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Assessing Pharma's Constraints, Opportunities, and Investment Options in Global Health R&D: An Analysis of U.S. Pharmaceutical Company SEC 10-K Filings

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Executive Summary

The private sector is the primary investor in health research and development (R&D) worldwide, with investment annual investment exceeding \$150 billion (West et al., 2017a; Jamison et al., 2013), although only an estimated \$5.9 billion is focused on diseases that primarily affect low and middle-income countries (LMICs) (West et al., 2017b). Pharmaceutical companies are the largest source of private spending on global health R&D focused on LMICs, providing \$5.6 billion of the \$5.9 billion in total private global health R&D per year (West et al., 2017a).

Private sector investment choices may simply reflect the most profitable use of funds or the most comfortable risk-return tradeoffs. There are, however, examples of privately funded R&D, blended financing, and public-private partnerships targeting diseases in LMICs. The detailed story, therefore, is likely more complex, with possibilities at the margin for catalyzing more private sector investment by increasing returns, lowering risk, or identifying policy or financial mechanisms to incent R&D funding. We look more closely at these nuances by examining the evidence for five specific disincentives to private sector investment in drugs, vaccines and therapeutics: scientific uncertainty, weak policy environments, limited revenues and market uncertainty, high fixed costs for research and manufacturing, and imperfect markets. Though all five may affect estimates of net returns from an investment decision, they are worth examining separately as each calls for a different intervention or remediation to incentivize expanded investment by private companies.

Our goal of examining these separate components of private sector investment decisions in global health R&D is made challenging by the scarcity and unevenness of publicly available information on private company decision-making. We therefore reference - and check against - multiple sources. An earlier report (West et al., 2017b) draws on consultations with over two dozen experts on global health R&D from multiple sectors and case studies of leading examples of venture capital investments and innovative finance. Anderson et al. (2017) reports on an expansive review of 285 papers from five primary academic search databases, five supplemental search databases, ten private pharmaceutical company websites, and twelve philanthropic and public organizations involved in health R&D worldwide.

This paper reviews a third information source, examining the risk factors, opportunities and stated incentives as reported by private sector pharmaceutical companies that filed 10-K forms with the U.S. Securities and Exchange Commission (SEC) in the year 2016. The sample is comprised of 132 10-K reports collected from a

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comprehensive sample of all 2016 SEC 10-K filings¹ by companies under the SIC code 2834 ('pharmaceutical preparations').² The SEC 10-K reports follow a standard format, including a business section and a risk section which include information on financial performance, investment options, lines of research, promising acquisitions and risk factors (scientific, market, and regulatory). As a result, these filings provide a valuable source of information for analyzing how private companies discuss risks and challenges as well as opportunities associated with global health R&D targeting LMICs.

Because we are interested in whether any investment barriers are particular to global health R&D investments, we categorized research firms in terms of their reported research focus. Based on the World Health Organization (WHO) typology we distinguish between firms that conduct R&D only on Type 1 diseases (diseases with equivalent or higher burden in high-income relative to lower income countries) and that conduct R&D on at least one Type 2 / Type 3 disease³ (diseases with a greater burden in low- and middle-income relative to high-income countries). The WHO typology uses global burden of disease data from the Institute for Health Metrics and Evaluation (IHME) to determine the ratio of disease burden (measured by DALYs - Disability-Adjusted Life Years) for populations in low- and middle-income countries (LMICs) over the disease burden for populations high-income countries (HICs), and distinguishes disease Types based on this ratio. We reviewed all 10-Ks of firms mentioning R&D on at least one Type 2/3 disease, and a random sample of 61 10-Ks mentioning only Type 1 disease R&D⁴.

Policy Incentives

As reported in Anderson et al. (2017), though a variety of policy tools exist to promote private sector investment in R&D, including push mechanisms (public research funding, R&D tax credits) and pull mechanisms (advance purchase commitments, orphan drug programs, priority review vouchers, and wild-card patent extensions), evidence of effectiveness is mixed. Thus in this review of industry self-reported barriers and opportunities in 10-K filings we further consider the roles that policy tools such as public research funding, R&D tax credits, advance purchase commitments, orphan drug programs, priority review vouchers, and wild-card patent extensions appear to play in catalyzing and sustaining private global health R&D.

In general, these policies apply across a wide range of companies (Table i), but some policies target specific disease Types (Table ii). Most policy incentives are mentioned by firms as having a positive impact on their R&D investments. R&D tax credits are the most commonly mentioned policy tool: 39 of 61 companies working only on Type 1 diseases mention R&D tax credits, compared to 15 of 71 companies working on at least some Type 2 or 3 disease R&D. Orphan drug status is the most commonly mentioned policy tool among companies researching Type 2 or 3 diseases, though it is more often mentioned with regard to Type 1 diseases that those companies work on. Priority review vouchers (a form of expedited review) are mostly mentioned by companies focused in Type 2 or Type 3 disease R&D but are also mentioned by companies involved in biodefense R&D. Advanced Purchase Commitments are not frequently mentioned.

¹ 10-K filings from fiscal year 2016 were used after initial search encompassing more years. Depending on individual company's fiscal year timeline, this could compass only calendar year 2016 or calendar years 2015 and 2016.

² Appendix A includes a summary of firms filing 10-Ks across a larger set of SIC codes that report involvement in some form of global health R&D.

³ Nearly all of these companies (69 of 71) also conduct R&D on at least one Type 1 disease.

⁴ We initially randomly sampled fifty 10-Ks for Type 1 only firms. An additional 11 were added from the sample of firms mentioning at least some Type 2/3 disease R&D, as further review revealed that those firms were not actually pursuing Type 2/3 disease R&D.

Table i. Mentions of policy incentives by impact on company R&D, by company R&D emphasis

Policy Incentive	Positive Impact		Negative Impact		Mixed Impact		Neutral		No Mention	
	Type 1 only	Type 2 or 3	Type 1 only	Type 2 or 3	Type 1 only	Type 2 or 3	Type 1 only	Type 2 or 3	Type 1 only	Type 2 or 3
Advanced Purchase Commitments	0	2	0	0	1	1	0	0	60	67
R&D Tax Credits	39	15	0	0	0	0	0	0	22	56
Orphan Drug Status	25	27	0	0	0	0	0	0	36	44
Expedited Review *	19	23	0	0	0	0	0	0	42	48
505(b)(2)	12	2	4	1	0	1	16	7	29	60
Hatch-Waxman Amendments	17	7	0	0	0	0	16	6	28	58
Other Policies	1	1	0	0	0	0	0	0	60	70

Note: There are a total of 61 companies working solely on Type 1 diseases and 71 companies working on Type 2/3 diseases

*The Expedited Review category includes Fast Track designation, Priority Review Vouchers, Qualified Infectious Disease Product designation, and Breakthrough Therapy designation

Among specific diseases mentioned in the company 10-Ks, orphan drug designation is mainly referenced in regard to Type 1 or rare diseases affecting high-income countries (Table ii). Expedited review policies mentioned include several aimed specifically at Type 2 or 3 diseases (notably Priority review Vouchers), though others such as “Fast Track” designation may also be applied to Type 1 disease R&D. Overall, expedited review policies are more frequently mentioned specifically for Type 1 diseases than for Type 2 or 3 diseases.

Table ii. Mentions of policy incentives for specific disease R&D investments, by disease type.

	Type 1 diseases (247)	Type 2 diseases (109)	Type 3 diseases (36)
Advanced Purchase Commitments	1%	3%	6%
Orphan Drug Status	25%	7%	11%
Priority Review Vouchers	4%	2%	8%
Expedited Review*	21%	12%	3%
Other Policies	4%	3%	6%

Note: A mention means that the company discussed the policy incentive as referring to a specific disease they were researching in their 10-K report. Hatch-Waxman amendments and R&D tax credits are not included in this table because they are mentioned primarily at the company level and not with respect to specific disease investments.

