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Novel Drug Movers and Shakers 2013-2016

Small and Medium Sized Companies in North America Lead Novel Drug Innovation

Small and medium sized companies and academia are important drivers of innovation in drug development. To investigate the profile of the organisations originating and developing novel drugs approved in the EU and US during 2013-2016 we have compiled all medicinal products containing novel substances (e.g. NAS, NME and Biologics)* from the EMA and FDA websites. For each novel drug we mapped the approval pathway, rare disease (orphan) status and post-approval licensee. The innovator(s)** and the development organisation(s)*** were mapped in accordance with the ADIS insights database. Each originator and developer was categorised as a large pharmaceutical company, a small or medium sized pharmaceutical company (SME) or an academic and/or public body****. We also mapped and analysed the geographical origin (e.g. Europe, North America or Rest of the World) of the SME or the academic and/or public body. Altogether, 178 novel drugs received approval from the EMA and/or the FDA during 2013-2016. A summary of the main findings are outlined below.

North American SMEs lead novel drug innovation

54% of the novel drugs approved in EU and/or US originated from SMEs. Academia and/or public bodies represented 7% of the originators and large pharma 28%. Furthermore, 3% were collaborations between SMEs and academia and/or public bodies. The rest of the novel drugs came from collaborations between all three parties, *figure 1*. Lincker et al has shown that in EU approximately half of the EMA approved products containing a NAS between the years 2010-2012 originated from a SME, academic public bodies and/or private collaborations [(1)].

We examined the geographical location of the SME and the academic and/or public bodies and found that 30% of the originators were based in Europe (EEA including Switzerland), 50% in North America (USA and Canada) and 14 % in rest of the world. 4% of the novel drugs were born of transatlantic collaborations and North America-Rest of the World cooperation yielded 2%, *figure 2.*

