feature

Characteristics of product recalls of biopharmaceuticals and small-molecule drugs in the USA

Hans C. Ebbers[1,2], Nina Fuentes de Tienda[1], Marcel C. Hoefnagel[3], Ria Nibbeling[3] and Aukje K. Mantel-Teeuwisse[1,*], A.K.mantel@uu.nl

Compared with chemically synthesized small-molecule drugs, the manufacturing process of biopharmaceuticals is more complex. Unexpected changes to product characteristics following manufacturing changes have given rise to calls for robust systems to monitor the postauthorization safety of biopharmaceuticals. We compared quality-related product recalls in the USA of biopharmaceuticals and of small molecules. Although the reasons for recalls for biopharmaceuticals differed from those for small molecules, adverse events were rarely reported. The relative contribution of recalls that could cause serious adverse health consequences was not greater for biopharmaceuticals than for small molecules. Therefore, these data do not give rise to concerns that biopharmaceuticals are more frequently associated with unexpected safety concerns.

Introduction

Over the past two decades, many biopharmaceuticals (here defined as proteins used for therapeutic or *in vivo* diagnostic purposes produced using recombinant technology) have entered clinical practice. The manufacturing process of pharmaceuticals should always be carefully controlled to ensure patient safety [1]; however, because the manufacturing process of biopharmaceuticals is more complex than for chemically synthesized small-molecule drugs, this could give rise to different quality problems. Previously, changes to the manufacturing of biopharmaceutical products have led to unexpected changes to the product, which led in at least one case to adverse events that did not become apparent until the product was prescribed to a considerable number of patients [2]. Such unexpected changes to product characteristics following manufacturing changes have given rise to calls for increased efforts to design robust systems to trace the origin of any adverse event that might arise after a product is placed on the market [3]. However, there are limited cases of postapproval safety concerns for biopharmaceuticals; in addition, not all manufacturing problems that might impact patient safety in fact lead to adverse events. Often, potentially hazardous quality problems are identified by the manufacturer or the US Food and Drug Administration (FDA) before adverse events emerge in patients. Little is known about the nature of quality-related problems of biopharmaceuticals and how these compare with those of small molecules and their potential impact on patient safety. Therefore, to contribute to the ongoing debate on the impact of manufacturing changes on the safety of biopharmaceuticals, we compared quality-related product recalls in the USA of biopharmaceuticals and small molecules.

Overview of quality-related recalls in the USA

Data for recalls for drugs and biologicals that occurred in the USA between January 2004 and October 2013 were obtained from the FDA through a Freedom of Information Act (FOIA) request. Recalls for small molecules and biopharmaceuticals meeting our definition were entered into a database (blood and blood

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TABLE 1

Summary of recall characteristics.[a]

	Biopharmaceuticals		Small molecules		*P* value group
	N	**%**	***N***	**%**	
Administration route					
Oral	0	N/A	1143	65	<0.001
Injectable	40	98	321	18	
Dermal	0	N/A	173	10	
Other[b]	1	2	114	7	
Class[c]					
I	1	2	91	5	0.025
II	31	76	949	54	
II	9	22	711	41	
Year					
2003	0	N/A	19	1	0.110
2004	5	12	132	8	
2005	4	10	210	12	
2006	1	2	143	8	
2007	2	5	106	6	
2008	2	5	155	9	
2009	5	12	121	7	
2010	12	29	233	13	
2011	6	15	290	17	
2012	3	7	190	11	
2013[d]	1	2	152	9	
Total	41	100	1751	100	

[a] Descriptive statistics were performed using the SPSS statistical package (version 20, IBM software). Differences between groups were tested using the X^2 test.
[b] Includes inhaled, intranasal, ocular, otic, and rectal.
[c] Class I: dangerous or defective products that predictably could cause serious health problems or death. Class II: products that might cause a temporary health problem, or pose only a slight threat of a serious nature. Class III: products that are unlikely to cause any adverse health reaction, but that violate FDA labeling or manufacturing laws.
[d] Until October 1, 2013.

components, nonrecombinant vaccines, antitoxins, and *in vitro* diagnostics were not included). Recalls concerning different dose presentations, but with the same event ID, were considered as a single recall. Given that we used quality-related recalls as a proxy for manufacturing issues, we excluded recalls from nonmanufacturing companies, such as wholesalers or compounders, as determined using public sources. Finally, we excluded recalls for nonpharmaceutical products (Figure S1 in the supplementary material online). For each product, the reason for the recall was determined as well as the year of the recall, its route of administration, and its FDA classification (http://www.fda.gov/Safety/Recalls/ucm165546.htm).

