JAMA study casts cloud over biologic safety

The first study to take an in-depth look at safety issues surrounding biologics suggests they pose a heightened risk of adverse events compared to other types of drugs. The disquieting figures published in October reveal that 24% of biologics approved in the US and Europe have prompted safety regulatory actions (*J. Am. Med. Assoc.* **300**, 1887–1896, 2008). As biologics and monoclonal antibodies (mAbs) continue to be widely embraced across the drug industry, making up a growing proportion of new drugs approved each year, their safety record is coming under greater scrutiny. This, together with an increasing emphasis on the use of biologics as blockbuster treatments for chronic conditions, such as rheumatoid arthritis, means that risk mitigation strategies are likely to continue to be an important facet of regulatory oversight for biotech drugs.

Between 2003 and 2006, biologic drugs represented about a quarter of the new molecular entities approved in the US and Europe. At the same time, these drugs now generate revenues to rival blockbuster small molecules (**Table 1**), especially where they are indicated for chronic conditions, such as rheumatoid arthritis, dialysis and multiple sclerosis. "Antibodies are resurrecting this business model. [That's why] billions of dollars are being poured into biologics developments," says Jeff Morhet, chairman and CEO of antibody producer InNexus Biotechnology, based in Vancouver, British Columbia.

The new study in *JAMA* follows a 2002 publication in the same journal (*J. Am. Med. Assoc.* **287,** 2215–2220, 2002) that looked at safety concerns surrounding new chemical entities (small molecules). The figures showed that 8% of drugs approved by the US Food and Drug Administration (FDA) between 1975 and 1999 drew black box warnings within ten years of approval. About 3% were withdrawn from the market.

For the biologics study, the authors included 174 biologics approved either in the US or Europe between January, 1995, and June, 2007. They excluded vaccines, allergenic and transfusion products, and products for further manufacture and transfusion purposes. The researchers chose to begin the study with products approved in 1995 because this was the year that the European Agency for the Evaluation of Medicinal Products (EMEA) was established, providing a centralized decision-making mechanism for Europe.

Of the total 174 biologics that qualified for inclusion, 41 (23.6%) prompted safety-related regulatory actions such as written communications to healthcare professionals. Although none were withdrawn for safety reasons, overall, a biologic had a 14% chance of prompting safety-regulatory action within three years of approval and a 29% chance within ten years.

The numbers don't compare favorably to new chemical entities. The 2002 study showed new chemical entities having an 8% chance of a black box warning within ten years of approval, compared to 17% for biologics according to the most recent study. But the authors point out that the studies can't be directly compared because safety awareness and access to safety data has been heightened in recent years. "Post-marketing surveillance has evolved over time and has been booming over the last decade. That's the main problem in comparing the studies," says Thijs Giezen, lead author of the 2008 study, who is a PhD student at Utrecht University in The Netherlands and also a pharmacovigilance assessor for The Netherlands Medicines Evaluation Board.

The biologics study also suffers from small sample size—a consequence of the team's decision to restrict the study to products approved after EMEA's establishment. Still, industry observers are hardly surprised by the unsettling safety numbers. "The complexity of biologics with their huge size and tremendous potential variations made it only a matter of time before folks started to wake up and realize that biologics are quite different from small-molecule drugs in their clinical behavior, both positive and negative," says Bryan A. Liang, co-director of the San Diego Center for Patient Safety at the University of California San Diego School of Medicine. "This was first really noted with the Epogen/Eprex [epoetin] case and pure red cell aplasia, but now with the *JAMA* study out, it's not a fluke." (See also **Box 1**.)

Others agree. "You take these large, active biological molecules that we don't fully understand, you put them in systems using a delivery route that is not [natural] to the body—there are a lot of good reasons biologically and statistically," says Stephen Buxser, a research analyst at the consulting firm Nerac in Tolland, Connecticut.

The results may call for an earlier emphasis on safety, including during pharmacology studies. "Maybe [companies] can focus on the mode of action and try to predict the potential safety problems that might occur," says Giezen, though he concedes that many safety problems will be too rare to show up during clinical trials. Nevertheless, companies can anticipate post-marketing studies and focus on them to better identify and quantify the risks, he says.

Most of the safety problems seem to be related to the parenteral mode of administration, such as reactions at the injection site, and to the immune system, infections or immune system disorders, or benign or malignant tumors. That doesn't come as a surprise to Morhet. "It should be expected. [Companies] have to recognize immunogenicity from day one. They have to build safety in from day one, not wait until they're done with the exploratory science," he says.