*The Expedited Review category includes Fast Track designation, Qualified Infectious Disease Product designation, and Breakthrough Therapy designation. Priority Review Vouchers are reported separately.

Investment Constraints and Opportunities

Drawing on Anderson et al. (2017) we evaluate constraints and opportunities to private sector investment in LMIC disease research using a framework derived from public goods theory and theories of private firm behavior, which includes five disincentives hypothesized to inhibit private investment in global health R&D. Most companies mention all five hypothesized disincentive at least once in their 10-K filings, though companies researching at least Type 2 or 3 disease are less likely to mention constraints or opportunities related to these hypotheses (Table ii).

Table iii. Count of companies mentioning each hypothesized disincentive, by company type

Factors hypothesized to affect company investment in R&D	Any Type 2 or 3 R&D (71 companies)		Type 1 R&D Only (61 companies)	
	Mentioned	Not Mentioned	Mentioned	Not Mentioned
1. Scientific Uncertainty	53 (75%)	18	55 (90%)	6
2. Policy and Regulatory Uncertainty	44 (62%)	27	53 (87%)	8
3. Limited Revenues / Market Risk	63 (89%)	8	59 (97%)	2
4. High Costs of Research and Manufacturing*	64 (90%)	7	58 (95%)	3
5. Imperfect Markets**	58 (86%)	13	50 (87%)	11

Note: A mention can be positive, negative, mixed, or neutral.

*Includes up-front costs for the R&D process, manufacturing costs for products of R&D, and discussion of concerns related to securing funding for the R&D process; **Includes licensing agreements

We find more variation of mentions for each hypothesized disincentive at the disease level as compared to the company level (Table iv). At the disease level we only consider hypotheses discussed in the context of a specific disease R&D investment; most hypotheses are mentioned generally by companies and not with reference to a particular disease R&D investment. For Type 1 diseases, the most frequently mentioned hypothesis - limited revenues - is mentioned more than twice as often as the least mentioned hypothesis, policy and regulatory uncertainty. This is similar for Type 2 diseases and Type 3 diseases, although the most frequently mentioned hypothesis for Type 3 diseases are fixed costs followed closely by limited revenues. Policy and regulatory uncertainties are the least mentioned hypothesized disincentive for all disease types.

Table iv. Count of companies mentioning each hypothesized disincentive, by disease type

	Type 1 diseases (247)		Type 2 diseases (109)		Type 3 diseases (36)	
	Mentioned	Not Mentioned	Mentioned	Not Mentioned	Mentioned	Not Mentioned
1. Scientific Uncertainty	141 (57%)	106	35 (32%)	74	8 (22%)	28
2. Policy and Regulatory Uncertainty	65 (26%)	182	12 (11%)	97	3 (8%)	33
3. Limited Revenues / Market Risk	179 (72%)	68	58 (53%)	51	18 (50%)	18
4. High Costs of Research and Manufacturing*	69 (28%)	178	18 (17%)	91	19 (53%)	17
5. Imperfect Markets**	159 (64%)	88	51 (47%)	58	10 (28%)	26

Note: A discussion can be positive, negative, mixed, or neutral.

*Includes up-front costs for the R&D process, manufacturing costs for products of R&D, and discussion of concerns related to securing funding for the R&D process; **Includes licensing agreements

Hypothesis 1: Scientific uncertainty

To what extent are investors deterred by the scientific uncertainty of developing an efficacious and safe therapy that will successfully make it through all clinical trials? This calculation is not unique to global health R&D, except to the extent that Type 2 and 3 diseases are associated with higher scientific uncertainty. Eighty-two percent (108 out of 132) of companies make some reference to scientific uncertainty in the business or risk section of their 10-K filings in 2016, including 75% of companies conducting R&D on some Type 2 or Type 3 diseases (53 out of 71), and 90% of companies focusing exclusively on Type 1 diseases (55 out of 61).

- Some companies (3 in our sample) are developing companion diagnostics alongside their products to increase the chances of success. These diagnostics will lower the risk of clinical trials by allowing researchers to select patients that will better respond to their therapies.
- Three companies report using disease, project, or computer modeling to reduce scientific uncertainty.
- One company uses publicly available information to identify therapies that were pulled off the market for adverse side effects so that it can reevaluate them for its “drug rescue program”.
- Other companies note that novel compounds can lead to more efficacious therapies with fewer adverse side-effects, however, there is more uncertainty as to whether a novel mechanism will result in a marketable product because there is no proof of concept.
- Other mentions include reports that designing studies to evaluate the safety and efficacy of new treatments for rare diseases with no currently available treatment is more difficult because there are no examples of study endpoints to prove efficacy to regulatory agencies.
- Two companies report that complex manufacturing processes have the upside of limiting competition.

Mentions of scientific uncertainty are quite common in 10-K filings relative to expert interviews and the secondary literature. Science was rarely mentioned in West et al. (2017b) and Anderson et al. (2017) found

only four of 285 studies emphasizing the complexity of research, access to existing research or the limited volume of existing knowledge as specific factors influencing private R&D investment decisions.

Hypothesis 2: Policy and regulatory environment

Macroeconomic and policy environments such as regulatory processes, regulatory costs, and weak or uncertain intellectual property (IP) protections - both where products are developed and where they are sold - may discourage private sector investment, particularly for low- and middle- income countries (LMICs). Seventy percent (92 out of 132) of companies in the sample reference policy or regulatory uncertainty in the business or risk section of their 10-K filing, including 62% of companies conducting R&D on Type 2 or Type 3 diseases (44 out of 71) and 87% of companies focusing solely on Type 1 diseases (53 out of 61).

- 86.4% of companies mention the uncertainty of patent and intellectual property rights in boilerplate statements. All five companies that develop products for Type 2/3 diseases and discuss specific negative impacts of weak IP protections, discuss their response to weaker IP systems in markets outside North America and Europe.
- The four companies which discuss health systems and health governance outside the US in detail focus on barriers associated with restrictive health policies or weak regulatory systems.
- One company mentions using Nigeria's regulatory and approval process as a model for submission in other African countries that do not have formal processes.
- Much of the discussion of policy and regulatory uncertainty occurs in general boilerplate language regarding risks and policy pathways open to companies.
- Companies that work on Type 2 and Type 3 diseases are relatively more likely to take advantage of US policies that have larger global reach such as priority review vouchers (PRVs) and fast track pathways. Policies which mainly target Type 1 diseases or products meant for US domestic markets such as Hatch-Waxman Act (dealing with IP rights) are not as widely used for Type 2 and Type 3 diseases or products.

Policy and regulatory environments likewise featured heavily in both expert interviews and the secondary literature review, though with varying specifics. Geo-political risks and unstable macroeconomic and policy environments are widely cited in industry reports as deterrents to private sector investment in global health R&D in West et al. (2017b). In Anderson et al. (2017) uncertainty in returns stemming from the regulatory environment, regulatory costs, and weak or uncertain intellectual property protections are among the more commonly cited policy challenges for private health R&D, rather than general macroeconomic volatility.

Hypothesis 3: Limited revenues and market uncertainty

Developing therapies for small or LMIC markets may not be seen as profitable, either because of a limited ability to pay, weak IP protection to support pricing, limited health care infrastructure to disseminate products, or pricing affected by third-party payers - all reducing the perceived potential for revenue.

Ninety-two percent (122 out of 132) of companies in the sample reference market potential or uncertainty in the business or risk section of their 10-K filing, including 89% of companies conducting R&D on Type 2 or Type 3 diseases (63 out of 71) and 97% of companies focusing solely on Type 1 diseases (59 out of 61).

- Companies (both those targeting Type 1 and Type 2 diseases) strive to differentiate their product candidates from existing products and products in development by other companies as a way of gaining competitive market advantage.
- Two companies describe strategies to create barriers to competition through IP rights and pursuing R&D for diseases with high barriers to entry.

