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Post-approval quality-related regulatory actions for biopharmaceuticals approved in the European Union and the United States between 1995 and 2019

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The quality of biopharmaceuticals is carefully monitored by manufacturers and regulators to ensure safety and efficacy throughout the entire product life cycle. Quality defects can lead to post-approval regulatory actions (RAs) to inform healthcare professionals (HCPs). The present study identified quality-related RAs for biopharmaceuticals approved in the European Union and United States between 1995 and 2019. Quality-related RAs were issued due to various quality defects and required different actions by HCPs. The quality defects were not identified due to a negative impact on efficacy and/or safety, which is reassuring. The findings reflect the capability of the stringent regulatory system and quality control to capture and counter various quality defects before the affected product and batches can harm patients.

Keywords: biotechnology; regulatory science; biopharmaceuticals; regulatory actions; post-approval quality surveillance; critical quality attributes

Introduction

Biopharmaceuticals have changed the prognosis of many difficult-to-treat or incurable diseases, and thus have become an integral part of the therapeutic arsenal.^{1,2} The manufacturing process of biopharmaceuticals is complex; slight changes in the process can affect the quality attributes and can potentially have an impact on the clinical outcomes of the drug.^{3,4} This is illustrated by the increased number of patients with pure red cell aplasia (PRCA) who received batches of Eprex[®]

(epoetin alfa) after a change in formulation. In 1998, human serum albumin was replaced by polysorbate 80 and glycine to reduce the risk of contamination with viral infections associated with human serum. The issue was solved after coating the rubber stoppers of the vial, supporting the formation of aggregates of epoetin alfa after leaking of leachable substance from the rubber stoppers due to the change in formulation as the most plausible explanation for the rise in the number of cases of PRCA.⁵ Since the Eprex[®] tragedy, the regulatory quality requirements and pharmacovigilance framework have been adapted to further limit and prevent the incidence of such episodes in the future.

The quality of biopharmaceuticals is carefully and constantly monitored by manufacturers and regulators to ensure consistency, safety, and efficacy throughout the entire product life cycle.⁶ It is the responsibility of the manufacturer to

report a quality defect to the regulatory authorities as soon as it is identified, which may occur before or after the product or specific batch has been released to the market. Studies have shown that, in general, the incidences of quality defects in drugs that fail to meet the stringent quality standards vary between countries and are less often reported in highly regulated markets.^{7–13} In turn, regulators can issue post-approval regulatory actions (RAs) to inform healthcare professionals (HCPs) of a quality defect along with the recommended actions to protect patients.

To date, studies on post-approval RAs of biopharmaceuticals have focused on RAs issued due to safety and/or efficacy concerns and not much is known about quality-related RAs for biopharmaceuticals.^{14,15} Ebbers *et al.* compared the number of and reasons for regulatory recalls issued in the United States (US) between 2003 and 2013 for biopharmaceuticals and small molecule drugs.¹³ The reasons for recalls of biopharmaceuticals were mostly related to defects of devices and containers, and packaging and labeling errors, which were unrelated to the complexity of the manufacturing process, and none of these were associated with unexpected clinical problems. The study by Ebbers *et al.* could not identify the products associated with the RA and did not assess the recommendations and actions required to be taken by the HCPs to protect the patients.

Therefore, our study aimed to identify type, content, timing, and frequency of post-approval quality-related RAs of biopharmaceuticals approved in the European Union (EU) and US from 1995 to 2019; assess whether quality-related RAs were prompted by safety or efficacy concerns; and provide learnings on actions to be taken by HCPs to protect patients from potential clinical consequences.

Quality-related RAs

All biopharmaceuticals approved between January 1, 1995 and December 31, 2019 by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) were included in this study. Biopharmaceuticals contain a therapeutic protein produced by recombinant DNA or hybridoma technology as active biological substance. Vaccines and naturally extracted biological drugs such as plasma-

derived (blood) and urine-derived products, products for further manufacturing and transfusion and transplantation, allergenic products, advanced therapy medicinal products, and biopharmaceuticals used for diagnostic testing were excluded. For each biopharmaceutical, the approval region, the approval period, product type, therapeutic protein class, and protein type was collected.

