Promoting Effective Drug Development Programs: Opportunities and Priorities for FDA's Office of New Drugs

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Reforming the FDA-managed, non-patent incentives for drug development, from rights in test data, orphan drug and pediatric testing exclusivity, to the priority review voucher.

Introduce economics to design incentives

Require transparency of trial costs

Design incentives to what is reasonably necessary to induce desired investments

Replace the priority review voucher with market entry rewards

Explicitly consider expected and actual on sales revenues

Make some incentives optional, and tied to affordability/reasonable pricing conditions, introduce means test for others.

Do not use exclusivity privileges when it is cheaper to achieve the same result by funding market entry rewards or subsidizing research.

Means test in original Orphan Drug Act, the 1984 Public Law 97-414

“SEC. 526. (a)(2). For purposes of paragraph (1), the term ‘rare disease or condition.” condition’ means any disease or condition which occurs so infrequently in the United States that there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug. Determinations under the preceding sentence with respect to any drug shall be made on the basis of the facts and circumstances as of the date the request for designation of the drug under this subsection is made.

(b) Notice respecting the designation of a drug under subsection (a) shall be made available to the public.

(c) The Secretary shall by regulation promulgate procedures for the implementation of subsection (a).

Means test in EU Orphan Regulation

Article 3 - Criteria for designation

1. A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish: (a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment; and (b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.

[Reduction in 10 year term]

2. This period may however be reduced to six years if, at the end of the fifth year, it is established, in respect of the medicinal product concerned, that the criteria laid down in Article 3 are no longer met, inter alia, where it is shown on the basis of available evidence that the product is sufficiently profitable not to justify maintenance of market exclusivity. To that end, a Member State shall inform the Agency that the criterion on the basis of which market exclusivity was granted may not be met and the Agency shall then initiate the procedure laid down in Article 5. The sponsor shall provide the Agency with the information necessary for that purpose.

REGULATION (EC) No 141/2000 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL, of 16 December 1999 on orphan medicinal products

Structure of voluntary incentives

A grant of a market entry reward, regulatory exclusivity, priority review voucher, or trial subsidies can be conditioned upon measures that would limit exclusivity or prices. One Example:

A fund for market entry rewards and/or trial subsidies, that is limited in aggregate size, with rewards/subsidies to qualifying projects larger or smaller depending upon demand with access to the fund tied to agreements to lower pricing and/or limit exclusivity when returns exceed targets.

The Pediatric testing extension is inefficient

2018. Michael S. Sinha, Mehdi Najafzadeh, Elizabeth K. Rajasingh, James Love, Aaron S. Kesselheim, *Labeling Changes and Costs for Clinical Trials Performed Under the US Food and Drug Administration Pediatric Exclusivity Extension*, 2007 to 2012. JAMA Intern Med. Published online September 24, 2018. doi:10.1001/jamainternmed.2018.3933

Results The 141 trials in our sample enrolled 20 240 children (interquartile range [IQR], 2-3 trials and 127-556 patients per drug). These trials led to 29 extended indications and 3 new indications, as well as new safety information for 16 drugs. Median cost of investment for trials was $36.4 million (IQR, $16.6 to $100.6 million). Among 48 drugs with available financial information, median net return was $176.0 million (IQR, $47.0 million to $404.1 million), with a median ratio of net return to cost of investment of 680% (IQR, 80% to 1270%).

Conclusions and Relevance Clinical trials conducted under the US Food and Drug Administration’s pediatric exclusivity program have provided important information about the effectiveness and safety of drugs used in children. The costs to consumers have been high, exceeding the estimated costs of investment for conducting the trials. As an alternative, policymakers should consider direct funding of such studies.

Some takeaways

Transparency is essential (R&D outlays, trail outcomes, prices, units sold, revenues, subsidizes, etc) if one is serious about reforming incentives

Prices are not the only thing, look at revenues

Technology transfer for biologic drugs, vaccines and cell and gene therapies, to enable competition, lower prices and safer biosimilars,

KEI Proposal to WHO (May 2017), and the FTC (August 2018)

As a condition of registration of biological products and services a person must agree to promptly, upon request, make available to providers of generic or biosimilar products or services certain materials, data, information and know-how, relating to the manufacture or supply of the regulated product, including but not limited to, when appropriate and relevant, the following:

a. Materials:

i. Cellular clones and hybridoma stocks;
ii. Plasmids, plasmid maps, and sequences of antibody complementarity determining regions (CDR); and
iii. Physicochemical/biophysical characterization;

b. Methods:

i. Growth conditions and protocols;
ii. Attenuation or inactivation protocols;
iii. Extraction and purification protocols; and
iv. Synthetic work-up and schemes;

c. Sufficient quantities of the approved medication for testing, and the protocols/methods used for testing the products, and the expected outcomes from those protocols.

Lisa Diependaele, Julian Cockbain, and Sigrid Sterckx, Similar or the Same? Why Biosimilars are not the Solution, The Journal of Law Medicine & Ethics, October 2018

We will argue that the regulatory pathway for biosimilars in the E.U. and the U.S. does not adequately serve the purpose of bringing safe and effective drugs onto the market without undue delay.[10] On the contrary, it has resulted in the allocation of substantial resources to the development of drugs equivalent to those that already exist, and has encouraged unnecessary performance of clinical trials — contrary to the Oviedo Convention[11] and recognized as a violation of important ethical principles guiding the conduct of medical research.

Nevertheless, solutions do exist: facilitating the development of a drug that more closely resembles the original product, a “biogeneric.” In addition to discussing some of the suggestions that have been made in this regard, we will argue that requiring the deposit of the original biologics’ cell line, which at a later stage generic companies can access, can be an effective remedy for some of the major shortcomings of the current situation.

11. “Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine,” Oviedo, April 4, 1997). ETS No. 164, available at <https://rm.coe.int/168007cf98> (last visited September 27, 2018).

Jeremy M. Levin, DPhil, MB BChir, Board & Health Section Chair of the trade association BIO, and Chairman & CEO, Ovid Therapeutics Inc.

. . . imagine if you offered a biologic developer, in exchange for guaranteed licensing of their cells and processes to any number of generic companies at the end of day “X” after some years of exclusivity, that they’d provide a perpetual license to all their processes and cell lines to those biosimilar manufacturers for a royalty stream in exchange. The original developer would be able to walk away from the original branded product that is now generic and still be guaranteed a royalty-based revenue stream.

. . . you wouldn’t have biosimilar companies developing poor-quality products because they’d be using the exact same cell lines and processes, and the new biosimilar product would be identical to the originator. And that benefits the patients.

Jeremy Levin Weighs In On Biosimilar Patent Thicket, Life Science Leader, August 30, 2019

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Some KEI links

https://keionline.org

http://delinkage.org

http://drugdatabase.info

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