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The rise (and decline?) of biotechnology

Michael S. Kinch, michael.kinch@yale.edu, kinchm@gmail.com

Since the 1970s, biotechnology has been a key innovator in drug development. An analysis of FDA-approved therapeutics demonstrates pharmaceutical companies outpace biotechs in terms of new approvals but biotechnology companies are now responsible for earlier-stage activities (patents, INDs or clinical development). The number of biotechnology organizations that contributed to an FDA approval began declining in the 2000s and is at a level not seen since the 1980s. Whereas early biotechnology companies had a decade from first approval until acquisition, the average acquisition of a biotechnology company now occurs months before their first FDA approval. The number of hybrid organizations that arise when pharmaceutical companies acquire biotechnology is likewise declining, raising questions about the sustainability of biotechnology.

Analysis of biologics approvals

The sustainability of biotechnology as a source of innovation for drug development is increasingly uncertain. An analysis of FDA-approved NMEs suggests a foundation for such concerns. The term biotechnology is ambiguous. To some, this represents biologically-derived or synthesized products. To others, it represents an approach of using knowledge from living systems to derive a novel approach or product. As a starting point, we first defined of biotechnology drugs as being a biologic medical product (as opposed to a synthetically produced molecule). In total, 94 biologic licensing applications (BLAs) were approved by FDA. Approvals rose from an annual average of 0.2 NMEs in the 1980s to a relatively consistent average of 4.7 NMEs per year since 2001 (Fig. 1a).

Roche received the first approved BLA in 1986 as well as the most recent approval in 2013. In between, 55 companies obtained approval for at least one biologic drug (not shown). As a consequence of mergers and acquisitions, 29 companies (52.7%) now remain active and independent.

Roche is generally viewed as a pharmaceutical company. To broadly distinguish pharmaceutical and biotechnology organizations, all companies founded after Cetus Corporation (1971) were defined as biotechnology for the analysis below. We asked how organizations contributed to biologics NMEs in terms of: 1) Filing the first patent; 2) Submitting the Investigational New Drug (IND) application; 3) Clinical development; or 4) Awarding of a BLA.

Pharmaceutical and biologics companies were awarded 41 and 53 BLAs, respectively. However, the impact biotechnology extended beyond approvals. Biologics companies contributed to 87 of 94 (92.6%) approved BLAs when considering the sources of first patents, preclinical and clinical development activities (not shown). The contributions of biotechnology remained steady over four decades, with increased early-stage contributions (patents and INDs). Pharmaceutical companies have increasingly gained a greater proportion of final approvals (from 44% in the 1990s to 64% in the current decade).

Broader overview of biotechnology

While biologics products encompass one impact of biotechnology, a broader view includes small molecules. If we define all organizations founded after Cetus as biotechnology, regardless of whether they developed biologics or small molecules, the number of NME approvals increased ten-fold since the 1970s (Fig. 1b). In comparison, the number of NMEs awarded to pharmaceutical companies decreased somewhat from 20.4 NMEs per year to 18.0 in the 1970s and 2010s, respectively. Biotechnology companies were awarded 5.5% of NMEs in the 1980s and 41.9% of NMEs today.