A quality-related RA is defined as a regulatory communication issued by regulators due to a quality defect that could either affect the drug in general or one or more specific batches. Information on quality-related RAs issued between January 1, 1995 and August 31, 2021 were obtained from the official website of the EMA, the Medicines Healthcare Products Regulatory Agency, and the Medicines Evaluation Board in the EU, and the FDA in the US (see [supplementary methods](#) in the [supplementary material](#) online for a more extensive description of the methods section). The quality-related RAs can be communicated through regulatory letters, including Direct Healthcare Professional Communications (DHPCs) in the EU and Dear Healthcare Professional Letters (DHPLs) in the US, recalls or market withdrawal for both the EU and the US cohorts. Cases of multiple quality-related RAs issued for the same biopharmaceutical at different times, due to different quality defects or due to follow-up of a previously communicated quality defect, were defined as separate RAs. When a quality-related RA involved multiple biopharmaceuticals, it was regarded as a single RA.

The outcomes were the type, content, timing, and frequency of quality-related RAs. The type of quality-related RA was categorized per RA into letters (DHPCs and DHPLs), recalls, or market withdrawal, and per product level into product in general or specific batches. The content of quality-related RAs was assessed to determine the nature of the underlying quality defect, the type of required actions to be taken by the HCPs, and whether quality-related RAs were initially triggered by safety or efficacy concerns ([Tables S1 and S2 in the supplementary material](#) online). The frequency of quality-related RAs was defined as the number of quality-related RAs stratified by the type of RA. The timing of the quality-related RAs was defined according to the calendar

date when they were issued by regulators relative to the date of approval. Descriptive statistics and graphics were used to analyze and summarize the outcomes using SPSS version 28 (SPSS Inc., Chicago, IL, USA).

Results

In this study, 324 unique biopharmaceuticals were included. Of the 2067 RAs in the EU and 2438 RAs in the US issued in the study period, a total of 67 quality-related RAs were issued for 41 of the 324 unique biopharmaceuticals ([Figure 1](#)). The mean time from marketing authorization to the issuing of the first quality-related RA was 9.5 years (standard deviation = 6.7 years), and 60% of the quality-related RAs were issued within 10 years after approval. Forty quality-related RAs were issued for one-third ($n = 14$, 35.0%) of biopharmaceuticals where each received multiple quality-related RAs during the study follow-up ([Table S1 in the supplementary material](#) online). All 41 biopharmaceuticals, for which an RA was issued, were originators from various therapeutic protein classes and none concerned biosimilars ([Table 1](#)).

The 67 quality-related RAs most often involved regulatory letters ($n = 45$; 67.0%), and to a lesser extent, regulatory recalls ($n = 22$; 33.0%). There were no market withdrawals due to quality defects. The quality-related RAs mostly concerned the product in general ($n = 40$; 60.0%) rather than specific batches ($n = 27$; 40.0%) ([Figure 2a](#)). Of the 67 quality-related RAs issued for 41 biopharmaceuticals, 59 RAs (37 in the EU, 12 in the US, and 10 in both regions) were issued for 32 biopharmaceuticals approved in both the EU and the US. Of these 32 biopharmaceuticals, only 5 biopharmaceuticals received 10 RAs due to the same underlying quality defects in both regions with slight differences in the type of actions required to be taken by HCPs between the EU and the US. For example, two recalls were issued for Cerezyme[®] (imiglucerase) and Fabrazyme[®] (agalsidase beta) due to the presence of particulate matters, where US regulators recommend additional HCP actions ‘inform’ and ‘monitor’ compared to ‘check’, ‘handle’, and ‘recall’ recommended by EU regulators ([Supplementary Table S4 in the supplementary material](#) online). The most frequently reported nature of underlying quality defects were ‘manufacturing’ (40.0%), mainly because of good manufac-

