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CASE 1

THE EVOLUTION OF THE U.S. PHARMACEUTICAL ECOSYSTEM

The story of U.S. pharmaceutical ecosystem regulation is punctuated by fits and starts and involves multiple actors.[1] In 1900, pharmaceutical producers may have possessed patents on their labels and bottles, but no controls were in place to protect consumers from harmful ingredients or their consequences. Technological advances abroad (the discovery of microbes, milk pasteurization, vaccines for anthrax and rabies) prompted an industry association, the American Medical Association (AMA), to offer manufacturers ingredient tests and rudimentary safety and efficacy evaluations in 1905. And by 1906, Congress had passed the Pure Food and Drug Act, which offered protection against adulterated or misbranded medicines and imposed a ban on dangerous ingredients. However, while the legislation inspired manufacturers to abandon many dangerous ingredients, efforts to prohibit false therapeutic claims on drug labels were defeated both by the Supreme Court and the U.S. Congress.

By the late 1930s, further advancements in drug technology (sulfanilamides, amphetamines, barbiturates, insulin) were entering the market and additional public health dangers emerged. For example, in 1937, a sulfaniliamide elixir containing toxic diethylene glycol was offered as a strep throat anti-infective. Congress reacted to the tragedy, which killed over 100 people, by enacting the 1938 Food, Drug, and Cosmetic Act. The Act delegated some authority to the nascent FDA (founded in 1930) - it could mandate the premarket submission of safety data for experimental drugs via an NDA (New Drug Application). Still, the power to determine methodologies for evaluating safety and efficacy remained firmly in the hands of practitioners and their professional associations.

During the 1950s, the NIH grew from a $161M to a $2.5B federal enterprise. Despite the centralization, peer-reviewed research grants continued to be designed individually, with collaboration solicited by principal investigators. Under such conditions, little but anecdotal evidence of drug safety and efficacy accumulated, and researchers retained considerable latitude. However, in

post-WW II trials of penicillin, a British epidemiologist and biostatistician introduced random assignment of patients to treatment and control groups. Subsequently, he and his North American counterparts began to map out general criteria for drug testing and to specify stages through which drug development should proceed. Nevertheless, during Congress's 1958 Kefauver hearings, it was revealed that in the typical investigation, a physician from a drug company would offer samples to a doctor who might try it on a few patients and offer his endorsement.

By 1962, another public health crisis had emerged surrounding thalidomide, a sedative turned morning sickness remedy for pregnant women. Linked to birth defects, the drug was never approved in the U.S., but unsuspecting doctors had nevertheless administered the experimental drug. Congress was finally motivated to make sweeping changes. In the 1962 Amendments and the 1963 IND regulations, Congress decreed that

1. No human testing for experimental drugs was to be conducted without preclinical (animal) studies,

2. Investigational New Drug (IND) applications were required prior to human clinical testing,

3.Standards were written for everything in the process (from lab to clinic),

4. Informed consent was incorporated into requirements for all clinical trial participants,

5. “Well-controlled clinical studies” involving control groups, random allocation of treatments, and criteria for judging effectiveness (e.g., end points) were required,

6. Phases of the clinical trial process were roughly outlined, and

7. An approval criterion for drug efficacy was to be included.

QUESTIONS

Q1: If this environment could be characterized as an “ecosystem,” who are the actors? Are there actors that might be excluded from the description offered in the case?

Q2: What is the overriding threat in this environment?

Q3: Who are the stakeholders that are most directly threatened? Which stakeholders are suppliers to them?

Q4: What core competences seem necessary to neutralize the threat? Which stakeholders in the ecosystem might possess them?

Q5: It seems that a resource which can be combined with these resources (salient core competences, relationships & reputation with customers) is lacking in this case. To what resource am I referring? Which organization(s) other than the government seem most likely to have been positioned to form the necessary resource combination?

Q6: The case also implies that constructing business- and corporate-level strategies are integral pieces of the leadership (first mover) strategy. What business-level and corporate-level strategies might you recommend that complement our resource-based view of this ecosystem?

Q7: By comparison, how does the Federal government ultimately seem to manage this ecosystem?

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1. Junod, S.W. FDA and Clinical Drug Trials: A Short History. Originally published as "FDA and Clinical Drug Trials: A Short History," in A Quick Guide to Clinical Trials, Madhu Davies and Faiz Kerimani, eds. (Washington: Bioplan, Inc.: 2008), pp. 25-55.

