was assessed from the date of MA until the regulatory approval of MCs or until 31 May 2021 (end of follow-up), allowing for at least one year of follow-up for each TNF-α-i product. The absolute number and incidence rate of post-approval MCs were stratified by type, risk level, calendar year and by TNF-α-i products (active substance, originator, biosimilar).

Cumulative curves were plotted, using R software (version 4.1.2) to explore patterns in the timing of implementation of post-approval MCs in general and high-risk MCs for both originators and biosimilars over the study period. All descriptive analyses were performed using the statistical software package SPSS version 27 (SPSS Inc, Chicago, Illinois).

3. Results

3.1. Characteristics of tumour necrosis factor monoclonal antibodies

Sixteen TNF-α-i products approved between August 1999 and May 2020, namely, three originators (Remicade® [infliximab], Enbrel® [etanercept], and Humira® [adalimumab]) and 13 corresponding biosimilars, were included in the analysis. Up to 31 May 2021, in total 801 post-approval MCs were introduced to these products. The number of MCs varied substantially between products: originators (mean = 137; range = 112–175) and biosimilars (mean = 33; range = 0–133) (Table 1).

3.2. Types of post-approval manufacturing changes

More than half of the MCs were related to manufacturing at the DS (26.8% for originators and 22% for biosimilars) and DP (27.7% for originators and 31.8% for biosimilars) levels; these changes were mainly related to the 'manufacturing site' and 'manufacturing process'. Approximately 25% of the total MCs were related to quality control at the DS (11.2% for originators and 14.1% for biosimilars) and DP (8.3% for originators and 5.1% for biosimilars) levels and were mainly related to 'specification parameters and limits'. Subtle differences were noted in absolute frequency between originators and biosimilars in few subtypes, namely, 'manufacturing process of the DS' (16% for originators versus 7% for biosimilars) and 'manufacturing site of the DP' (9% for originators versus 20% for biosimilars). The type of MCs implemented for biosimilars were not related to the type of MCs already implemented for originators. (Table 2).

3.3. Risk level of post-approval manufacturing changes

The majority of the 801 implemented MCs for originators and biosimilars were classified as low (62.5%) or medium (25.6%) risk, while a small fraction were considered high-risk MCs (11.9%) (Table 2). The high-risk MCs involved both originators (15%) and biosimilars (10%). At least one high-risk MC was implemented with all originators and seven of included biosimilars during the study period. The high-risk MCs were relatively more often related to DS quality control, mainly concerning 'specification parameters and limits' (35.1% for originators and 23.7% for biosimilars), DP composition (15.8% for originators and 18.5% for biosimilars), and DS manufacturing, predominantly the 'manufacturing process' (17.5% for originators and 18.4% for biosimilars). In a limited number of cases, some high-risk MCs that were never implemented for originators were implemented for a few biosimilars, for example, high-risk MCs related to 'in-process test or limits

Table 1
Characteristics of originators and corresponding biosimilars of TNF-α-i products approved in the EU up to May 2020.

Active substance	Trade name	Company code (BS order)	EU MA date (mm-yyyy)	Number of post-approval MCs(*n*)	Follow-up to May 2021 (years)	Average incidence rate of MCs/year (high-risk/year)
Infliximab	Remicade®	Originator (RP)	08-1999	112	21.8	5.2 (0.8)
	Remsima® Inflectra®	CTP13(BS1)[b]	09-2013	133	7.7	17.3 (2.7)
	Flixabi®	SB2 (BS2)	05-2016	57	5.0	11.4 (1.4)
	Zessly®	GP111 (BS3)	05-2018	9	3.0	3.0 (0.0)
Etanercept	Enbrel®	Originator (RP)	02-2000	175	21.3	8.2 (0.9)
	Benepali®	SB4 (BS1)	01-2016	43	5.3	8.1 (0.5)
	Erelzi®	GP2015 (BS2)	06-2017	30	3.9	7.7 (0.0)
	Nepexto®	YLB113 (BS3)	05-2020	8	1.0	8.0 (0.0)
Adalimumab	Humira®	Originator (RP)	09-2003	124	17.7	7.1 (1.0)
	Amgevita® Solymbic®[a]	ABP501 (BS1)[b]	03-2017	11	4.2	2.6 (0.2)
	Imraldi®	SB5 (BS2)	08-2017	45	3.8	12.0 (0.5)
	Cyltezo®[a]	BI695501 (BS3)	11-2017	1	1.3[c]	0.8 (0.0)
	Hefiya® Halimatoz® Hyrimoz®	GP2017 (BS4)[b]	07-2018	28	2.8	9.9 (0.7)
	Hulio®	FKB327 (BS5)	09-2018	18	2.7	6.8 (0.7)
	Idacio® Kromeya®	MSB11022 (BS6)[b]	04-2019	7	2.1	3.4 (0.0)
	Amsparity®	PF06410293 (BS7)	02-2020	0	1.3	-