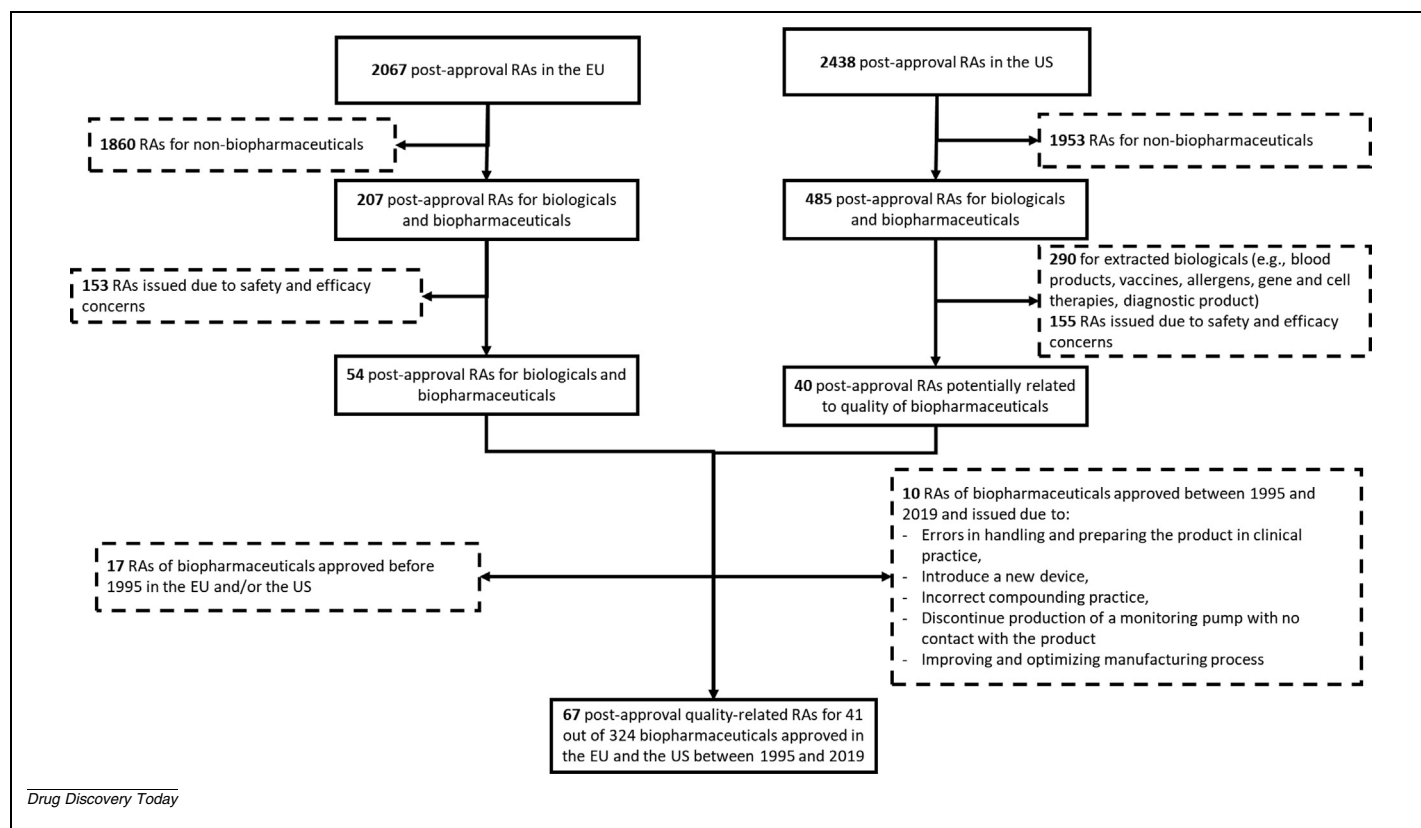


FIGURE 1 Flowchart of data collection of quality-related regulatory actions for biopharmaceuticals approved in the EU and US between 1995 and 2019. Abbreviation: RA, regulatory actions.

turing practice deviations and ‘specification’ (24.0%), mainly related to the presence of particulate matter. The ‘packaging’ accounted for 20.9% of quality-related RA followed by ‘adulteration’ and ‘stability’ (both 6.0%). An example for a packaging issue includes damage to part of primary packaging with direct and immediate contact to the drug product leading to a loss in sterility, which can potentially cause infections in patients. The adulteration includes counterfeiting and falsification where a fake product and batch do not meet regulatory standards and mimics the real drug, which cannot be considered safe and effective. The stability issue includes a drug product exposed to unrecommended storage conditions, which could potentially impact clinically relevant quality attributes of the drug. Two cases of contamination (3.0%) were related to microbial contamination of the alcohol preparation pad supplied with the drug product (Figure 2b).