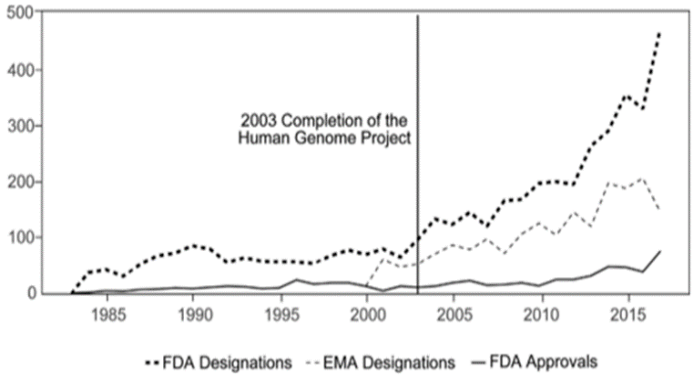
CASE 2

THE RARE DISEASE "INDUSTRY"

Market size. In the United States, a rare disease is defined as a condition that affects fewer than 200,000 people.[1] According to Global Genes,[2] about 400 million people suffer from rare diseases around the world. In the U.S. some 30 million people are afflicted,[3] while in Europe, some 27-36 million individuals also suffer from rare diseases.[4]

Regulators, scientists, clinicians and patient advocacy groups often cite ~7,000 as the number of rare diseases, or between 5,000 and 8,000 depending on the source.[22] Why do estimates of the number of rare diseases vary? One reason is a lack of consistency in defining discrete disease entities and their incidence in different countries or demographics. Some terminologies do not include chromosomal disorders, or other structural variations such as inversions, while others do not include rare diseases with environmental causes, such as toxin exposure.

Recently, several terminological resources have come together to harmonize disease definitions in the Monarch Disease Ontology. While this consensus process is still ongoing, we currently estimate the number of rare diseases to be more than 10,000. Even that number may be an underestimate as the number depends on our ability to not only define them, but to distinguish them as well. Thus, the number should continue to increase in line with our new emphasis on personalized medicine and along with our understanding and capacity to diagnose them.[23] Anyway, of the 7,000 identified rare and neglected diseases for which we know the molecular cause, only about 500 have approved treatments.[2]



As Figure 1 at the above suggests,[25] improvements in technology may also be responsible for some of the growth in orphan drugs.[5] It is estimated that >70% of rare diseases are genetic.[15] Furthermore, advances in biomarker technology may have also allowed for more precise definitions of patient populations, creating more opportunities for successful orphan drug applications.[13] For example, from 2009 to 2015, 16% of orphan drug approvals were based on biomarker-defined subsets of diseases.

Finally, the industry segment appears to be more profitable than other segments of the pharmaceutical industry. According to a study orphan published in 2016, orphan drug makers have a 9.6% higher return on assets

and a 9.9% higher Tobin's Q than non-orphan drug makers.[24]

Q1: What is the nature of the opportunity presented in this case?

Government involvement

The "rare disease" definition was created by Congress in the Orphan Drug Act (ODA) of 1983. Rare diseases became known as orphan diseases because drug companies were not interested in adopting them to develop treatments.[1] The United States enacted the first orphan drug law in 1983, followed by Japan in 1993, and the EU in 2000.[5] Several other countries—including Australia, Korea, and Hong Kong—have adopted similar legislation, but orphan drug laws do not exist in Africa, South America, and most of Asia (Gammie, Lu, and Babar 2015).[6] Residents in many of these countries do, however, have access to products developed in other markets.