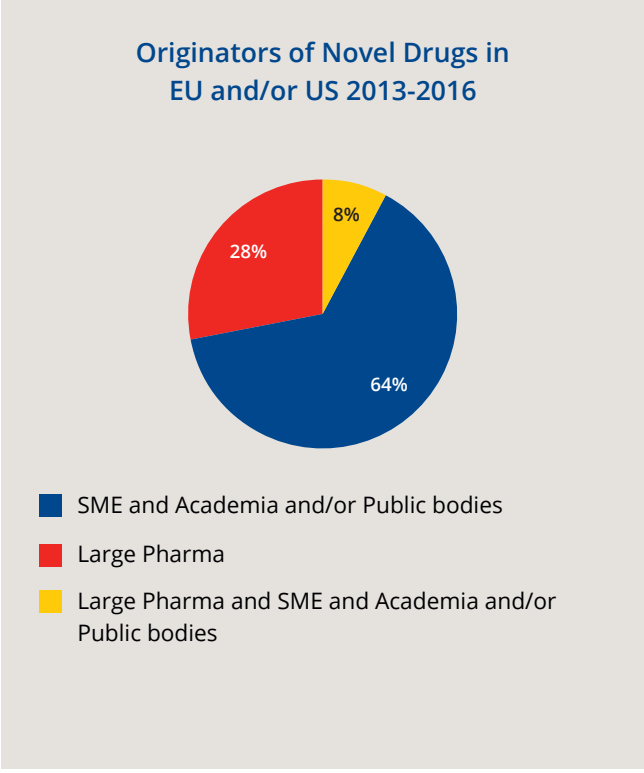

Figure 1

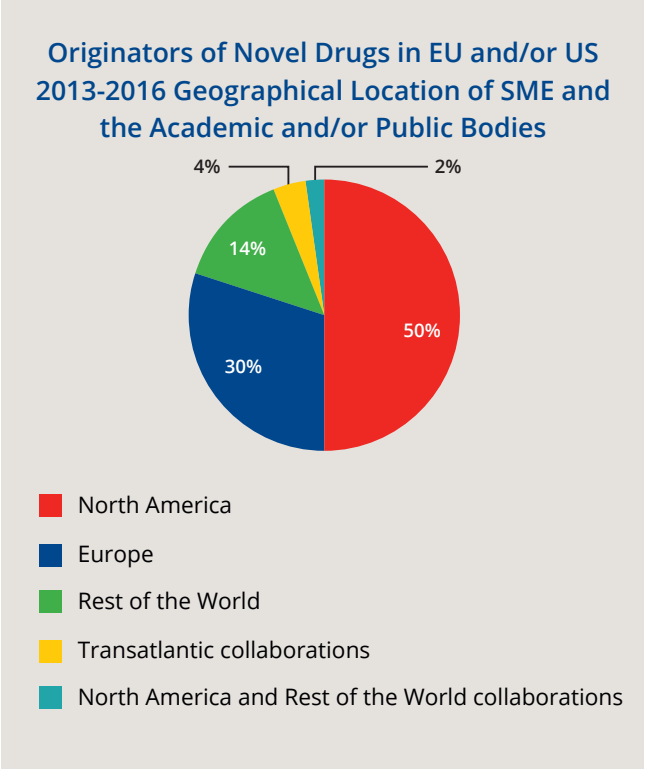

Figure 2

Does this indicate that North America is more inventive *per se* than Europe when it comes to novel drugs? Likely not, as there is no difference in the quality of science in Europe or North America [2-4]. The explanation may lie in disparities in drug research funding, availability of European venture capital, and the fact that European universities don't traditionally train scientists in entrepreneurship. Some cutting edge scientific discoveries currently applied in drug development originated in Europe: RNAi, CRISPR-Cas9 and the next generation of T-cell receptors are some examples. Going forward, Europe would benefit from creating a more fruitful environment for organisations applying downstream translational research resulting in novel drugs. To encourage collaboration with academia, EMA recently launched a framework to formalise, structure and further develop interactions with the academic community. The framework aims to integrate cutting-edge scientific knowledge more tightly into EMAs activities and will help academic start-ups to benefit from advice from the EU regulatory network.

A high number of novel drugs are developed by SMEs

SMEs developed 24% of the novel drugs in the EU and/or US and 7% of the novel drugs were developed in collaborations between SMEs and academia and/or public bodies This is impressive, given that only about ten percent of clinical programs result in regulatory approval and smaller players may have an even lower success rate due to limited internal experience in clinical development, manufacturing and clinical supply [5]. The key to successful development and regulatory approval seems to be in the cooperation of several SME companies and academia and/or public bodies working together.

Many SMEs rely on development partnerships with large pharma

23% of the novel drugs were developed by large pharma. Of those, large pharma developed 22% in collaboration with SMEs, 7% together with academia and/or public bodies and 17% in collaborations with both latter parties, *figure 3*. This suggests that smaller players are boosting the product pipeline of larger companies, given that 64% of the novel drugs originated from SMEs and academia and/or public bodies. Hence, large pharma are continuing their efforts to acquire novel molecules from the promising portfolios of smaller players who may lack adequate resources to bring the products to approval.