[a]Trade names of biosimilars that received marketing authorization (MA) from the European Commission but were voluntarily withdrawn by the applicant for commercial reasons. [b]Biosimilars produced from the same development programmes and available on the EU market under several trade names. [C]The end of follow-up was the date of withdrawal of marketing authorization (MA) by EU. RP, reference product; BS, biosimilar.

Table 2
Type and risk level of manufacturing changes for TNF-α-i originators (1999–2020) and biosimilars (2013–2020).

Types of MCs	All MCs (n = 801)		Low-risk MCs (n = 501)		Medium-risk MCs (n = 205)		High-risk MCs (n = 95)	
	Originators 411 (100%)	Biosimilars 390 (100%)	Originators 255 (100%)	Biosimilars 246 (100%)	Originators 99 (100%)	Biosimilars 106 (100%)	Originators 57 (100%)	Biosimilars 38 (100%)
Drug substance (DS)	**146 (39.9%)**	**162 (41.5%)**	**28 (11.2%)**	**34 (13.9%)**	**98 (99%)**	**106 (100%)**	**38 (66.6%)**	**22 (57.9%)**
DS manufacturing	**110 (26.8%)**	**86 (22%)**	**5 (2%)**	**6 (2.4%)**	**87 (87.9%)**	**67 (63.2%)**	**18 (31.5%)**	**12 (34.2%)**
Manufacturing site	18 (4.4%)	31 (7.9%)	0 (0%)	0 (0%)	14 (14.1%)	30 (28.3%)	4 (7%)	1 (2.6%)
Manufacturing process	67 (16.3%)	28 (7.2%)	0 (0%)	0 (0%)	57 (57.6%)	21 (19.8%)	10 (17.5%)	7 (18.4%)
Batch size	2 (0.5%)	2 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (3.5%)	2 (5.3%)
In-process test or limits	23 (5.6%)	25 (6.4%)	5 (2%)	6 (2.4%)	16 (16.2%)	16 (15.1%)	2 (3.5%)	3 (7.9%)
DS quality control	**47 (11.2%)**	**55 (14.1%)**	**23 (9%)**	**25 (10.2%)**	**4 (4%)**	**21 (19.8%)**	**20 (35.1%)**	**9 (23.7%)**
Specification parameters or limits	24 (5.8%)	30 (7.7%)	0 (0%)	0 (0%)	4 (4%)	21 (19.8%)	20 (35.1%)	9 (23.7%)
Analytical test procedures	23 (5.6%)	25 (6.4%)	23 (9%)	25 (10.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
DS packaging system	**1 (0.2%)**	**3 (0.8%)**	**0 (0%)**	**0 (0%)**	**1 (1%)**	**3 (2.8%)**	**0 (0%)**	**0 (0%)**
Primary (immediate) packaging	1 (0.2%)	3 (0.8%)	0 (0%)	0 (0%)	1 (1%)	3 (2.8%)	0 (0%)	0 (0%)
DS stability	**6 (1.4%)**	**18 (4.7%)**	**0 (0%)**	**3 (1.2%)**	**6 (6.1%)**	**18 (14.1%)**	**0 (0%)**	**0 (0%)**
Shelf life	5 (1.2%)	12 (3.1%)	0 (0%)	0 (0%)	5 (5.1%)	12 (11.3%)	0 (0%)	0 (0%)
Storage conditions	1 (0.2%)	3 (0.8%)	0 (0%)	0 (0%)	1(1%)	3 (2.8%)	0 (0%)	0 (0%)
Stability protocol	0 (0%)	3 (0.8%)	0 (0%)	3 (1.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Drug product (DP)	**265 (60.1%)**	**228 (58.5%)**	**222 (88.1%)**	**211 (86.1%)**	**1 (1%)**	**0 (0%)**	**24 (33.4%)**	**17 (42.2%)**
DP Composition	**16 (3.8%)**	**7 (1.8%)**	**7 (2.8%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**9 (15.8%)**	**7 (18.5%)**
Strength	8 (1.9%)	5 (1.3%)	2 (0.8%)	0 (0%)	0 (0%)	0 (0%)	6 (10.5%)	5 (13.2%)
Formulation	8 (1.9%)	2 (0.5%)	5 (2%)	0 (0%)	0 (0%)	0 (0%)	3 (5.3%)	2 (5.3%)
DP manufacturing	**114 (27.7%)**	**124 (31.8%)**	**100 (40%)**	**119 (48.9%)**	**1 (1%)**	**0 (0%)**	**8 (14%)**	**3 (7.9%)**