All quality-related RAs reported statements related to at least one action required to be taken by HCPs. A substantial variation was observed between the

types of HCP actions, ranging from 82.1% for the action ‘report’ to 6% for the action ‘ensure’. The action ‘report’ includes reporting of suspected adverse drug reactions or quality problems to regulatory agencies. The action ‘ensure’ means prescribe and dispense the correct strength, and identify patients to whom the affected product has been dispensed. The most frequent type of HCP actions at product level were ‘recall’ (40.3%), which was often recommended to counter specification issues (e.g., particulate matters, and out of specification (OOS) in volume, potency, strength, and preservative). The most frequent type of HCP actions at patient level were ‘monitor’ (28.4%) and ‘restrict’ (26.9%), which were often recommended to counter manufacturing issues that mostly led to drug shortages (Figure 2c). The action ‘monitor’ includes close monitoring of patients for specific changes in certain biomarkers and signs and symptoms. The action ‘restrict’ includes a reduction in treatment frequency or adjustment of dose and preparation, or limiting available treatments to already started patients.

None of the quality-related RAs were initiated following safety or efficacy concerns. There was, however, a limited number of RAs (1 of 18 RAs in the US and 2 of 49 RAs in the EU) associated with a few spontaneous reports identified before the communication of quality-related RAs. In the US, regulators received a few reports of poor control of glucose level for patients after using the affected batches Levemir® (insulin detemir) that was exposed to improper storage condition. In the EU, regulators received a few spontaneous reports of an increase in clinical manifestation and disease progression for patients receiving lower doses than recommended to counter shortage of Fabrazyme® (agalsidase beta) due to manufacturing issues. In addition, EU regulators received reports of three cases of bacterial endophthalmitis for batches of Lucentis® (ranibizumab) with a higher rate of blocked needle complaints.

Discussion

The present study identified 67 quality-related RAs issued for 41 of 324 biopharmaceuticals approved in the EU and the

TABLE 1

Characteristics of biopharmaceuticals approved in the EU and the US between 1995 and 2019.

Product characteristics	EU cohort (N = 275)	US cohort (N = 236)	Product with at least one quality-related RA (N = 41)
Approval region			
Both regions	187 (68.0%)	187 (79.2%)	32 (78.0%)
EU only	88 (32.0%)	-	5 (12.0%)
US only	-	49 (20.8%)	4 (10.0%)
Approval period			
1995–2004	68 (24.7%)	65 (27.5%)	21 (51.0%)
2005–2012	62 (22.5%)	54 (22.9%)	14 (34.0%)
2013–2016	61 (22.2%)	60 (25.4%)	4 (10.0%)
2017–2019	84 (30.5%)	57 (24.2%)	2 (5.0%)
Product type			
Originators	214 (78.0%)	208 (88.0%)	41 (100%)
Biosimilars	61 (22.0%)	28 (12.0%)	-
Therapeutic protein class			
Monoclonal antibodies	108 (39.3%)	98 (41.5%)	7 (17.0%)
Growth factors	58 (21.1%)	39 (16.5%)	7 (17.0%)
Hormones	46 (16.7%)	35 (14.8%)	17 (41.5%)
Clotting factor	30 (10.9%)	29 (12.3%)	2 (5.0%)
Enzymes	23 (8.4%)	23 (9.7%)	6 (14.5%)
Fusion proteins	10 (3.6%)	12 (5.1%)	2 (5.0%)
Protein type			
Glycosylated protein	181 (65.8%)	157 (66.5%)	25 (60.0%)
Non-glycosylated protein	94 (34.2%)	79 (33.5%)	16 (40.0%)
Pharmaceutical dosage form			
Solution	174 (63.3%)	136 (57.6%)	25 (60.0%)
Powder	85 (30.9%)	86 (36.4%)	13 (32.0%)
Solution and powder	15 (5.5%)	12 (5.1%)	3 (8.0%)
Others	1 (0.4%)	2 (0.8%)	-

US between 1995 and 2019. Although quality defects in medicines could potentially harm patients, none of these quality-related RA were initiated following safety or efficacy concerns. This finding shows that the regulatory systems together with quality control strategies of manufacturers were capable to capture quality defects and initiate actions to be taken by HCPs to protect patients from any potential risks.