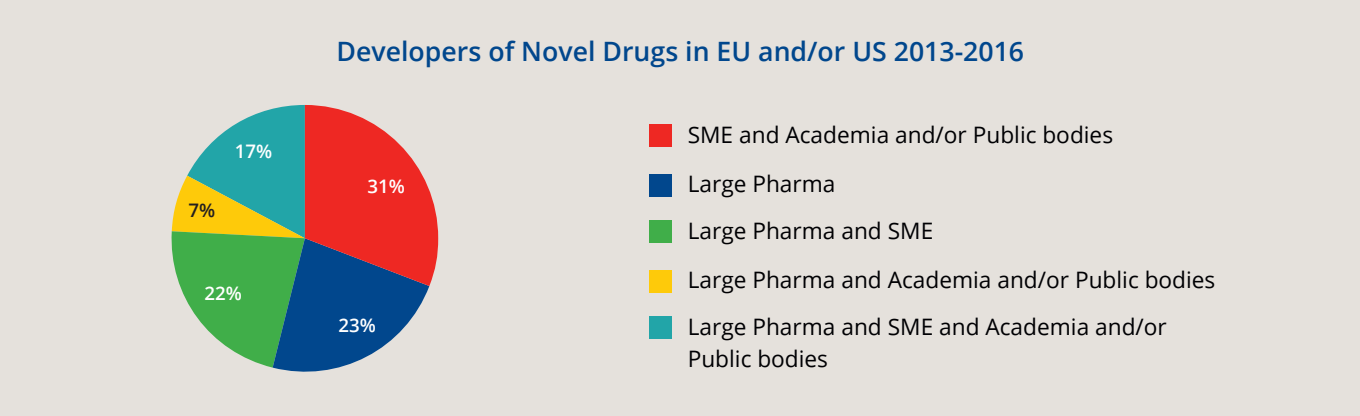

Figure 3

Securing adequate capital is an issue for leaner organisations, and academia may run into challenges related to the institution's technology licensing practices. Further factors contributing to cost challenges for smaller parties lie in the FDA's and EMA's sometimes divergent approaches to assessing benefit/risk - causing the need for larger clinical trials, label differences and some drugs not reaching certain markets.

A third of novel drugs for rare diseases originates from and are developed by small players

Our data also reflect the difference between the orphan classification systems in the EU and US; 41% of the novel drugs approved in the US were classified as orphans and 32% in the EU. Altogether 21% of the novel drugs approved in EU and US were classified as orphans in both regions. In EU 60% of the orphans drugs originated from SMEs and academic and/or public bodies and in US 74%. In both EU and US approximately 30% of the orphan drugs were also developed through regulatory approval by SMEs and academic and/or public bodies. 31% of the novel drugs that were classified as orphans in both regions originated from and were developed through regulatory approval by SMEs and the academic and/or public bodies.

For orphan drug developers, both the EMA and FDA offer incentives such as fee reductions (and free scientific advice for paediatric studies in EU), ten years of market exclusivity in EU (seven years in the US), and waived payment of regulatory fees. FDA also has a Rare Paediatric Disease Priority Review Voucher program: Upon receiving approval for a rare paediatric disease, the applicant receives a voucher that can be redeemed (or sold) for priority review of a different product.

Some novel drugs not approved in EU but the majority are approved in both EU and US

Of the novel drugs submitted in 2013-2016, 83% were approved in the EU and 93% in the US. In the US, expedited drug development and nonstandard review approval pathways were commonly used (55%), but in the EU special approval procedures were not as common (21%).

To facilitate early drug development the EMA recently launched the PRIority MEdicines scheme (PRIME). SME and the academic sector can apply for PRIME status earlier on the basis of compelling non-clinical data and tolerability data from clinical trials. Another alternative EU tool is the adaptive pathway pilot option (formerly adaptive licensing), based on the current EU legal framework and processes (parallel scientific advice, Conditional Marketing Authorisation (CMA) subject to specific obligations, risk management plans, observational studies, and post-approval safety/efficacy studies) aiming to provide a CMA or approval in a staggered fashion. In parallel to the adaptive pathways pilot project, the Innovative Medicines Initiative (IMI) runs ADAPT-SMART that investigates the conceptual framework used in adaptive pathways, including tools and methodologies. However, drug developers looking to apply expedited drug development pathways in EU should take the divergent views among the EU HTA bodies into consideration. Early dialogue with EMA and the European Network for Health Technology Assessment (EUnetHTA), in particular in the area of coordinated advice is advisable.

NDA supported over 40% of the novel drugs approved in the EU during 2013-2016

Our analysis show that over the last four years NDA has supported over 40% of the novel drugs that received approval in Europe with a great breadth of services. Earlier this year, NDA also published data demonstrating support of over 40% of total drug approvals (not just novel) in the EU from 2013-2016. Additionally, through NDA's expanding activities in the US the company also supported over 20% of new drugs that achieved approval by the FDA during 2016 [6].