We identified 1792 recalled products during the study period; 41 recalls occurred for biopharmaceuticals and 1751 for small molecules (Table 1). As expected, for biopharmaceuticals all but one recall concerned injectables, whereas recalls for small molecules concerned mostly oral products. The mean [95% confidence interval (CI)] number of recalls per year for biopharmaceuticals was 3.7 (1.5–6.0), peaking in 2010, when 12 recalls occurred. The mean number of recalls per year for small molecules was 159.2 (111.2–207.2). Also for small molecules, a peak was observed in 2010 and 2011, with 233 and 290 recalls, respectively.

Differences were observed in the overall distribution of recalls for biopharmaceuticals and small molecules in terms of severity of the recall. Class I recalls (i.e., dangerous or defective products that predictably could cause serious health problems or death) concerned 2% of the recalls for biopharmaceuticals and 5% for small molecules. Of note, within the category of small molecules, injectables were considerably more likely to result in a class I recall: 43/321 (13%) when compared with 48/1382 (3%) for other administration routes ($P < 0.001$). Reporting of adverse events led to six recalls, three class I recalls, and three class II recalls, none of which concerned biopharmaceuticals (Table S1 in the supplementary material online). The class I recalls concerned two recalls of the same contaminated heparin product and a class I recall related to cases of loss of smell (anosmia) reported for a nasal gel.

The most frequently reported reasons for recall for biopharmaceuticals were 'defective devices and containers' (34%), mainly because of broken or miscalibrated delivery systems (Fig. 1). 'Packaging and labeling errors' accounted for 20% of the recalls followed by 'adulterations and chemical contaminations' (17%). The latter category comprised exclusively glass flakes found in vials, mainly reported for epoetins (five of which occurred in 2010). 'Sterility issues' accounted for 10% of all recalls issued for biopharmaceuticals. The only class I recall for a biopharmaceutical concerned the presence of glass particulates in vials of diluent for trastuzumab. For small molecules, 'stability issues' accounted for 34% of the recalls, followed by 'packaging and labeling errors' (16%), and 'out of specification' results (16%). The last category accounted for most of the class I recalls ($N = 30$) and comprised mainly sub- or superpotent products and the presence of particulate matter in the product.

Given that biopharmaceuticals are mostly injected, we performed a subgroup analysis comparing small-molecule injectables with injectable biopharmaceuticals (Table S2 in the supplementary material online). Also for injectable small molecules, 'stability issues' and 'out of specifications' accounted for most recalls (24% and 21%, respectively). Sterility concerns accounted for a considerable fraction of recalls for small-molecule injectables (17%).