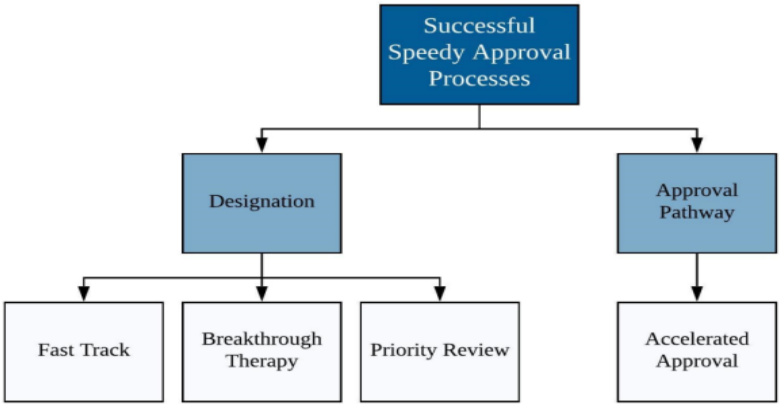
Developing new and innovative pharmaceutical products requires enormous up-front and fixed investments that do not meaningfully vary by the size of

the prospective market for the drug.[5] Thus, there is the possibility that the small markets in rare diseases could give rise to monopoly profits. The test for contestability is *not* the actual number of manufacturers with the technical means to produce competitor drugs, or the existing number of competitors. Instead, markets are considered contestable based on the number of manufacturers that *could* rationally enter. If that number is small - whether due to small market size or high R&D and production costs that prevent manufacturers from achieving minimum efficient scale -the original manufacturer will remain a natural monopolist, allowing it to reap the gains of monopoly pricing well beyond the officially granted exclusivity period.

The cost of clinical trials could also be larger for smaller market products, where patient recruitment and other costs for clinical trials can be larger per person. Thus, FDA-approved orphan drug trials are generally smaller (single arm, no placebo arm), nonrandomized, and open label. Safety Phase 1 trials are not usually required, and Phases 2 and 3 can be combined when the patient population is very low.[7]

In addition, most orphan drug laws reduce the time and expense associated with securing regulatory approval. In fact, a 2015 study suggests that time to FDA approval is reduced by almost three (10.1 vs. 12.9) years for orphan drugs.[14] This is because sponsors of an orphan drug can make use of expedited Food and Drug Administration (FDA) programs such as the Fast Track, Breakthrough Therapy, and Priority Review designations, as well as the Accelerated Approval pathway and unique grant funding opportunities, such as the Orphan Products Clinical Trials Grant program.[7]

Fig. 2 Expedited FDA approval programs



Fast Track (designation). This designation facilitates the development and speeds up the FDA review process of drugs that would treat serious conditions and fill an unmet medical need. To be eligible as a drug that treats a serious condition, the drug must positively impact such factors as survival, day-to-day functioning, or the likelihood that the condition, if left untreated, will progress from a less severe condition to a more serious one. Filling an unmet need means that no current therapy is available for the condition or that the proposed therapy is potentially better than available therapies. If there are available therapies, a Fast Track drug must show some advantage over available therapy, such as evidence of superior effectiveness, improved effectiveness on serious outcomes, or lesser side effects.[7]

The benefits of Fast Track designation include more frequent meetings and written communication with the FDA and rolling review. Rolling review refers to the ability of the FDA to begin review of the BLA or NDA as sections are completed, rather than waiting for the finalized NDA or BLA to begin the review.[7]

Breakthrough Therapy (designation). This program is like the Fast Track program in providing quick review of drugs that are intended to treat a serious condition and are better than any available therapy. The most important difference between the two is the type of data that needs to be submitted to get a Breakthrough Therapy designation, which is preliminary clinical evidence indicating that the drug may demonstrate substantial improvement over available therapy on (a) clinically significant endpoint(s). Substantial improvement is judged based on the magnitude of the treatment effects and the importance of the observed clinical outcome. A clinically significant endpoint is one that measures an effect on irreversible morbidity or mortality (IMM) or on symptoms that represent serious consequences of the disease. It can also refer to findings that suggest an effect on IMM or serious symptoms.[7]

Along with the benefits of a Fast Track designation, Breakthrough Therapy drug sponsors are also given intensive guidance on an efficient drug development program and have the involvement of FDA senior managers. It is fairly common for a drug on the

fast track to be granted Breakthrough Therapy designation during the drug development process.

Priority Review (designation). In 1992, under the PDUFA, the FDA agreed to a Priority Review designation of any drug for which the agency would act within six months to review the application, as opposed to ten months otherwise. The sponsor must apply for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. Other eligibility criteria can be seen on the FDA website.[7]

Accelerated Approval. Instituted in 1992 by the FDA, Accelerated Approval regulations allow drugs for serious conditions that fill an unmet medical need to be approved based on a surrogate endpoint. This endpoint should be a marker like a laboratory measure or a radiographic image but is not itself a clinical benefit. Surrogate endpoints may be used because the number of patients with the rare disease is too small to conduct a clinical trial with a traditional clinical endpoint.