- Companies that research Type 2 and 3 diseases mention market advantages from expanding to markets outside of the United States more often than companies that research Type 1 diseases only.
- Companies that receive reimbursement for their products from national insurance programs, private insurance companies, and other third party payers are not only able to charge higher prices and recover more of their R&D costs but also enjoy a larger market for their products.
- Most companies (both those targeting Type 1 and Type 2 diseases) describe cost containment measures and downward pricing pressure on healthcare expenditures as significant threats to profitability.
- Specific challenges from market competition that both types of companies list are other companies developing drugs for similar indications (33 companies), increasing competition from “biosimilar” drugs (9 companies), the introduction of cheaper generic or OTC drugs (8 companies), well-established existing treatments (3 companies), disease specific competition increasing (4), and competition for government contracts (1 company).

Industry experts, secondary authors, and firm filings all discuss low or uncertain revenues as stifling investment in diseases affecting LMICs. However only two sources cite small market size as the deterrent - most highlight pricing (low and/or uncertain LMIC prices). Incentives to invest in R&D targeting diseases prevalent in the U.S. and other high-income countries are higher given the ability to set prices at what the market will bear, relative to prices in LMICs which may be lower, regulated, or unknown.

Hypothesis 4: High Costs of Research and Manufacturing

Specific concerns related to fixed costs for R&D are mentioned by less than one quarter of the companies in our sample (30 out of 132) and mostly relate to the need to seek out additional sources of funding, but costs and approaches to the manufacturing process for R&D products are mentioned by 98% of companies (129 out of 132). We find that comparable proportions of companies that research Type 1 diseases and Type 2 or 3 diseases discuss positive, negative, and mixed effects of manufacturing costs on research and development.

- Most companies (82%, or 108 out of 132 companies) including both those targeting Type 1 and Type 2/3 diseases in relatively equal numbers, include boilerplate 10-K language reporting the need to ensure additional funding to continue R&D activities.
- Companies report that additional funding from outside sources helps to offset expenditures related to research and development/commercialization of product candidates - additional funding sources discussed are public/philanthropic and other collaborative.
- More companies that research any Type 2/3 diseases reported receiving public funding compared to companies that research Type 1 diseases only.
- Companies that work primarily on diseases that are classified as bio-threats as well as certain Type 3 diseases (especially hemorrhagic fevers) report the U.S. government as the primary purchaser of their product.
- Some companies possess the ability to manufacture small amounts of product, however, scaling up production of products to commercial scale is difficult and comes with risks.
- Outsourcing manufacturing allows companies to avoid expending resources on fixed costs like facilities and instead focus resources on research and development, but problems can arise from limited manufacturers who are able to produce a specific product.
- Manufacturing products internally allows companies to maintain control over processes, “know how” and intellectual property, but facilities can be difficult to finance and use to their full potential.

Similar to scientific uncertainty, cost considerations (as opposed to revenues or local policy environments) are unique to global health R&D only to the extent that Type 2 and 3 diseases are associated with more specific up-front costs than Type 1 diseases. High initial investment costs with difficult to re-purpose capital are often cited as barriers to all health R&D, not particular to global health, reflected in a range of cost estimates for bringing a drug to market between \$802 million and \$2.2 billion (Anderson et al., 2017). In firm filings, however, costs associated with the manufacturing process for R&D outputs are mentioned more than concerns

over upfront specific investments for the R&D process, perhaps because those filing had already incurred such costs.

Hypothesis 5: Imperfect markets

The ability of large firms with downstream capacity to purchase the rights to upstream R&D at a lower cost than producing it internally may reduce incentives for private investment in new global health R&D. Opportunities or constraints related to imperfect markets are mentioned by less than half of all companies for every category of evidence, except for licensing agreements, which are mentioned by 90 out of 134 companies in the sample.

- Type 1 companies in our sample report out-licensing their products more frequently than in-licensing. Type 2/3 companies reported out-licensing their products as frequently as they reported in-licensing. Companies use in-licensing agreements to fill gaps in their research during clinical development, or to gain access to the rights to commercialization and development of a product at the end of (and dependent on the success of) clinical trials.
- Companies most frequently use out-licensing agreements to access global markets, gain revenues to support their R&D base, reduce risks and costs associated with commercialization and marketing, shift disease or product focus, and assist partner companies and organizations in advancing their research.
- Several companies discuss the uncertainties related to their business practice of out-licensing commercialization of their products, noting the risks of giving up rights to a product that would have been more valuable had the company developed it in-house as well as the potential to in-license a product that was riskier than anticipated and does not generate the desired revenue.
- Two companies describe leveraging patent expirations to develop and commercialize biosimilars and generics, allowing them to avoid the risky process of clinical trials.
- Three companies report the market for product candidates is dominated by one or a few companies.

Theory predicts that the nature of the pharma R&D industry and current regulatory structure create incentives for large firms with downstream capacity to increasingly move resources out of upstream R&D, especially in the U.S., if they are able to purchase rights to the results of upstream R&D at lower cost than producing those R&D outputs themselves. Upstream competition can make it more profitable for large firms with a downstream presence to purchase patent rights rather than invest in their own upstream R&D, which Roy & King (2016) note is a common industry practice. Nonetheless, these hypothesized disincentives to R&D were seldom mentioned by industry experts (West et al., 2017b) or in the secondary literature (Anderson et al., 2017) or directly by firms. Five secondary sources (compared to one firm filing) describe private R&D efforts to improve the efficacy or effectiveness of existing treatments – so-called “me-too” drugs – as examples of private investors’ preference to secure downstream rents rather than invest in new health R&D ventures. The suggestion repeated in the literature that limited patent windows may encourage private firms to divert resources towards marketing rather than additional R&D in order to maximize profits during the period of exclusivity (Love, 2005) is not referenced in the 10-Ks.

Triangulating 10-Ks with Expert Interviews and Literature Findings

We find some corroboration between expert opinion as reported in West et al. (2017b) and in the review of literature undertaken by Anderson et al. (2017). West et al. (2017b) found six main factors reported by industry experts to explain limited global health private sector R&D: *Limited Markets for Certain Diseases* (illnesses that affect small numbers), the *Cost of Drug Development* (long development cycle), *Geo-political Risks* (risks to long-term investments and revenue streams), *Macroeconomic Difficulties* (recession, exchange rate, and interest rate risks), *Poor Health Governance* (difficulty in products reaching intended beneficiaries), and a *Lack of Systematic Data* (evidence on what works). Anderson et al.’s (2017) review of literature as well as the

current review of industry 10-Ks suggest that in the revenue calculation, LMIC pricing is the primary disincentive (even in cases where the LMIC market size is large), especially relative to drug pricing in the U.S. and other HICs. Limited market size was seldom mentioned as a deterrent among the 10-Ks we reviewed (9 out of 132 companies). Rather, company 10-Ks were more likely to cite challenges related to market competition, which were mentioned by 27 companies. Another common problem cited in company 10-Ks references downward pricing pressure and cost-containment from governments and other third-party payers in high income countries. Other factors cited by experts in West et al. (2017b) including *Geopolitical Risks*, *Macroeconomic Difficulties*, *Poor Health Governance*, and a *Lack of Systematic Data* are less frequently cited in the literature or 10-Ks as key determinants of private sector investment decisions - although all broadly relate to private firms' perceptions of risks and potential revenues associated with R&D investments.

Largely absent from factors highlighted in expert consultations but frequently mentioned in the literature is the effect of an imperfectly competitive market structure. This potentially grants larger pharmaceutical firms sufficient market power to buy or license R&D below a competitive market price (rather than conduct their own R&D) and enough market and regulatory influence to sell final products above a competitive market price. Patents, licensing, and royalties were mentioned by a majority of firms in the 10-K filings, with approximately half (65 out of 132) specifically mentioning purchasing licenses for R&D. Companies in the 10-K sample report that in-licensing occurs through all stages of drug development, with companies acquiring R&D to either fill gaps in their research during clinical development, or to commercialize and market after clinical trials have been completed. We find evidence that the current health R&D market structure is characterized - and likely constrained - by specialization, high entry costs, regulatory rents and privately held information; a result of both the nature of disease research and the policy environment.