It remains to be seen whether the cumulative safety data on biologics as a whole will have any influence over regulatory agencies. Although FDA has received a mandate to perform more post-marketing surveillance, it is still underfunded and understaffed. Buxser also points out that the agency suffers from an aging technological infrastructure. "They've got to correct the people problem and the infrastructure problem, and then you may see some improvement," he says.

"It's a very good study, (but) it needs to be further looked at," says Marisa Papaluca-Amati, deputy head of EMEA's sector for safety and efficacy of medicines. Papaluca-Amati points out that EMEA's requirements for safety monitoring have changed dramatically in the past decade, which complicates the study's conclusion that biologics have a 14% chance of a safety-related action in 3 years and 29% in a decade. Those regulatory

The TeGenero disaster was a wake-up call to the industry. Six healthy men became seriously ill during phase 1 trials after receiving the antibody TGN1412 produced by the German company, whose headquarters are pictured here.

Box 1 Avastin safety signals spotlighted

The safety risks of some prominent biologic blockbusters have come to light recently. Genentech's anti-vascular endothelial growth factor (VEGF) antibody drug Avastin (bevacizumab) has been linked to a 33% increase in risk of blood clots in veins, according to a meta-analysis published recently in *JAMA* (*J. Am. Med. Assoc.* **300**, 277–285, 2008), although the S. San Francisco-based company is disputing the findings. Avastin already has a black box warning about risks of hemorrhaging and perforations of the bowel.

Genentech published its own pooled analysis of five studies last year (*J. Natl. Cancer Inst.* **99**, 1232–1239, 2007), concluding that there was no increased risk of blood clots. The current *JAMA* publication pools 15 studies with a total of 7,956 subjects. They conclude that the 1,745 patients in Genentech's pooled analysis were insufficient to detect a statistically significant risk. *JK*

changes "should be taken into account," she says.

FDA's Sandra Kweder, deputy director, office of new drugs at the Center for Drug Evaluation and Research, adds a caveat about the study's conclusions. Biological therapeutics are more likely to be developed to treat serious illnesses, she points outs, and "serious illnesses themselves are fertile ground for 'toxicity' whether related to the drug or disease, so interpreting data on the drug's or biological's risk must take that into account."

The paper also does not take into account expansions in indications, which could explain the increasing safety-related actions. As companies expand a biologic's indication, safety actions "may not be reflecting more safety issues but more simply an extension of the impact of the product and an extension of the population treated," Papaluca-Amati says. She added that EMEA's Committee on Medicinal Products for Human Use hasn't yet considered the study.

The study could also have implications for the follow-on biologics debate. Generics companies argue that they can prove that a follow-on biologic has a similar safety and efficacy profile to the innovator's product and, like generic small-molecule drugs, should be excused from conducting clinical trials. Innovator companies argue that biologics can differ significantly when produced at different manufacturing facilities and therefore any follow-on product should have to undergo clinical trials to demonstrate an acceptable safety and efficacy profile. "This study will put weight on the side that the brand name folks have advocated: clinical trials for any follow-on attempting to come into the market," says Liang. Europeans have already adopted such a structure, and the *JAMA* study will no doubt persuade many quarters that safety activities need to be heightened in the US. "The safety of the drugs approved by the FDA is being questioned, even by the general public, so I doubt policy makers will only focus on price," Liang adds.

The finding that immune system problems crop up frequently for biologics should help guide safety monitoring, says Giezen. "[Physicians] probably know about most of the safety problems with small molecules, such as liver toxicity, but for biologics those safety problems are different. There might be infections, or some malignancies, and [they may develop] a long time after starting the treatment, or after treatment has stopped," says Giezen.

Other industry insiders agree that long-term safety monitoring will be crucial for biologics. "That long-term use may lead to problems I think is a given," says Thomas Kindt, who is InNexus's chief scientific officer. Despite the latest study's confirmation of that suspicion, Morhet finds at least one important consolation: the study showed that no biological was pulled from the market for safety reasons.

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Table 1 Top-selling blockbuster biologics in 2007

Biologic	US sales (billions)	Rank[a]
Aranesp (darbepoetin alfa)	$3.2	5
Neulasta (PEG-filgrastim)	$3.1	6
Epogen	$3.1	6
Remicade (infliximab)	$2.8	9
Eprex	$2.4	12
Rituxan (rituximab)	$2.3	14
Avastin	$2.3	14
Lantus (insulin glargine, rDNA origin)	$1.7	23
Avonex (interferon β-1a)	$1.2	33
Humalog (insulin lispro)	$1.0	44

[a]Based on US sales of all drugs (small molecules and biologics); Lipitor is ranked number 1 at $6.2 billion. Source: Ranking, Verispan, VONA; revenues, company literature.