Our results showed that quality-related RAs were issued for various characteristics of biopharmaceuticals. The number of biopharmaceuticals that received at least one quality-related RAs decreased over time. One could attribute the decrease to the differences in follow-up time between products, which might also have resulted in differences in the number of quality-related RAs issued for originators and biosimilars. None of the quality-related RAs were triggered by safety or efficacy concerns where a limited number of spontaneously reported adverse events could be related to quality defects. Based on our data, these few spontaneously reported adverse event were identified before the

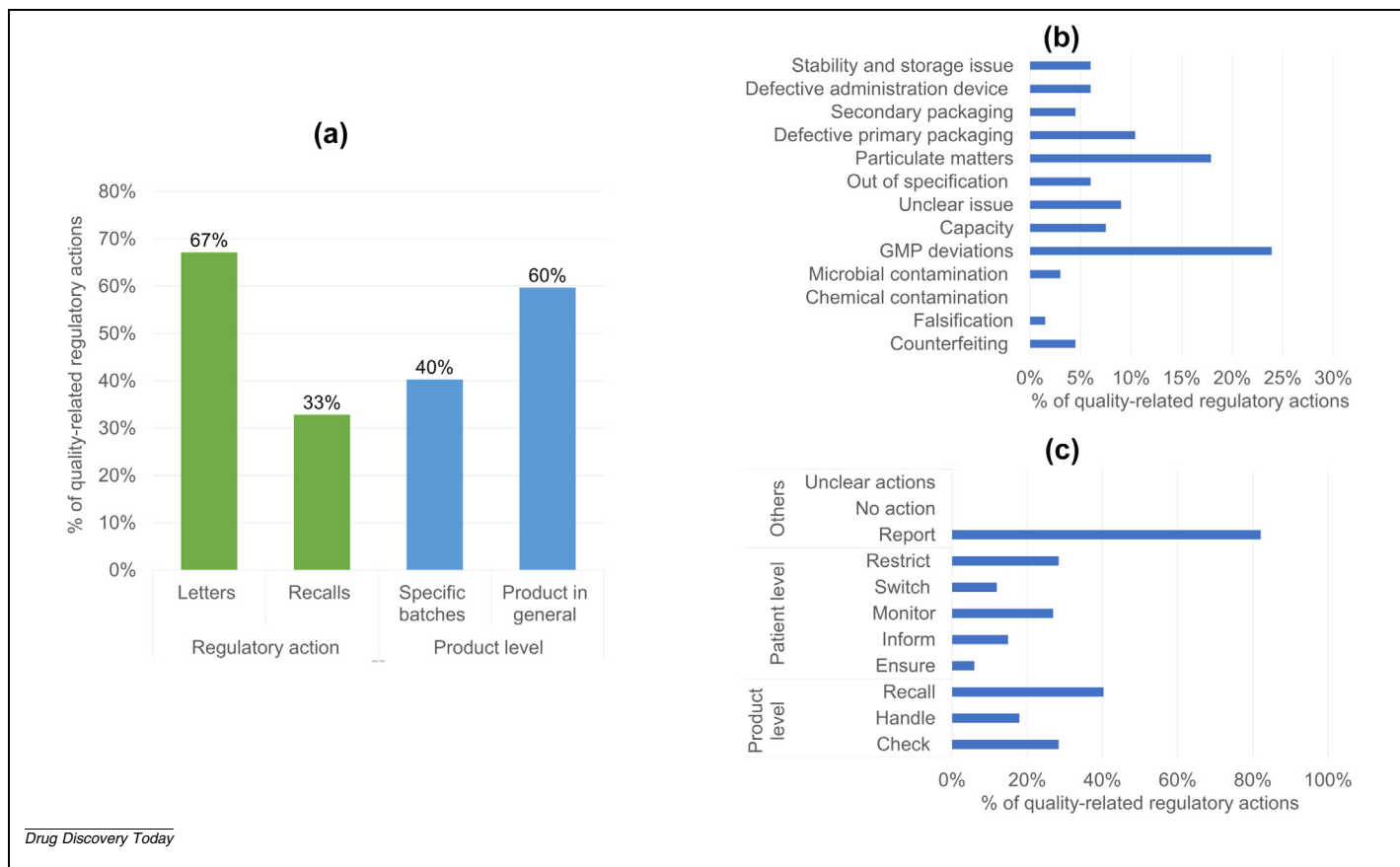
communication of quality-related RAs. This finding reflects that there is more stringent quality control and proactive pharmacovigilance system, which might result in quick detection of quality defects before they reach and harm patients.