Though a variety of policy tools exist to promote private sector investment in R&D, including push mechanisms (public research funding, R&D tax credits) and pull mechanisms (advance purchase commitments, orphan drug programs, priority review vouchers, wild-card patent extensions), evidence of effectiveness is mixed. Advanced purchase or market commitments (AMC) guarantee markets for new, viable products that can incentivize developing products for diseases with limited markets, but are mentioned by very few companies in our sample (four). Orphan drug status is most commonly applied by companies to Type 1 disease R&D. Expedited review policies mentioned include several aimed specifically at Type 2 or 3 diseases, though others such as "Fast Track" designation may also be applied to Type 1 disease R&D. The attractiveness of licensing upstream research rather than conducting it internally is likely to increase as more computing and data-based aspects of R&D occur in biotech companies relative to the physical science labs of traditional pharmaceutical companies.

Lastly, to the extent that health data are more limited for global health diseases, there is reason to speculate that as the industry shifts more R&D to biotechnology even less will be directed at diseases prevalent in LMICs. Both industry experts and the literature lament the limited market data available to assess potential market outcomes - yet despite potential industry-wide gains, there is no incentive for any individual firm to either fund or contribute to such a data service. We found some evidence in our review of 10-Ks that point to collaborations between companies, academic institutions, medical centers, or government agencies, although this was mentioned by only a relatively few (6 out of 71) companies that research Type 2 or 3 diseases.

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Introduction

The private sector is the primary investor in health research and development (R&D) worldwide, with annual investment exceeding \$150 billion (West et al., 2017a; Jamison et al., 2013). The amount of private investment that focuses on diseases primarily affecting populations in low- and middle-income countries (LMICs), however, is estimated to be just \$5.9 billion annually (West et al., 2017a).

Private sector investment choices may simply reflect the most profitable use of funds or the most comfortable risk-return tradeoffs. There are, however, examples of privately funded R&D, blended financing, and public-private partnerships targeting diseases in LMICs. The detailed story, therefore, is likely more complex, with possibilities at the margin for catalyzing more private sector investment by increasing returns, lowering risk, or identifying policy or financial mechanisms to incent R&D funding. We look more closely at these nuances by examining the evidence for five hypothesized disincentives to private sector investment: scientific uncertainty, weak policy environments, limited revenues and market uncertainty, high fixed costs, and imperfect markets. Though all five may affect estimates of net returns from an investment decision, they are worth examining separately as each informs a different policy, regulatory, information sharing, financial, or other mechanism to change behavior.

A collaboration between the Brookings Institution and the University of Washington's Evans School on "Private Sector Global Health R&D" has explored the factors that may influence private company decisions to invest in drugs, vaccines, and therapeutics of diseases prevalent in LMICs. An initial paper (West et al., 2017b) assesses health governance capacity across 25 indicators in 18 countries in Sub-Saharan Africa and Asia. The authors find that LMICs could attract greater private investment in health R&D by "improving transparency, strengthening management capacity, lowering tariffs on incoming medical products to the extent that is fiscally possible, expediting regulatory reviews of new drugs, building effective health infrastructure, and increasing appropriately-targeted and efficient public spending on healthcare" (p. 2).

Building on this landscape of the current health governance capacity in LMICs, our next goal was to examine the separate components of private sector investment decisions in global health R&D; a task made challenging by the scarcity and unevenness of publicly available information on private company decision-making. We therefore reference - and check against - multiple sources: consultations with industry experts in West et al. (2017a), and academic and industry reviews in Anderson et al. (2017).

In their second paper (West et al., 2017a) draws on expert consultations, company investment data, and case studies of leading examples of venture capital investments and innovative finance to explore barriers and opportunities to private sector investment in global health R&D. Among the challenges they identify are "limited markets, the high cost of drug development, macroeconomic difficulties, geo-political risks, a lack of systematic data about investment returns, and poor health governance that discourages higher investment in the developing world" (p. 2). To improve private investment in global health R&D, the authors recommend efforts to create viable markets, increase the availability of systematic R&D data, expedite regulatory reviews of new drugs and vaccines, improve tax incentives and provide results-based financing, implement a World Health Organization (WHO) vaccine platform, utilize artificial intelligence advances in drug development, and pursue investment opportunities in China and India (West et al., 2017a).

In a third paper, Anderson et al. (2017) complement this analysis with an expansive review of 285 papers from five primary academic search databases, five supplemental search databases, ten private pharmaceutical company websites, and twelve philanthropic and public organizations involved in health R&D worldwide. Their review highlights five key categories of disincentives to private sector global health investment discussed in this literature: scientific uncertainty, policy and regulatory uncertainty, limited revenues and market

uncertainty, high fixed and sunk costs, and imperfect markets. The authors report that challenges related to policy and regulatory uncertainty and limited revenues and market uncertainty are the most frequently mentioned barriers to private investment. LMIC market data gaps and health science data gaps from proprietary R&D arise as important challenges. The review further indicates that policy tools such as public research funding, R&D tax credits, advance purchase commitments, orphan drug programs, priority review vouchers, and wild-card patent extensions appear to have a largely positive impact on catalyzing private global health R&D, though evidence of effectiveness is mixed.

This paper draws from a third data source and the risk factors, opportunities and stated incentives for all private sector pharmaceutical companies in 2016 required to file 10-K forms with the U.S. Securities and Exchange Commission (SEC). Pharmaceutical (“Pharma”) companies are the largest source of private global health R&D spending, providing \$5.6 of the \$5.9 billion in total private global health R&D focused on the developing world (West et al., 2017a). The SEC 10-K reports from Pharma companies follow a standard format and include information on risk factors (scientific, market, and regulatory), financial performance, investment options, lines of research, and promising acquisitions. As a result, these filings provide a valuable source of information for analyzing how private companies discuss risks and challenges as well as opportunities associated with global health R&D targeting LMICs - allowing us to use industry self-reports to triangulate findings from earlier interview- and literature-based reviews.

A small number of recent studies have drawn on 10-K data to analyze trends in risk factors facing public companies and resultant effects on investment in R&D spending across various industries (Baker et al., 2016; Koijen et al., 2016). Baker et al. (2016) used the risk factors section of 10-Ks from 2005 to 2013 to analyze the proportion of 10-Ks (across a range of U.S. industries) that reference certain government policies or regulations. They use this proportion as a factor in their model explaining trends in economic policy uncertainty. Koijen et al. (2016) used the risk factors section of a large sample of 10-K forms across a range of industries to show that private firms in the health care sector overall tend to reference government-related risk significantly more frequently than firms in other sectors, but they do not distinguish R&D for LMICs from high-income countries, nor do they look at opportunities or incentives described within these industry filings. Our paper thus offers the largest review and analysis of information on global health R&D from Pharma companies’ 10-K forms undertaken to date.

We distinguish between firms that conduct R&D only on Type 1 diseases (with equivalent or higher burden in high-income relative to lower income countries) and that conduct R&D on at least one Type 2 / Type 3 disease⁵ (with a greater burden in low- and middle-income relative to high-income countries) based on World Health Organization (WHO) typology. The WHO typology uses global burden of disease data from the Institute for Health Metrics and Evaluation (IHME) to determine the ratio of disease burden (measured by DALYs - Disability-Adjusted Life Years) for populations in low- and middle-income countries (LMICs) over the disease burden for populations high-income countries (HICs), and distinguishes disease Types based on this ratio.

We manually review 2016 10-Ks for all 71 Pharma firms mentioning R&D on at least one Type 2/3 disease, and a random sample of 61 10-Ks mentioning only Type 1 disease R&D. For each 10-K, we systematically record how risk factors, market challenges, and opportunities are discussed both generally at the company level and for any Type 2 or Type 3 disease mentioned.