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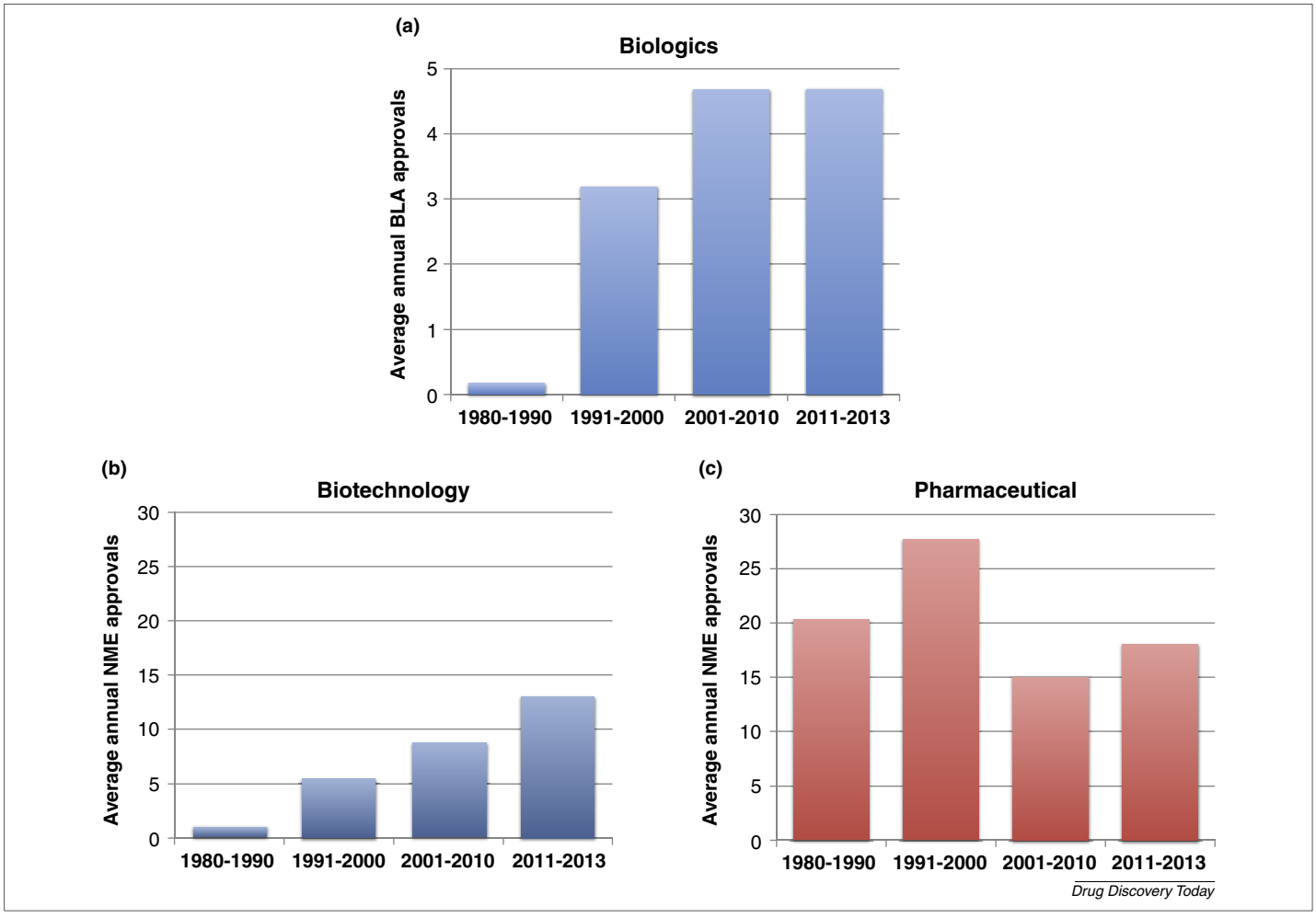

FIGURE 1

Approval rates of biotechnology and pharmaceutical products. The average annual approval rate of **(a)** Biologics products; **(b)** biotechnology products from organizations founded in or after 1971 or **(c)** pharmaceutical products from organizations founded before 1971 are indicated.

We also assessed the role of biotechnology on NMEs awarded to pharmaceutical companies. One-third of all NMEs awarded to pharmaceutical companies had at least one critical contribution (first patent, IND or clinical trial) from a biotechnology company (Fig. 2). Over time, the role of biotechnology increased from 1.3% of pharmaceutical NMEs in the 1980s to 35.2% in the ongoing decade. At present, >20% of patents for NMEs were awarded to biotechnology companies and almost 25% pharmaceutical NMEs had biotechnology contributions in the form of preclinical or clinical activities.

We assessed further the organizations responsible for preclinical and clinical development activities. When evaluating organizations that filed the IND or held the end of phase 2 (EoP2) meetings, biotechnology gained parity with the pharmaceutical companies within the past decade and surpassed the pharmaceutical industry in terms of IND submissions and initial EoP2 interactions (Fig. 2b and data not shown).

Attrition of biotechnology contributors

Many biotechnology companies have been acquired by pharmaceutical organizations. Thus, we determined the fate of all biotechnology organizations that contributed to the research, development or approval of at least one NME. Specifically, we tabulated the number of active and independent biotechnology companies as assessed by new entries and exits (as a result of acquisition or dissolution) (Fig. 3a,b). The number of biotechnology companies grew steadily over three decades and peaked at 143 active and independent organizations in 2001 (Fig. 3a). Since then, the number has shrunk to 71.

A stable accumulation of entries characterized the period from 1981 through 2000 (Fig. 3b). New entries rose from an annual average of 1.5 in the 1970s to a peak of 8.6 in the 1990s. Thereafter, the number of new entries collapsed. In parallel, exits increased. Since the turn of the century, exits have outpaced entries at a rate of more than four to one. The net effect is that from a total number of 187 biotechnology companies, 116 exited and 71 remain.

Analysis of exits

We then asked whether the type of contribution towards an NME related to the likelihood of an acquisition. To our surprise, biotechs who were awarded an NME were less likely to be acquired (50.9%; not shown). In contrast, organizations that had participated in clinical development (79.5%) were more frequently acquired.

We also asked how key milestones related to acquisition. The average time from biotech founding until the first FDA approval was consistent at just over 11 years (Fig. 3c). The average time from founding until acquisition varied (from 13.9 to 17.7 years) but did not show a consistent trend. In contrast, the average time from first approval to exit (acquisition) dramatically and consistently decreased (Fig. 3d). Biotechnology companies receiving their first approval in the 1980s remained active and independent for an