Manufacturing site	39 (9.5%)	80 (20.5%)	39 (15.3%)	80 (32.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Manufacturing process	45 (10.9%)	18 (4.6%)	36 (14.1%)	17 (6.9%)	1 (1%)	0 (0%)	8 (14%)	1 (2.6%)
Batch size	6 (1.5%)	7 (1.8%)	6 (2.4%)	7 (2.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
In-process test or limits	24 (5.8%)	19 (4.9%)	24 (9.4%)	17 (6.9%)	0 (0%)	0 (0%)	0 (0%)	2 (5.3%)
Excipient quality control	**1 (0.2%)**	**5 (1.3%)**	**1 (0.4%)**	**5 (2%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**
Specification parameters or limits	1 (0.2%)	4 (1%)	1 (0.4%)	4 (1.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Analytical test procedures	0 (0%)	1 (0.3%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
DP quality control	**34 (8.3%)**	**20 (5.1%)**	**33 (12.9%)**	**15 (6.1%)**	**0 (0%)**	**0 (0%)**	**1 (1.8%)**	**5 (13.2%)**
Specification parameters or limits	9 (2.2%)	9 (2.3%)	8 (3.1%)	4 (1.6%)	0 (0%)	0 (0%)	1 (1.8%)	5 (13.2%)
Analytical test procedures	25 (6.1%)	11 (2.8%)	25 (9.8%)	11 (4.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
DP packaging system	**56 (13%)**	**45 (12%)**	**55 (21.6%)**	**44 (17.9%)**	**0 (0%)**	**0 (0%)**	**1 (1.8%)**	**1 (2.6%)**
Primary (immediate) packaging	18 (4.4%)	10 (2.6%)	17 (6.7%)	9 (3.7%)	0 (0%)	0 (0%)	1 (1.8%)	1 (2.6%)
Secondary packaging	38 (9.2%)	35 (9%)	38 (14.9%)	35 (14.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
DP stability	**26 (6.3%)**	**27 (7%)**	**26 (10.3%)**	**27 (10.9%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**
Shelf life	15 (3.6%)	18 (4.6%)	15 (5.9%)	18 (7.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Storage conditions	4 (1%)	4 (1%)	4 (1.6%)	4 (1.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Stability protocol	7 (1.7%)	5 (1.3%)	7 (2.7%)	5 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

of the DP', 'batch size of the DS', 'formulation of the DP', and 'primary (immediate) packaging of the DP'. Detailed information on the type and nature of high-risk MCs implemented for originators and biosimilars is available in supplementary Table S1.

3.4. Timing of post-approval manufacturing changes

The follow-up time was, on average, 20 years for originators and 3 years for biosimilars. The implementation of MCs for originators and biosimilars follow a similar pattern, which is increasing overtime (Fig. S1). Although there was a large variation between products in the absolute number of MCs (Table 1, Fig. 1), no substantial variation in incidence rate i.e., taking follow-up time into account, was observed between originators and biosimilars. The overall average incidence rate of MCs per year was 7 for originators (range: 5.1–8.2) and 7.6 for biosimilars (range: 0.8–17.3) (Table 1). Similar patterns were observed when limiting to the high-risk MCs, where incidence rate was on average 0.9 MC for originators (range: 0.8 – 1.0) and 0.6 MC for biosimilars (range: 0.0 – 2.7) (Table 1, Fig. 2). The type of MCs related to the stability, among other types, was introduced sooner after the regulatory approval for both originators and biosimilars.