The resulting dataset allows us to compare the risks and opportunities discussed in company 10-K filings from the largest Pharma companies to the smaller start-ups, and across companies that are investing in different types of diseases. We are able to record differences in factors affecting R&D for companies investing in

⁵ Nearly all of these companies (69 of 71) also conduct R&D on at least one Type 1 disease.

different types of diseases and with different characteristics (e.g., number of employees, larger revenues, etc.).

The remainder of the paper proceeds as follows. First, we present additional information on our data and sample and review methods. Then we present findings on the investment incentives and challenges discussed by Pharma companies. We report on the specific policy incentives mentioned by the sampled companies, then report company mentions of constraints and opportunities organized according to the five hypothesized disincentives to private sector global health investment as discussed in the literature: scientific uncertainty, policy and regulatory uncertainty, limited revenues and market uncertainty, high fixed and sunk costs, and imperfect markets. We discuss trends and conclusions looking across Pharma companies investing in R&D for Type 1 and Type 2/3 diseases and for specific diseases with different scientific and market characteristics. Finally, we discuss how the findings from this review compares with findings triangulated from the previous reviews of private sector global health R&D incentives and challenges in West et al. (2017a) and Anderson et al. (2017).

Methods

Because private sector data are proprietary and company websites and industry interviews are subjective and selective, research on the private sector requires additional attention to the data sources and sampling in order to distill findings, and have confidence in those findings. Table 1 notes some general trade-offs across information sources, though this does not imply that any particular interview, website, or 10-K would fall into these categories. The experts interviewed had different roles within the industry and the authors of the literature sampled had different purposes, with the work subject to different degrees of peer review. The sample of 10-K filings is relatively free of selection bias, as all firms filing in a particular SIC code were reviewed, though as with the other sources, the coding and extrapolation of information from the sample are subject to human judgement.

Table 1. Comparison of data sources on private investment in global health R&D

	Scope and scale (sample size & breadth)	Objectivity (unbiased sample)	Contextually relevant
Expert Opinion	Low	Low	High
Company Websites	High	Low	High
Literature Review	Medium	Medium	Low
SEC 10-K Filings	High	High	Medium

With this in mind, and assuming that the subjectivity is relatively constant across sources, reviewing industry’s self-reporting allows us to triangulate findings from earlier interview- and literature-based samples and gives us a comprehensive view into what are seen as the primary challenges to private sector investment.

Data and Sample

The SEC requires public companies file 10-K reports each year. Reports from Pharma companies are rich repositories, with information on risk factors (scientific, market, and regulatory), financial performance, investment options, lines of research, and promising acquisitions. Since 2005, 10-K filings have included a risk factors section, and since 2011, companies have been submitting financial statements that generally include line items associated with revenue and research and development spending.

The sample for this review was collected from all 2016 SEC 10-K filings by companies under the SIC code 2834, classified as ‘pharmaceutical preparations’ companies. Appendix A includes a summary of firms filing 10-Ks across a larger set of SIC codes that report involvement in some form of global health R&D.

The SEC provides a suggested layout for filers, and 10-K filings largely follow that guideline, with each filing including the same sections. Using data from 10-Ks thus allows us to analyze similar types of information across the population of public pharmaceutical companies. In particular, two sections (“Items”) within each 10-K were of interest for the purpose of this study: Item 1 describes company business operations, and Item 1a describes company risk factors. These two sections typically include information concerning the diseases targeted and products under development for each company as well as the anticipated and realized risk factors faced by each company. Other sections of the 10-Ks do not include relevant information pertaining to the incentives and challenges companies face in their health R&D investments. As a result, our review focuses on the text included in Item 1 and 1a of the 10-K filings.

Company characteristics including number of employees, financial data, country of R&D operations, etc. are found in Item 2 (Properties), Item 6 (Selected Financial Data), and Item 7 (Management’s Discussion and Analysis of Financial Condition and Results of Operations). This information is recorded separately from the analysis of the text under Items 1 and 1a.

We focus on Pharma 10-K filings from 2016, the most recent year when complete filings were available.⁶ Our aim was to review 10-Ks for all companies discussing R&D efforts related to diseases more prevalent in low- and middle-income countries (LMICs). Following the WHO model, we group diseases into three categories based on the relative burden of disease (measured by DALYs) in high-income countries (HICs) and LMICs, as follows:

- **Type 1 diseases** are present in both HICs and LMICs. The ratio of the burden of disease is no more than three times higher in LMICs as compared to HICs.
- **Type 2 diseases** are present in both HICs and LMICs, but with a disproportionate number of cases in LMICs. The ratio of burden of disease is between 3 and 35 times higher in LMICs as compared to HICs.
- **Type 3 diseases** are predominantly present in LMICs. The ratio of the burden of disease is more than 35 times higher in LMICs as compared to HICs.⁷

Our analysis then considers two sub-samples of 10-Ks separately: those discussing any Type 2 or 3 diseases R&D investment (“Any Type 2 or 3 R&D”) and those discussing only Type 1 disease R&D investment (“Type 1 R&D Only”). Through manual searches of the SEC Edgar database we identify all 2016 Pharma 10-K filings that discuss R&D investments in Type 2 or 3 diseases, and retrieve all of these for review. This sample includes 71 filings discussing either current or previous investments in Type 2 or 3 disease R&D, of which 69 filings also discuss Type 1 R&D. Out of these 71 firms, 62 of them are currently researching at least one Type 2 or 3 disease, and the remaining nine had formerly researched at least one Type 2 or 3 disease and mention these in their 2016 10-Ks.

In addition, in order to examine whether there are any differences in the incentives and challenges to health R&D mentioned by companies focused more on diseases prevalent in low-income versus high-income countries, we randomly selected a sample of 61 filings from the remaining Type 1-only 2016 Pharma 10-Ks (i.e., those

⁶ The number of companies under the 2834 SIC code is 6,549 according to the North American Industry Classification System website, but not every company files a 10-K every year (<https://www.naics.com/standard-industrial-code-divisions/?code=28>).

⁷ To determine the relative burden of disease in high-income countries compared to low-income countries, we use the Institute for Health Metrics and Evaluation’s (IHME) *GBD Results Tool*.⁷ We downloaded the total number of disability-adjusted life years (DALYs) lost due to each disease by country in 2016. We also downloaded the population from each country in 2016 from IHME’s website. We then merge these data with the World Bank income classification for each country (categorizing countries as high-income or low- and middle-income). We determine the overall burden of disease for each disease by adding up the total number of DALYs for HICs and dividing that by the total population of HICs for each disease, giving us a single rate of DALYs per person for each disease in HICs. We do the same for LMICs. To determine the disease classification we divide the rate of DALYs per person for each disease in LMICs by the rate in HICs.

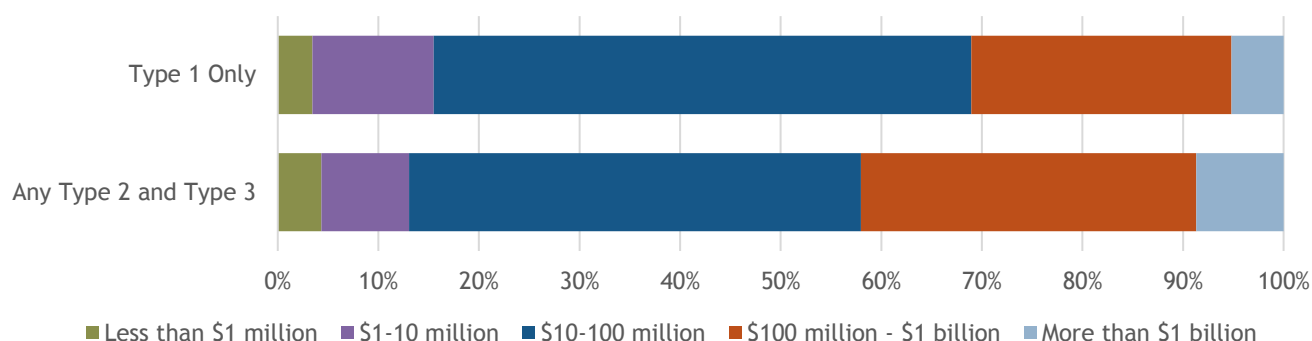
Pharma 10-K filings which did not discuss any Type 2 or 3 disease R&D)⁸. Links to the specific 10-Ks reviewed are included in Appendix F.