In recent decades, multiple strategies have been developed and implemented for in-process control, quality by design, and quality indicators, which result in better process and product understanding for biopharmaceuticals. These developments resulted in the production process becoming more robust. Advancements in the analytical characterization methods and instrumentations have become more precise and sensitive over the last decade.^{16,17} Furthermore, the implementation of risk-based approaches to quality control where potential risks associated with each manufacturing steps are identified and assessed. In addition, various tools such as automated image analysis, predictive modeling, and real-time monitoring have been implemented to improve the quality control of biopharmaceuticals. Other strategies include the implementation of internal audits to assess effectiveness of

quality systems and corrective and preventive actions to identify and address quality defects. These advancements in science and technology can contribute to identification of quality defects and prevent biopharmaceuticals with quality defects from being released to the market.^{18–21} In addition, to improve process and product understanding, the advancements in analytical technology together with regulatory efforts may increase the possibility of detecting quality defects before the affected products or batches reach the patients and ultimately lead to safer and more effective products for patients. Finally, the advancement towards more pro-active pharmacovigilance might help to identify safety problems, potentially related to quality defects, at an earlier stage.

Quality-related RAs of biopharmaceuticals were often communicated through letters sent to HCPs ($n = 45$) and less frequently as recalls ($n = 22$), which shows that looking at recalls only could underestimate the quality-related RAs for biopharmaceuticals. The higher number of letters compared to recalls could be attributed to follow up letters issued due to the same quality defect. This observation suggests that some quality defects may take a while to address and solve, and it shows the willingness of the regulators to update, inform and advise HCPs, who continuously have to make informed decisions based on the most recent information.

Our study identified a lower number of recalls in the US ($n = 11$) compared to the study by Ebbers *et al.* ($n = 41$), despite the use of the same definition for biopharmaceuticals in the two studies.¹³ This difference could be attributed to the fact that Ebbers *et al.* detected recalls of products approved outside our study period and included recalls unrelated to manufacturing issues that were not included in the current study. Moreover, Ebbers *et al.* obtained recall data from the FDA through a Freedom of Information Act request, whereas our study retrieved quality-related RAs from the official websites of regulatory agencies. Quality-related RAs for small molecules were excluded from the present study because they are of different complexity with regards to the molecule and manufacturing process when compared to biopharmaceuticals. In addition, previous publications have

**FIGURE 2**

A relative proportion of quality-related regulatory action, per the type of regulatory action (a), the nature of the underlying quality defects (b), and the type of actions required to be taken by healthcare professionals (c).

focused only on recalls and thus a direct comparison with our findings is not possible. Future studies should explore differences in the type of RAs, the underlying nature of quality defects, and type of HCPs actions between small molecules and biopharmaceuticals. Although there might be differences, we expect that quality control and regulatory system capable of capturing quality defects to protect patients from potential impact will remain unchanged.