4. Discussion

Approximately 800 post-approval MCs to the three originator TNF-α-I products and the 13 corresponding biosimilars were implemented during an average period of 20 years for originators and 3 years for the biosimilars corresponding to on average 7 MCs and 0.8 high risk MCs per year. Key differences between originators and biosimilars with regards to type of MC were only found for MCs related to the DS manufacturing

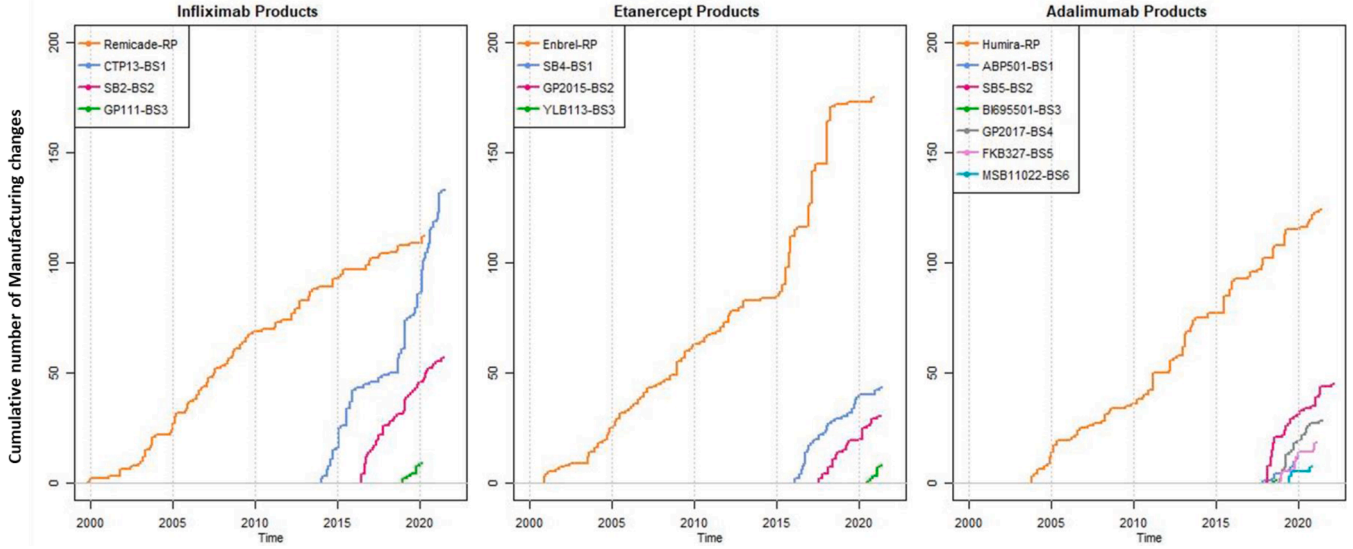

Fig. 1. Cumulative number of post-approval MCs since the date of marketing authorization.