Table 2. Summary of companies included in sample (all currencies reported in millions of USD)

	Any Type 2 or 3 R&D (71 companies)				Type 1 R&D Only (61 companies)			
	Mean	Min	Max	Median	Mean	Min	Max	Median
Net Income (USD)	439.4	-472.0	15,409.0	-25.8	-28.5	-349.1	630.1	-28.2
Total Revenues (USD)	1,648.0	0	39,807.0	11.5	155.6	0	3,084.0	2.0
Operating Expenses (USD)	784.9	0.128	16,254.0	79.9	178.7	0.150	2,159.0	39.9
Research and Development Expenses (USD)	579.3	0	10,124.0	43.5	73.3	0.017	757.0	25.9
Ratio of R&D Expenses to Total Operating Expenses	0.520	0	0.961	0.585	0.542	0.015	0.916	0.628
Number of Employees	4,002	3	127,100	93	294	0	6,041	38
Number of R&D Investments in Type 1 Diseases	3.59	0	27	2	3.26	1	11	3
Number of R&D Investments in Type 2 Diseases	1.48	0	5	1	0	0	0	0
Number of R&D Investments in Type 3 Diseases	0.46	0	7	0	0	0	0	0

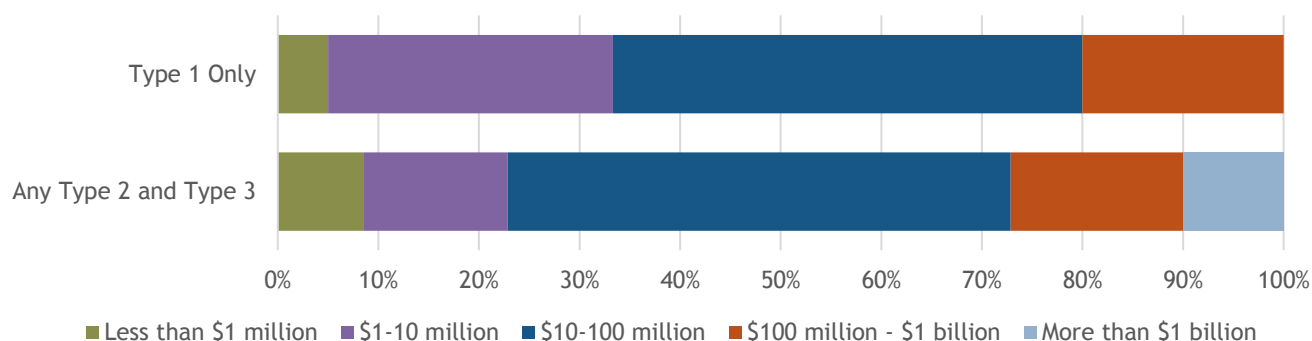
The size of companies' operating budgets show some relation to their investment in Type 2 and Type 3 diseases. Companies involved in Type 2 and Type 3 disease R&D tend to have larger operating expenses as compared to companies only working on Type 1 diseases (Figure 1), potentially indicating that primarily larger Pharma firms diversify into Type 2 or 3 R&D. This trend is also seen in R&D expenses where the only companies with R&D expenses over \$1 billion are involved in at least some Type 2 or Type 3 R&D (Figure 2).

Figure 1. Company operating expenses, by company type



⁸ We initially randomly sampled fifty 10-Ks for Type 1 only firms. An additional 11 were added from the sample of firms mentioning at least some Type 2/3 disease R&D, as further review revealed that those firms were not actually pursuing Type 2/3 disease R&D.

Figure 2. Company R&D expenses, by company type



Review Methods

We systematically code the content of each 10-K using a customized data extraction form that captures basic information about each company and a review framework organized according to five factors hypothesized to influence R&D investment decisions. Drawing on Anderson et al. (2017) we evaluate constraints and opportunities to private sector investment in LMIC disease research using a framework derived from public goods theory and theories of private firm behavior, which includes five disincentives hypothesized to inhibit private sector investment in global health R&D:

- *Scientific uncertainty*: Investors may be deterred by the scientific uncertainty related to developing an efficacious and safe therapy that will successfully make it through all clinical trials.
- *Policy and regulatory environment*: Macroeconomic and policy factors such as regulatory processes, regulatory costs, and weak or uncertain intellectual property protections - both where products are developed and where they are sold - may further discourage private sector investment.
- *Limited revenues and market uncertainty*: Developing therapies for small or LMIC markets may not be seen as profitable, either because of a limited ability to pay, weak IP protection to support pricing, limited health care infrastructure to disseminate products, or pricing affected by third-party payers - all reducing perceived potential revenue.
- *High costs of research and manufacturing*: The higher the initial costs and the more specialized “sunk costs” - with less resale or repurposing value such as preclinical research, clinical trials, and IP payments to access previous research - the greater the deterrent to private investment, all else equal. High costs for manufacturing the outputs of the R&D process - particularly for new products with untested production methods - may further discourage investment.
- *Downstream rents from imperfect markets*: The ability of large firms with downstream capacity to purchase the rights to upstream R&D at a lower cost than producing it internally may reduce incentives for private investment in new health R&D.

All of these hypotheses also apply to health R&D generally, though some LMIC contexts or Type 2 or 3 disease patterns across the hypotheses may differentially deter global health R&D. In addition to these five hypotheses, we also code for mentions of specific policy incentives. Appendix B includes a detailed outline of the topics included in the review framework. Information from the 10-Ks was coded into an Excel spreadsheet for analysis.

We code whether companies discuss the topics in the review framework in terms of positive, negative, or mixed (both positive and negative) effects on their R&D investments. This mixed category lowers the number

of pure positive and negative mentions. Positive mentions are reported as incentives or enabling factors, and negative mentions are reported as challenges to R&D investment. We also coded when companies discussed these topics in a more neutral sense, i.e., mentioning the topic without commenting on the nature of its effect on their R&D investment.⁹

Our data extraction template thus allows us to analyze the relative frequency of positive, negative, mixed, or neutral mentions of each constraint or opportunity across our sub-samples of companies based on the types of diseases discussed. For each topic coded into our review framework, we also record qualitative descriptions and quotations supporting the coding decision.

In addition to the discussion of incentives, risks, and challenges affecting R&D investments that are specific to each company and to their specific R&D efforts, most companies also mention a similar set of “anticipated risks” in their 10-K filings. These anticipated risks are typically discussed with identical “boiler-plate” language across 10-Ks, and reflect concerns that the companies may report for reasons of transparency and to avoid potential litigation from investors or stakeholders. During our 10-K review, we collected a list of the anticipated risks mentioned in general terms across the documents, and then recorded whether or not the same sets of generally standardized text was or was not found in each 10-K. A summary of this boilerplate risk language is included in Appendix C. Appendices D and E provide summaries of other patterns in language observed across 10-Ks in the sample, drawing automated machine coding across a broader sample of company 10-Ks (Appendix D) and on manual coding across specific diseases (Appendix E).^{10, 11}

In the results section below we discuss each policy incentive and hypothesized barrier to private sector R&D investment in the coding framework is reported separately. We first report on the specific policy incentives discussed in the 10-Ks, before reporting findings for each hypothesis. We start by describing in more detail the different aspects of each hypothesis, followed by a graphic showing the results of the overall hypothesis coding at the company level and at the disease level. We then report the enabling factors for each hypothesis, including specific examples from some companies that illustrate that factor. Finally, we finish each section with a description of the challenges related to each hypothesized disincentive to private sector global health R&D investment reported in the 10-Ks.

