BIOBUSINESS BRIEFS

REGULATORY WATCH

Innovation in biologic new molecular entities: 1986–2014

Determining the innovativeness of a therapeutic biologic is not straightforward. In the United States, all such agents have been approved by the US Food and Drug Administration (FDA) as unique, new drugs, whether or not there were structurally related biologics already marketed. So, classifying innovation in therapeutic biologics by taking into account previously approved therapies may help in understanding the degree of innovation that is inherent in these products.

We used an internal FDA data set containing all of the new molecular entities (NMEs) — small-molecule and biologic — approved between 1986 (coinciding with the first approved therapeutic monoclonal antibody product) and 2014. We defined therapeutic biologics as products that were produced by a biological expression system that had been manipulated using techniques such as genetic engineering, cell fusion or other technologies. We limited this list to include only those drugs that are currently regulated by the Center for Drug Evaluation and Research (CDER) and therefore did not include non-CDER-regulated biologic products, such as vaccines, gene therapies or plasma-derived products.

During this time period, 1986–2014, 125 biologics were approved (see Supplementary information S1 (table) for a list), accounting for 15% of total NME approvals (844 total approvals). In the most recent ten years, 2005–2014, 55 biologic NMEs were approved, accounting for 20% of total NME approvals in this time period (269 total approvals). In 2014, CDER issued 11 biologic NME approvals, the highest total for a single year.

To investigate the level of innovation in biologic NMEs, we classified all NMEs, including therapeutic biologics, as first-in-class, advance-in-class or addition-to-class. First-in-class drugs were the first drugs to be approved in their class, advance-in-class drugs provided significant clinical benefits over existing therapies in the class, and addition-to-class drugs were NMEs that did not provide any clinical advantage over existing therapies in the class (for details of the classification criteria, see *Health Affairs* **32**, 1433–1439; 2013). This classification scheme allowed us to distinguish between the truly innovative biologics (the first-in-class and advance-in-class) and the less innovative biologics (addition-to-class).

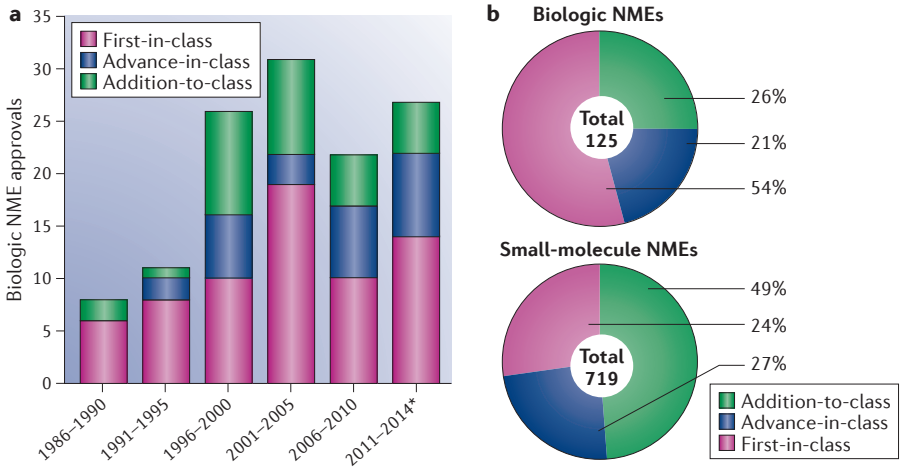

Figure 1 | **Innovation in biologic new molecular entities.** **a** | Biologic NME approvals by the US Food and Drug Administration in 1986–2014, split into innovation categories and 5-year time periods. **b** | Comparison of the innovativeness of biologic and small-molecule NMEs approved in 1986–2014. NME, new molecular entity. *The last bar is only a 4-year time period.

Between 1986 and 2014, 54% (67) of the approved biologic NMEs were considered first-in-class and 21% (26) were considered advance-in-class (FIG. 1), whereas the corresponding proportions for small-molecule NMEs were 27% (197) and 24% (173), respectively. Conversely, during this time period, only 26% (32) of biologic NMEs were determined to be an addition-to-class, whereas 49% (352) of small-molecule NMEs were considered to be an addition-to-class. So, compared with small-molecule NMEs, almost twice the proportion of biologic NMEs were first-in-class and half the proportion were addition-to-class drugs, suggesting that biologic NMEs were, on average, more innovative than small-molecule NMEs in the studied period. We also found that, compared with their small-molecule counterparts, a higher proportion of biologic NMEs focused on rare diseases; 47% (59) of biologic NMEs received an orphan designation, versus only 21% (152) of small-molecule NMEs.

Legislation to establish a regulatory pathway for biosimilars was created when the Biologics Price Competition and Innovation Act was passed by the US Congress under the Affordable Care Act in 2010. Of the 21 biologics approved from 2012–2014, 7 came from classes that were expected to have had a notable branded biologic coming off patent in upcoming years (and so were potentially subject to biosimilar competition); 5 of these 7 were considered advance-in-class. Although the future implications for the biosimilars market are unclear, it is possible that the potential for biosimilar competition may be spurring drug developers to further innovate and introduce 'next-generation' products to compete with incoming biosimilar versions of first-generation products (*Nature Rev. Drug Discov.* **11**, 426–428; 2012).

Overall, the results of this analysis provide further evidence of the differences between the biologic and small-molecule markets, and indicate that, compared with small-molecule drugs, therapeutic biologics approved in the past ~30 years have been more innovative on average. Additionally, the biologic NME market may be evolving to counteract the threat of upcoming biosimilar competition.

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The authors declare no competing interests.