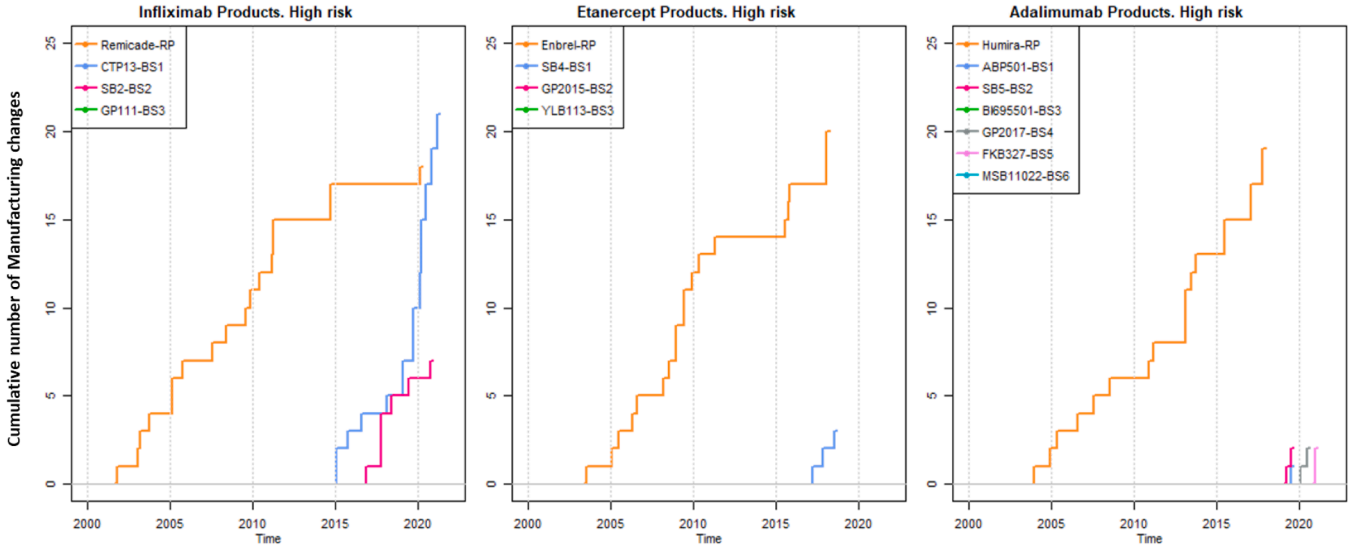

Fig. 2. Cumulative number of post-approval high-risk MCs since the date of marketing authorization.

process, which were twice as frequent for originators when compared with biosimilars, and the DP manufacturing site, which occurred more frequently for biosimilars. Approximately 10% of the post-approval MCs were classified as high risk and these were relatively more frequently related to DS quality control and DS manufacturing and to DP composition for both originator and biosimilars.

Our results are consistent with Vezér et al. (2016) that showed that MCs are implemented frequently and even long after approval and that the vast majority were low or medium risk. We found on average an annual incidence rate of 7 MCs (both for originators and biosimilars) which is considerably higher than the annual incidence of 1.8 MCs reported by Vezér et al. (2016). This discrepancy could be explained by the fact that most post-approval MCs identified for originators in our study were implemented after the period studied by Vezér et al. (2016). The continuous modernization of manufacturing processes and optimization of the quality of biopharmaceuticals (both originators and biosimilars) likely contributes to this finding (Schneider, 2013; Vezér et al., 2016). Further, the relatively quick introduction of MCs related to stability for both originator and biosimilars after approval could relate to obligatory post-approval regulatory commitments or to support the extension of the shelf life based on a longer data period. We also found that the type of MCs for biosimilars were not related to the type of MCs already implemented for originator, which reflects that biosimilars and originators are standalone products after approval.

Our analysis found that MCs related to the DS manufacturing process were more frequently implemented for originators which includes advancements in knowledge and technical innovations introduced in recent decades to scale manufacturing and optimize the purification and characterization of biopharmaceuticals (Berkowitz et al., 2012; Háda et al., 2018; Parr et al., 2016; Sandra et al., 2014; Beck et al., 2015; Fekete et al., 2016). The higher frequency of implementing MCs related to the DP manufacturing site for biosimilars could be attributed to biosimilar companies scaling up or building of new production sites, enabling them to provide sufficient stock to meet market demand. It is important to note that these MCs mainly involved non-critical activities, such as the addition of sites for batch release, quality control tests, and secondary packaging. We argue that these subtle differences in post-approval MCs between originators and biosimilars most likely do not lead to differences in clinical practice. To the best of our knowledge, no safety and efficacy concerns have been reported from post-marketing

pharmacovigilance systems following implementation of post-approval MCs for the studied TNF-α-i products.