Results: Specific Policy Incentives

The US and other HICs have specific policies meant to encourage investment in specific diseases by lowering R&D costs or approval times. As reported in Anderson et al. (2017), though a variety of policy tools exist to promote private sector investment in R&D, including push mechanisms (public research funding, R&D tax credits) and pull mechanisms (advance purchase commitments, orphan drug programs, priority review vouchers, and wild-card patent extensions), evidence of effectiveness is mixed. Thus in this review of industry

⁹ For example, under the topic “general scientific uncertainty”, coding “negative” signifies that the company discusses low confidence or high uncertainty that their research will successfully advance any candidate through all clinical trials to approval (usually due to a lack of efficacy or the presence of unintended side-effects). Coding “positive” for “general policy or regulatory uncertainty” signifies the company mentions a high certainty of successfully navigating the regulatory process. Finally, an example of a “neutral” mention for “general limited revenues and market uncertainty” is when a company discusses license agreements with other companies or universities but does not mention whether this reduces their own risk.

¹⁰ Appendix D includes a summary of findings from an exploratory exercise using automated structural topic modeling for the full set of SEC 10-K filings from 2005-2016 under SIC code 2834, comparing prevalence of certain topics in 10-Ks of firms focusing on different types of diseases.

¹¹ We code specific diseases mentioned by each company using the same framework described in the methods text. Each disease was coded following the same company-level review framework, with disease-specific mentions also coded positive, negative, mixed, or neutral. To be included in the disease specific coding, the company had to mention an aspect of one hypothesis or policy incentive that pertained to that specific disease. For example, they may report the scientific certainty of progressing a hepatitis B drug candidate through all phases of research to a marketable product. Our disease-specific coding sample includes 247 Type 1 diseases, 109 Type 2 diseases, and 36 Type 3 diseases. We include a summary of disease-level findings in Appendix E.

self-reported barriers and opportunities in 10-K filings we further consider the roles that policy tools such as public research funding, R&D tax credits, advance purchase commitments, orphan drug programs, priority review vouchers, and wild-card patent extensions appear to play in catalyzing and sustaining private global health R&D.

Types of policies mentioned by companies include policies that address patents, review time, regulatory costs, approval time, and tax-based incentives. In general, these policies apply across all disease types, but some policies target Type 3 diseases specifically, including neglected tropical disease priority review vouchers and advanced market commitments. Most policy incentives are mentioned by firms as having a positive impact on their R&D investments (Table 3). R&D tax credits are mentioned most often, especially by Type 1 only companies. R&D tax credits are the most commonly mentioned policy tool, especially by Type 1 only companies. Orphan drug status is the most commonly mentioned policy tool among companies research Type 2 and Type 3 diseases. Priority review vouchers (a form of expedited review) are mostly mentioned by companies focused in Type 2 or 3 disease R&D but are also mentioned by companies involved in biodefense R&D. Advanced Purchase Commitments are not frequently mentioned.

Table 3. Mentions of policy incentives by impact on company R&D, by company R&D emphasis

Policy Incentive	Positive Impact		Negative Impact		Mixed Impact		Neutral		No Mention	
	Type 1 only	Type 2 or 3	Type 1 only	Type 2 or 3	Type 1 only	Type 2 or 3	Type 1 only	Type 2 or 3	Type 1 only	Type 2 or 3
Advanced Purchase Commitments	0	2	0	0	1	1	0	0	60	67
R&D Tax Credits	39	15	0	0	0	0	0	0	22	56
Orphan Drug Status	25	27*	0	0	0	0	0	0	36	44
Expedited Review **	19	23	0	0	0	0	0	0	42	48
505(b)(2)	12	2	4	1	0	1	16	7	29	60
Hatch-Waxman Amendments	17	7	0	0	0	0	16	6	28	58
Other Policies	1	1	0	0	0	0	0	0	60	70

Note: There are a total of 61 companies working solely on Type 1 diseases and 71 companies working on Type 2/3 diseases

*Only 9 of these companies received Orphan Drug Status for non-Type 1 diseases

**The Expedited Review category includes Fast Track designation, Priority Review Vouchers, Qualified Infectious Disease Product designation, and Breakthrough Therapy designation

Advanced purchase or market commitments (AMC) guarantee markets for new, viable products that can incentivize developing products for diseases with limited markets, but are mentioned by very few companies in our sample (four). Orphan drug status is most commonly applied by companies in our sample to Type 1 disease R&D. Expedited review policies mentioned include several aimed specifically at Type 2 or 3 diseases, though others such as “Fast Track” designation may also be applied to Type 1 disease R&D.

Table 4. Mentions of policy incentives for specific disease R&D investments, by disease type.

	Type 1 diseases (247)	Type 2 diseases (109)	Type 3 diseases (36)
Advanced Purchase Commitments	1%	3%	6%
Orphan Drug Status	25%	7%	11%
Priority Review Vouchers	4%	2%	8%
Expedited Review*	21%	12%	3%
Other Policies	4%	3%	6%

Note: A mention means that the company discussed the policy incentive as referring to a specific disease they were researching in their 10-K report. Hatch-Waxman amendments and R&D tax credits are not included in this table because they are mentioned primarily at the company level and not with respect to specific disease investments.

* The Expedited Review category includes Fast Track designation, Priority Review Vouchers, Qualified Infectious Disease Product designation, and Breakthrough Therapy designation

Key Takeaways: Policy Incentives

In this review of industry self-reported barriers and opportunities in 10-K filings we further consider the roles that policy tools such as public research funding, R&D tax credits, advance purchase commitments, orphan drug programs, priority review vouchers, and wild-card patent extensions appear to play in catalyzing and sustaining private global health R&D.

In general, these policies apply across a wide range of companies, but some policies target specific disease Types. Most policy incentives are mentioned by firms as having a positive impact on their R&D investments. R&D tax credits are the most commonly mentioned policy tool: 39 of 61 companies working only on Type 1 diseases mention R&D tax credits, compared to 15 of 71 companies working on at least some Type 2 or 3 disease R&D. Orphan drug status is the most commonly mentioned policy tool among companies researching Type 2 or 3 diseases, though it is more often mentioned with regard to Type 1 diseases than those companies work on.

Expedited review policies mentioned include several aimed specifically at Type 2 or 3 diseases (notably Priority review Vouchers), though others such as “Fast Track” designation may also be applied to Type 1 disease R&D. Priority review vouchers (a form of expedited review) are mostly mentioned by companies focused in Type 2 or Type 3 disease R&D but are also mentioned by companies involved in biodefense R&D. Overall, expedited review policies are more frequently mentioned specifically for Type 1 diseases than for Type 2 or 3 diseases.

Advanced Purchase Commitments

Advanced purchase or market commitments (AMC) guarantee markets for new, viable products that can incentivize developing products for diseases with limited markets. Under an AMC, a purchasing entity agrees to purchase a set amount of product still in development and/or purchase it at a certain price.¹² The four companies that discuss AMC all develop products for Type 2 diseases and for anti-terrorism indications. Emergent Biosolutions Inc. has signed a contract with the CDC to supply 29.4 million doses of their anthrax product, BioThrax, to the Strategic National Stockpile. Chimerix, Inc. is in discussion with the Biomedical Advanced Research and Development Authority (BARDA), a section of the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services, regarding supplying their smallpox and adenovirus drug, Brincidofovir, to the Strategic National Stockpile. PharmAthene, Inc, mentions that they receive advanced funding from their two primary customers, BARDA and the US Department of Defense, but that these may be subject to budget cuts. Chembio Diagnostics, Inc. received AMC for their HIV diagnostics from the President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Health Fund.