Summary

SMEs and academia and/or public bodies are important drivers of innovation in drug development. The majority of the novel drugs approved in EU and/or US during 2013-2016 originated from SMEs and an academic and/or public body, 64% in total. 50% of these were based solely in North America. A high number of novel drugs are also developed by SMEs or by SMEs in collaboration with an academic and/or public body, e.g. 31% altogether. Looking at both EU and US, 31% of the novel drugs that were classified as orphans in both regions originated from and were developed through regulatory approval by SMEs companies and academic and/or public bodies.

Definitions

***** Some general inclusion and exclusion criteria have been applied to create consistent indicators for NAS, NMEs and Biologics due to differences in classification and reporting styles in EU and US: *A new chemical, biological, biotechnology or radiopharmaceutical substance that has not been previously available for therapeutic use in humans and is destined to be made available as a "prescription only medicine", to be used for the cure, alleviation, treatment, prevention or in vivo diagnosis of diseases in humans.* The definition also includes an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously available as a medicinal product but differing in properties with regard to safety and efficacy from that substance previously available. A biological or biotech substance previously available as a medicinal product, but differing in molecular structure, nature of source material or manufacturing process and which will require clinical investigation. A radiopharmaceutical substance which is a radionuclide or a ligand not previously available as a medicinal product, alternatively, the coupling mechanism linking the molecule and the radionuclide has not been previously available. New developments of previously authorised products, classified as having a significant technical or therapeutic innovation by FDA and/or EMA were included in the analysis. Only new developments of orphan designated products were included in the analysis. Under this definition, biosimilar products may also be considered as novel substances, however, for the analysis in the article the definition has been amended to exclude biosimilar products -as these were not deemed to be truly new developments. Combination products (combinations of previously authorised substances), generic applications and well established use (literature-based) dossiers were excluded for the same reason. Vaccines have been omitted from the analysis.

****** The originator organisation(s) were profiled the from the ADIS insight database taking into account company agreements and key development milestones. The originator is defined as the "organisation originating the drug or therapy". The organisation that owns the intellectual property rights is defined as the 'owner' and might differ from the originator. Each originator entity was then categorised as a large company in accordance with the list of the top 50 pharma companies from www.currentpartnering.com, all other entities were classified as a small and medium sized company, or an academic/public body.

*** The development organisation(s) were profiled the from the ADIS insight database taking into account company agreements and key development milestones. The developer definition relates to all organisations that have been involved with scientific development of the drug – this could be partner companies or institutions that were involved in preclinical experiments but also clinical trial sites. Each originator entity was then categorised as a large company in accordance with the list of the top 50 pharma companies from www.currentpartnering.com, all other entities were classified as and small and medium sized company, or an academic/public body.

**** A large pharmaceutical company was defined as one the top 50 pharmaceutical companies ranked by revenue in accordance with revenue listings from www.currentpartnering.com. The rest of the organisations were defined as small and medium sized pharmaceutical companies (SMEs) and/or an academic/public body. For the purpose of this publication the definition of a SME includes a medium-sized company classified by default as neither complying with the EU SME criteria (listed below) nor being a large company in accordance with revenue listings from www.currentpartnering.com. The EU criterion for categorising a Small and Medium sized Enterprise is: headcount less than 250 and not more than €50 million in turnover or €43 million on the balance sheet in accordance with Recommendation 2003/361/EC of 6 May 2003).

References

(1) Regulatory watch: Where do new medicines originate from in the EU? Lincker H. et al; Nat Rev Drug Discov. 2014 Feb;13(2):92-3

(2) Global University rankings: https://www.timeshighereducation.com/world-university-rankings/2016

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(5) Clinical development success rates for investigational drugs; Hay M. et al; Nat Biotechnol. 2014 Jan; 32(1):40-51

(6) Europe vs USA: new drug product approvals in 2016, Johansson T. et al (in print)