At the time of approval, biosimilars are required to demonstrate biosimilarity against the originator based on comparability exercises (Alsamil et al., 2021a, 2021b). Regulators may allow differences in certain aspects between biosimilars and originator, such as the formulation (e.g., excipients), presentation (e.g., powder to be reconstituted versus solution ready for injection), and administration device (e.g., type of delivery pen), if these do not affect the biosimilarity on biological and pharmacological functions and clinical outcomes. After approval, the originator and biosimilars are considered standalone products and redemonstration of biosimilarity is not required following post-approval MCs. However, bringing innovative solutions for patient care may trigger companies to implement certain MCs after approval. This is illustrated by two examples developing novel formulation and new route of administration for biopharmaceuticals. The marketing authorization holder of adalimumab originator (Humira®) developed a new citrate-free formulation to reduce pain associated injection site reaction providing comfort for patients and improve adherence (Rojas-Chavarro and de Mora, 2021). The marketing authorization holder of the first infliximab biosimilar (Remsima®/Inflectra®) developed the first infliximab for subcutaneous use, which allows self-administration and reduces time associated with the intravenous infusions to improve patient compliance and adherence (Schreiber and Dudkowiak, 2019; Westhovens and Zawadzki, 2019). These examples show that both originators and biosimilars can bring novel solutions by optimizing and improving the quality of the product.

It is never clear in advance whether post-approval MCs might lead to changes in clinically relevant QAs and clinical outcomes. As an example, the mAb towards HER2, trastuzumab (Herceptin®), for which the company producing a trastuzumab biosimilar (Ontruzant®; SB3) discovered differences in the glycosylation and potency (antibody-dependent cell-mediated cytotoxicity) in the originator in batches with different expiry dates, which might potentially impact clinical outcomes (Lüftner et al., 2020). These alterations were linked to multiple changes in the manufacturing site and process and resulted in seemingly reduced efficacy in patients who received the affected batches of Herceptin®, based on the 3-year follow-up of the Phase III trial (Kim et al., 2017; Pivot et al., 2019). However, the 3-year follow-up result was not confirmed in the 5-year follow-up, which further confirmed the similarity in clinical outcomes in term of the response rate and long-term survival between the originator (Herceptin®) and biosimilar (Ontruzant®; SB3) (Pivot et al., 2021). Although this case demonstrates that clinical outcome of Herceptin® is unaffected by the drift in glycosylation and potency, it shows how important it is to understand the clinical meaning of small differences in clinically relevant QAs, known as critical QAs. Nevertheless, this trastuzumab case raised questions about the variability range that should be used for drifted or shifted QAs to support the comparability evidence for biosimilar approval. What can be learnt from the case of trastuzumab is that biosimilar companies need to consider post-approval MCs implemented to originators when establishing the variability range for biosimilar development and approval.

Companies are required to send a notification or request a regulatory approval before implementing (major) changes to the manufacturing process, and regulators may demand comparability exercise of QAs to ensure batch-to-batch consistency and minimize the risk of potential divergence between batches from the same manufacturer (i.e., pre-, and post-change batches) (Prior et al., 2021; Ramanan and Grampp, 2014; Lamanna et al., 2018). Consistency in clinically relevant QAs is a key quality issue to ensure that therapeutic biological function and clinical outcomes are not affected by post-approval MCs. Several biopharmaceutical companies have reported results for a selection of QAs of multiple batches produced over extended periods to demonstrate consistency in manufacturing processes (Tebbey et al., 2015; Ebbers et al., 2020; Melsheimer et al., 2018; Hassett et al., 2018; Melsheimer et al., 2018). However, these assessments are manufacturer-focused and do not allow the comparison of products or batches from different manufacturers. Since product or batch divergence may occur transiently following post-approval MCs, which might result in an unnoticed shift or drift of clinically relevant QAs from the acceptable variability range or limit, and potentially impact clinical outcomes (Prior et al., 2021; Ramanan and Grampp, 2014; Lamanna et al., 2018). The study finding highlights the importance of ensuring consistency in clinically relevant QAs, for example, glycosylation and potency between originators and biosimilars, for which, theoretically at least, the potential risk of divergence between products or batches (horizontally) or over extended periods (longitudinally) cannot be excluded.