Other government support. Governments around the world also provide other incentives for entry

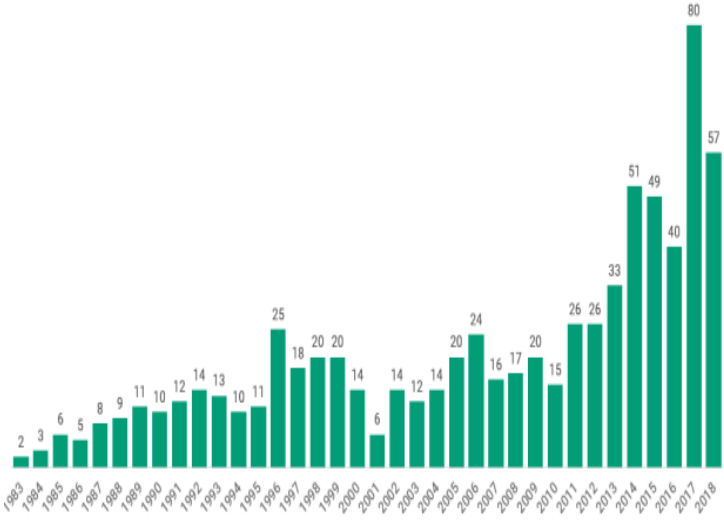
into rare disease markets. Although the details of laws and policies designed to induce orphan drug innovation differ across countries, they typically offer a fixed period of market exclusivity starting at the time of regulatory approval and running concurrently with any patents. The European Union and Japan offer ten years of exclusivity; the United States offers seven years.[5] This market exclusivity precludes sale of similar products into the same indication but does not preclude sale of significantly different products into the same indication.

R&D activities related to orphan drugs also receive substantial tax advantages under most orphan drug laws. In the US, for example, the 1983 Orphan Drug Act extends a tax credit for all R&D conducted on a drug that has secured an "orphan drug designation" from the US Food and Drug Administration (FDA).[5]

Q2: The case suggests that the rare disease "industry" is an attractive one. Usemodels of the environment (e.g., Porter's Five Forces, PESTEL) to explain why this is the case.

Accelerating Firm Entry. Prior to 1983, only 38 drugs were approved to treat rare diseases. But since the passage of the Orphan Drug Act, more than 7,000 rare diseases have been identified and over 1,100 orphan indications for treatments have obtained FDA approval.[8] In the last three years, there have been 246 new orphan indications, which is approximately 30% of the total indications ever granted under the Orphan Drug Act (ODA)[9]. The number of approved orphan indications is growing faster than the number of drugs, as some drugs have multiple indications.

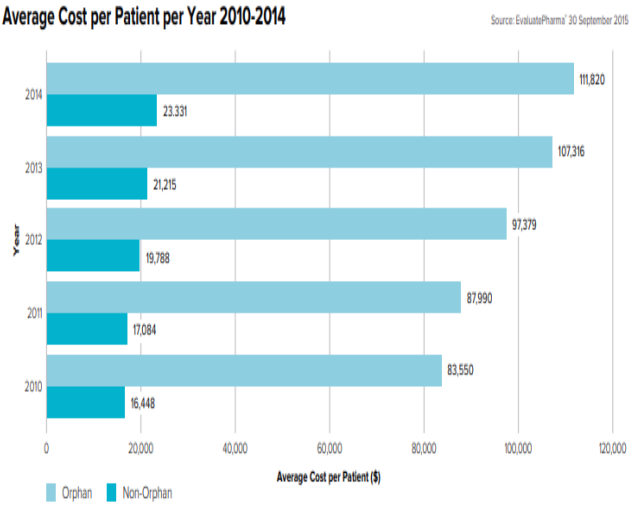
Fig. 3. Number of Orphan Indications Approved in the United States, 1983-2017



Pricing. Sources including NORD, FDA, academic journals such as JAMA, Health Affairs, Pharmacoeconomics, New York Times, Forbes, and Stat News[11] suggest that though estimates are varied, since the enactment of the Orphan Drug Act, the prices of orphan drugs have increased significantly. In the early 1990s, the average annual cost of an orphan drug was around $10,000. By 2010, the average cost had increased to around $200,000 per year. In the United States, the

median price of an orphan drug in 2015 was nearly US$100,000 per year -almost 20 times the median price of a nonorphan drug—and some drugs cost much more (EvaluatePharma 2015).[14]