The number of quality-related RAs slightly differs between the EU and the US. More quality-related RAs were issued in the EU compared to the US, which could be attributed to the higher number of follow-up letters issued in the EU, particularly to address the manufacturing issues due to a viral contamination of a bioreactor for Cerezyme[®] (imiglucerase) and Fabrazyme[®] (agalsidase beta). The virus Vesivirus 2117 does not cause human infections but impairs the growth of the producing cell line, and as a result stalls

the manufacturing plant, which led to shortage of multiple products.²² The difference in the number of quality-related RAs might suggest that quality-related RAs are country- or region-specific since the manufacturers that supply a country or region can be from different manufacturing sites. This is supported by our finding where only 5 of 32 biopharmaceuticals approved in both the EU and the US received quality-related RAs due to the same quality defects.

Predicting the impact that a quality defect may have on clinical outcomes and patient care is challenging, and preventing quality defects remains a key quality control and regulatory strategy. The type of RAs adopted by regulators is weighted based on the potential impact on safety and efficacy profiles. A clear example is the presence of particulate matters that is a common challenge for biopharmaceuticals and injectables in general. In some cases, particulate matters do not lead to regulatory recalls, especially

where there are no alternatives. Regulators may recommend the HCPs to administer the product through a 0.2 μm filter to remove particulates to minimize the potential clinical implications such as the occurrence of infusion-associated reactions.²² However, regulators acknowledged that the pharmacopeia test for particulate matters may be insufficient to detect particulates during quality control and lot-release testing.²³ In response to this, the FDA recently published a draft guidance for an inspection program for injectables including biopharmaceuticals, which provides a risk-based approach to control, assess, correct and prevent the potential risk of particulates. The implementation of this guidance is expected to reduce the incidence of quality-related RAs issued due to unacceptable particulate matters illustrating the continuous effort to improve product quality.

Regulators provide a set of actions that are required to be taken by HCPs to minimize the potential risk for patients. The

type of HCP actions depends on the underlying nature of the quality defect and the information available at the time of communication. For example, the manufacturing issues often required HCP to take actions at the patient level such as ‘restrict’, ‘monitor’, ‘switch’, and ‘inform’ to minimize risk of shortage. On the other hand, the specification issues, including OOS in volume, potency, strength and preservative, and particulate matters, often required HCP actions at product level such as ‘check’, ‘handle’, and ‘recall’ to avoid potential clinical consequences. Nevertheless, the quality and applicability of actions to be taken by HCPs is important for HCPs to understand the problem and make informed decisions in clinical practice. The available method to assess the quality and applicability of actions to be taken by HCPs in regulatory letters is limited to the HCP action ‘monitor’, which is often found to be insufficient for decision makers in clinical practice.^{24–26} Future studies are needed to develop a methodology and assess the quality and applicability of actions to be taken by HCPs associated with quality-related RAs.

The different types of RAs; the length of the study period, which included 25 years of follow up; the large sample size of biopharmaceuticals that have been approved in the EU and the US, the largest global pharmaceutical markets; and the identification of biopharmaceuticals that had received quality-related RAs were important strengths of this study. However, a potential for missing a quality-related RA of biopharmaceuticals that could raise a question on data completeness is a limitation, which should be acknowledged. However, an extensive search strategy was applied to minimize the probability of missing a quality-related RA for the EU and the US cohort. The study could not provide information on penalties paid by companies or how quality defects were addressed to prevent future episodes, because corrective and preventive actions submitted to regulators are currently not available in the public website of regulatory authorities. This is an interesting topic for future research.

Concluding remarks

The study identified 67 quality-related RAs for 41 of 324 biopharmaceuticals approved in the EU and the US during the study per-

iod. These quality-related RAs were issued due to various quality defects that required a different set of actions to be taken by HCPs to minimize potential risk for patients. Although none of these quality-related RAs were initiated following safety or efficacy concerns, regulators and industry should continue efforts in maintaining and upgrading the current quality control strategy to reduce the occurrence and quick detection of quality defects before affected products or batches reach patients. Nevertheless, our results validate that the regulatory system and quality control strategy are capable of capturing quality defects before they can harm patients.

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Compliance with ethical standards

Not applicable.

Declarations of interest

No interests are declared.

CRediT authorship contribution statement

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

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.drudis.2023.103725>.

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