Our findings confirm the new regulatory challenge of ensuring consistency of clinically relevant QAs (i.e., critical quality attributes) in products and batches after approval, as highlighted by Prior et al. (2021). The comparability exercise is a powerful regulatory tool to assess the biosimilarity of biosimilars at the time of approval and ensures consistency in products or batches of the same manufacturer after approval. However, it cannot be used to guarantee consistency in clinically relevant QAs between products of different manufacturers since each has a separate lifecycle. Although not all post-approval MCs cause shifts or drifts in QAs and not all shifts and drifts in QAs have clinical consequences, it is assumed that the risk of product divergence only increases with time, the number of products, and post-approval (high--risk) MCs (Prior et al., 2021; Ramanan and Grampp, 2014; Lamanna et al., 2018). Therefore, there is a need to develop a tool to address the challenge of potential product divergence that regulators and manufactures are likely to encounter in the future. One ideal solution is to develop and promote reference standards for clinically relevant QAs such as biological activity (potency), as proposed and extensively explained by Prior et al. (2021). Consistency in potency is critical to ensure that patients receive comparable product and harmonized doses, especially when considering interchangeability or switching of biosimilars and originators (Ebbers et al., 2012; Kurki et al., 2017; McKinnon et al., 2018; Ebbers and Schellekens, 2019). This may require the development of relevant potency assays that correlate with the size of the clinical effect. Recently, the Expert Committee on Biological Standardization established the first World Health Organization reference standards for several mAbs (Haiyan Jia et al., 2020; Sandra Prior et al., 2020; Wadhwa, 2019; Metcalfe et al., 2019; Prior et al., 2018). These reference standards would allow regulators and manufacturers to detect potential product or batch divergences and prevent undesirable clinical events for both originators and biosimilars over their lifecycle. Moreover, reference standards may help to standardize and harmonize potency estimates and clinical monitoring assays that would be useful for clinical decision making and treatment strategies in medical practice.

This study is the first to provides insights into characterization of the type and risk level of MCs implemented for TNF-α-i products over a period of 20 years. Nevertheless, this study is not without limitations. First, the findings are limited to post-approval MCs of TNF-α-i products and may not be generalizable to other groups of biopharmaceuticals. Although post-approval MCs are product-, company-, and time-dependent, comparable findings are expected for other biopharmaceuticals as they share the same degree of complexity in the manufacturing process. Second, the rating of MC risk levels may be subjective and prone to misclassification bias. However, the classification of the risk levels was validated by an expert in quality and manufacture of biopharmaceuticals to reduce the effect of misclassification, and the classification can be used in future studies. Third, it was not possible to identify the QAs relevant to the MCs and determine to which extent the high-risk MCs influenced the clinically relevant QAs, because pertinent data are not available in publicly accessible regulatory documents. Such information on comparability of QAs would be very helpful in identifying the clinically relevant QAs and their margins and assess the potential impact of MCs on QAs. And lastly, the data we used in our study does not allow us to assess or conclude on the impact of these MC on clinical outcomes. However, with the retrospective nature of the

present study there are no signals of a negative impact of the MCs on clinical practice.

5. Conclusions

To conclude, many post-approval MCs were implemented for TNF-α-i products introduced to the European market during the last two decades, with a comparable overall incidence rate for both originators and biosimilars. Most of MCs were related to manufacturing and quality control which reflects that the modernization process and optimization of quality of originators and biosimilars are never finished. Differences in the type of MCs between originators and biosimilars were limited to the DS manufacturing process and the DP manufacturing site, which may be explained by the development within the technological space to enhance product quality, manufacture upscaling to meet market demands, and bring innovative solutions for patient care. As far as our data shows there is no reasons to assume that post-approval MCs will lead to differences between TNF-α-i originators and biosimilars in clinical practice.

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Compliance with ethical standards

Not applicable.

Availability of data and materials

Datasets used in this study can be requested from the corresponding author.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Ali M. Alsamil: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Funding acquisition. **Thijs J. Giezen:** Conceptualization, Methodology, Validation, Investigation, Writing – review & editing, Supervision, Project administration. **Toine C. Egberts:** Conceptualization, Methodology, Investigation, Resources, Writing – review & editing, Supervision, Project administration. **Erik Doevendans:** Validation, Writing – review & editing. **Hubert G. Leufkens:** Conceptualization, Methodology, Investigation, Resources, Writing – review & editing, Supervision, Project administration. **Helga Gardarsdottir:** Conceptualization, Methodology, Validation, Investigation, Resources, Writing – review & editing, Supervision, Project administration.

Declaration of Competing Interest

AMA, TJG, TCE, ED, HGL, and HG declare that they have no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejps.2022.106227.

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