Figure 4: Average cost per patient per year, orphan vs. non-orphan drugs



In 2019, the average annual cost of an orphan treatment per treated patient was $32,000, with treatments ranging from $6,000 to $500,000 per year.[16] In 2017, the average cost of an orphan drug was $147,308 per year. And a 2017 Harvard Business Review article by Gordon A. Smith puts the average annual price

of drugs for rare diseases at $118,000.[12] At a price of $118,000 per year, and assuming 30 million rare disease sufferers in each of the US, Europe, and Japan, the addressable market for rare diseases may approach $10.6 trillion.

Historically, higher prices for orphan drugs have not been associated with greater barriers to insurance coverage, in part because it was widely recognized by insurers that even very high prices, when multiplied by small patient numbers, would produce a limited impact on budgets and insurance premiums. In addition, there was a general sense that what can be termed “orphan prices” needed to be high on a per-patient basis for innovators to make a reasonable profit after recouping research and development costs. Beyond these practical considerations has always been the strong societal impulse to prioritize treatment for conditions that are severe, inherited, and disproportionately affect the very young. This impulse is strong, reflecting what ethicists have called the “rule of rescue.” Whether and how much the rule of rescue should drive policymaking regarding

pricing and access to orphan drugs is a topic of ongoing debate among ethicists.[18]

Nevertheless, orphan drugs are no longer a small minority of drug approvals. The number of new regulatory submissions for orphan indications is at an all-time high: Food and Drug Administration (FDA) orphan designations totaled 350 in 2015, 6 and 41% of the drugs the agency approved in 2016 carried an orphan designation.

Health technology assessment (HTA) methodologies. The high prices that have been set for orphan drugs are in part an outgrowth of the perceived need to achieve "reasonable" profit from a small patient base, but these higher prices have meant that these orphan drugs rarely meet commonly accepted cost-effectiveness thresholds that represent the foundation of judgments of value for other drugs.[18]

NICE, the National Institute for Health Care excellence in the UK and ICER in the US are organizations that produce recommendations for value-based price benchmarks. NICE is a governmental organization that makes recommendations regarding the

use of technologies in a single payer health care system, whereas ICER is an independent, nonprofit, nongovernmental organization.[19] ICER stands for "Incremental Cost-Effectiveness Ratio," and it is a metric used in health economics to evaluate the value of new pharmaceutical interventions. The ICER compares the incremental costs of a new treatment to the incremental benefits it provides over an existing treatment or no treatment at all.

In other words, ICER is a measure of how much it costs to gain one additional unit of health benefit from a new pharmaceutical intervention compared to other available treatments. The ICER is calculated by dividing the difference in costs between the new treatment and the existing treatment by the difference in health outcomes between the two treatments.

The ICER is often used by health technology assessment agencies and payers to inform coverage and reimbursement decisions for new pharmaceutical interventions. If the ICER is below a certain threshold, the new treatment is considered cost-effective and may be covered or reimbursed by insurers. If the ICER is

above the threshold, the new treatment may not be covered or reimbursed, or may only be covered under certain conditions.

Consistent with results reported earlier in this paper, a study published in the Journal of Managed Care & Specialty Pharmacy in 2019 compared the ICERs of 79 drugs approved by the FDA between 2011 and 2017. The study found that oncology drugs had the highest median ICERs, followed by drugs for rare diseases and immunology drugs. Cardiovascular drugs had the lowest median ICERs.[20] in 2020, ICER also published a report on "Challenges and Opportunities for Assessing Drugs with Limited Clinical Evidence and Implications for ICER Reviews." This report discussed the challenges in assessing drugs for rare diseases, which often have limited clinical evidence, and compared the cost-effectiveness of drugs for rare diseases with that of drugs for more common conditions. The report found that the ICERs for drugs for rare diseases tended to be higher than those for drugs for more common conditions.

Q3: Does the case suggest any threats in the future that might disrupt the attractiveness of this industry? Use theories of opportunity cost and rule of rescue to predict the future attractiveness of the industry.