feature

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

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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

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