Implications

Adverse events were rarely reported in quality-related product recalls of both

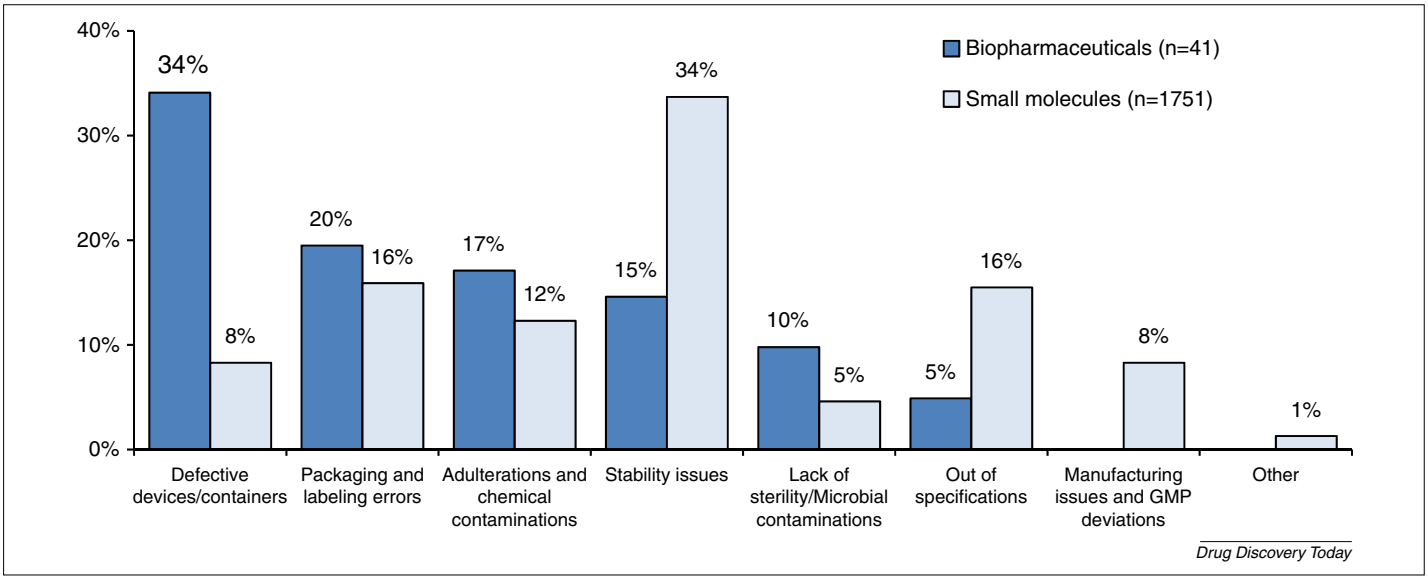

FIGURE 1

Relative proportion of recalls by recall category. A categorization for the reason for recall was developed (see supplementary information). All recalls were scored by H.E. To verify the robustness of the categorization a subset of 400 recalls was validated by a second rater (M.H., R.N., N.F.dT. or D.Z.). The overall inter-rater reliability was 92.8% (kappa = 0.911).

biopharmaceuticals and small molecules in the USA and, as such, do not imply a cause for concern. However, our results could underestimate the frequency of recalls associated with adverse events, because those associated with quality issues might not be identified as such by patients and, thus, not reported. Furthermore, it might be that adverse events occurred but were not included in the enforcement report. Our data suggest that, within the group of small molecules, Class I recalls occurred more frequently for injectables, a finding that supports earlier observations [4].

We looked at recalls as a way to determine the influence of manufacturing complexity on the nature of recalls. We observed differences between biopharmaceuticals and small molecules in terms of reason for recall. Recalls that concern the manufacturing of drug product, including stability, out-of-specification results and good manufacturing practice (GMP) issues occurred more frequently for small molecules. A possible explanation for this could be that the cost of manufacturing biopharmaceuticals is higher than for small molecules, which could translate into more careful control of the manufacturing process to prevent loss of batches. It must be noted that not all recalls are the result of manufacturing issues. Over 50% of all recalls concerning biopharmaceuticals were unrelated to the complexity of manufacturing the drug product (i.e., defective devices, and packaging and labeling issues). For example, several products were recalled because of glass lamination of vials provided by third parties (http://www.amgen.com/media/media_pr_detail.jsp?year=2010&releaseID=1474613). The FDA has recognized this problem and provided advice to prevent the formation of lamellae from vials (http://www.fda.gov/Drugs/DrugSafety/ucm248490.htm). Given that most biopharmaceuticals are injectables, this might account for the relatively large share of container problems. Taken together, the complexity of manufacturing was not reflected in the distribution of manufacturing-related recalls for biopharmaceuticals compared with small molecules in USA-based recalls.

Our research was done using USA-based data, because the FDA has the most complete overview of recalls. However, these data are not necessarily representative of other regulatory regions. For example, we observed a peak in recalls in 2010–2011, which appeared to coincide with an increased number of quality-related warning letters issues by the FDA [4]. According to some, this could be a sign of an allegedly more stringent approach of the FDA towards GMP following the contaminated heparin crisis [4,5]. The increase in drug shortages and recalls because of substandard practices has led to an increased focus from the FDA on ensuring quality of pharmaceuticals with a particular focus on sterile injectables, which has resulted in steps to transform its review and inspection practices [4]. It might be that our study is more a study of FDA behavior, rather than of industry manufacturing practices. However, most recalls were initiated by manufacturers and not mandated by the FDA (https://open.fda.gov/drug/enforcement/). Nonetheless, even nonmandated recalls might have been triggered by FDA inspections. Unfortunately, in our data set, we could not distinguish between recalls initiated on the sole initiative of the manufacturer and FDA-triggered recalls; therefore, we are unable to comment on the relative contribution of any changes in FDA behavior.

Clearly, there is a paucity of data in the public domain on product recalls and similar data from the European Medicines Agency (EMA) could not be retrieved. Initiatives such as open FDA (https://open.fda.gov/) that provide more insight into data collected by the FDA are welcomed. However, limited data are currently available relating to the underlying reasons for recall and more studies are required to investigate root causes and preventability of product recalls; however, this was beyond the scope of the current study. It has been reported that the problem of poor-quality medicines is particularly pertinent in emerging economies [6]. Research using different data sources is needed to investigate the incidence of recalls and should also investigate other regulatory regions where the level of regulatory oversight might not be as stringent.

Given that we were interested in differences between recombinant therapeutic proteins and small molecules, we excluded recalls for a considerable number of biologicals that did not meet our definition, such as plasma-derived products. However, some of the complexity of manufacturing might also apply to nonrecombinant biologicals, as illustrated by the suspension

of the intravenous immunoglobulin product Octagam® in the European Union (EU) following an increase in reported thromboembolic events resulting from changes in its manufacturing process (http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Octagam_31/WC500154855.pdf). In addition, we did not differentiate between different sorts of small molecule. For example, nonbiologic complex drugs, such as heparin, were categorized as 'small molecules'. In the USA, heparin is authorized as a drug (either via a new drug application or an abbreviated new drug application), whereas in the EU it is considered a biopharmaceutical [7]. Such differences also give rise to caution to extrapolate our results to other regulatory regions.

Looking only at recalls might underestimate the number of product quality issues. Some quality-related problems might have escaped the attention of the manufacturer and the FDA and not all quality-related problems will lead to recalls. For each quality problem, the FDA and the company need to balance the impact of a product recall, because it might also have unwanted consequences, such as drug shortages [4]. For example, in 2009, several Genzyme products were contaminated with foreign particles, including steel fibers. This led to warnings to physicians to carefully inspect the product, but the product was not recalled because it was the only available treatment option [8]. Given that they are more often produced by a single manufacturer, it might be that quality issues for biopharmaceuticals result less frequently in recalls, compared with small molecules.

Ideally, we would comment on the incidence of recalls as a fraction of all available products of biopharmaceuticals *versus* small molecules. However, we were limited by our data sources and were unable to link recall data to authorized products for the obtained recalls. If we took all authorized products as the denominator and the average number of yearly recalls as the numerator, this would lead to 3.7/139 (2.7%) and 159.2/8023 (2.0%) of recalls for biopharmaceuticals and small molecules, respectively. However, care must be taken when interpreting this number because we do not have insight into whether products were marketed and/or their volume of use, which could lead to an over- or underestimation of the actual incidence of recalls.

Concluding remarks

A very limited number of recalls in general, and none for biopharmaceuticals, were initiated following adverse events. Our results do not indicate that biopharmaceuticals are more susceptible to potentially dangerous product errors and, as such, the complexity of manufacturing biopharmaceuticals is not reflected in our data set. Limited data are publicly available on product recalls. To investigate root causes of product recalls, learn from past experiences, and prevent recalls in the future, more detailed data on product recalls should be made publicly available for future studies.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drudis.2015.10.020.

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Hans C. Ebbers[1,2]
Nina Fuentes de Tienda[1]
Marcel C. Hoefnagel[3]
Ria Nibbeling[3]
Aukje K. Mantel-Teeuwisse[1,*]

[1]*Utrecht University, Faculty of Science, Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht, The Netherlands*
[2]*Utrecht University, Faculty of Science, Utrecht Institute for Pharmaceutical Sciences, Department of Pharmaceutics, Utrecht, The Netherlands*
[3]*Medicines Evaluation Board (CBG-MEB), Utrecht, The Netherlands*