R&D Tax Credits

Internal Revenue Code section 41 U.S. provides taxes credits for investments in R&D performed in-house or through a contract partner paid directly by the filing company (IRC §41). Thus, most companies engaged in any form of R&D should be receiving general tax credits. 54 companies mention the use of R&D tax credits, including 21 companies researching products for Type 2 or 3 diseases. 40 of these 54 companies mention the risk of not being able to carryforward tax credits due to either previous or future changes in ownership. Despite this concern, no company states that they have experienced any difficulty in claiming this credit due to ownership changes. 19 companies specifically mentioned the added benefit of R&D tax credits related to orphan drug status designation.

¹² Thus, this excludes contracts among companies or between companies and governments for intermediate products, production quotas, or products that have already been developed..

Orphan Drug Status

The Orphan Drug Act provides companies developing drugs for rare diseases (affecting less than 200,000 people in the US) or diseases for which they are not expected to recoup development costs with benefits such as enhanced tax credits (50% of clinical research expenditures), market exclusivity (seven- year exclusivity), New Drug Application or biologics license application fee waivers (FDA, 2017). The two qualification criteria for orphan drug status allow for all types of diseases to receive such designation, whether or not they are prevalent in the US. However, companies in this review predominantly received orphan drug status for rare diseases in the US (84%).

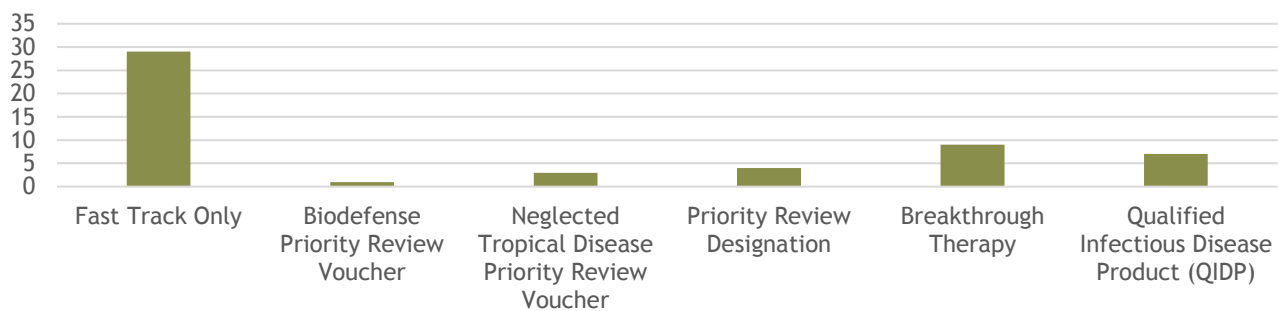
Fifty-two companies mention orphan drug designation as affecting their business, with 51 having received the designation and 1 planning to pursue designation. Of those receiving orphan drug designation, 8 received it for products addressing Type 2 diseases, 1 received it for a product addressing the Type 3 disease Ebola, and 2 received designation for products addressing other diseases (specifications of Anthrax and Lung-ARS). The other companies had received designation for Type 1 diseases, although in some cases the resulting products had broader applications. For example, Matinas Biopharma Holdings, Inc. received orphan drug designation for the broad spectrum anti-fungal, MAT2203, which can be used for multiple fungal infections that span disease types but only states the product received orphan drug status for its Type 1 indications.

Orphan drug status designation is also a policy in the European Union. One company (Chimerix, Inc.) reports that a benefit of orphan drug status in the EU is receiving free scientific advice. Chimerix describes themselves as “a biotechnology company committed to discovering, developing and commercializing medicines that address significant, unmet medical needs”, and their research streams include two Type 1 diseases (smallpox and herpes) and three Type 2 diseases (norovirus, adenovirus, and HIV). They have previously received orphan drug designation for three products which treat adenovirus, cytomegalovirus, and smallpox.

Expedited Review

Multiple policies expedite the review and approval of particular health R&D products. Fast Track Designation (FTD) is meant to speed the review of products addressing serious conditions or unmet medical needs (FDA, 2018). Twenty five companies state that their products had received FTD while four state that they are pursuing FTD. Kalabios Pharmaceutical, Inc. said they expect to receive such designation for Chagas disease.

Figure 3. Mentions of expedited review policies, company level



Eight companies discuss the impact of Priority Review, with four stating they have received priority review designation for product addressing Type 2 diseases and four stating they may receive Priority Review Vouchers. Unlike designation, vouchers are provided to companies upon approval and allow the company to speed up the review time of another product to six months (Soligenix, 2016, pg. 10). These vouchers can be sold to other companies and have sold for up to \$350 million. Emergent Biosolutions Inc. believes they can receive neglected

tropical disease (NTD) PRV for two products targeting dengue fever and Zika, Medical Countermeasure PRV for a product targeting *Burkholderia pseudomallei* infection, and that their product targeting hemorrhagic fever could receive either PRV. Kalabios Pharmaceuticals, Inc. believes they can receive a PRV for their Chagas disease product. Arbutus Biopharma Corporation had stopped development of their RNAi product candidates for filoviruses Ebola and Marburg but in light of the inclusion of filoviruses as PRV candidates in 2014, they state that they are willing to partner with other companies to continue development. Soligenix believes their product targeting ricin toxin is eligible for a biodefense PRV.

Nine companies have received or are planning to pursue Breakthrough Therapy Designation for their products. The only company pursuing this designation for a Type 2/3 disease is CytoDyn, Inc., which has received BTM for their HIV drug.

Eight companies mention having Qualified Infectious Disease Product (QIDP) designation. Three of these QIDP designations for products that addressed acute bacterial skin and skin structure infections (ABSSSI), a Type 2 disease. The other four received designation for products addressing Type 1 diseases. Matinas Biopharma Holdings, Inc., whose broad spectrum anti-fungal can address leishmaniasis received QIDP designation but did not mention leishmaniasis as one of the indications included in the designation.

The Hatch-Waxman Act

A total of 62 companies discuss the impact of two different parts of the Drug Price Competition and Patent Term Restoration Act of 1984, known as the Hatch Waxman Act. Section 505(b)(2) provides companies with an Abbreviated New Drug Application (ANDA) pathway that allows companies to file “an application that contains full reports of investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference” (FDA, 1999).¹³ By allowing companies to use other companies’ research outcomes, this approval pathway can reduce the monetary and time investment required to conduct clinical trials and reduces approval time.

The Hatch-Waxman Amendments allow companies to extend patent terms up to five years to recoup patent term losses resulting from development and approval times. This only applies to a limited number of companies as the Amendment cannot extend the patent term beyond 14 years from the original approval date. The Cellceutix Corporation discusses the double-edged nature of this Act: “The law ... creates both opportunities for exclusivity periods and patent protections and the possibility of generic competition once such periods or protections have either expired or have been successfully challenged by generic entrants” (Cellceutix Corporation, 6)

Overall, 42 companies discuss the 505(b)(2) pathway but 23 of those companies simply describe the pathway when they detail the general approval process and do not mention taking advantage of it. Fourteen companies, two of which research Type 2/3 diseases, state that they planned to or had used this approval pathway. Axsome Therapeutics, Inc. states the benefit of the pathway as allowing them “to leverage previous preclinical and clinical experience with the active molecules in our product candidates and potentially forego conducting certain lengthy and costly preclinical studies, reduce clinical and regulatory risk, limit development costs, and accelerate our time to commercialization (Axsome Therapeutics Inc, p. 7).

Five companies discuss the possible negative impact of the pathway resulting other companies infringing on their research and market. Omeros Corporation and Horizon Pharma Public Limited Company discuss specific

¹³ A right of reference is the legal authority to use another research or investigation stream for a New Drug Application (NDA).

incidences of companies using their research for Type 1 disease products. Omeros believes the competing company did not have merit to use their research but do not mention any recourse they had taken. Pharma Public Limited was in litigation with a company. The other 3 companies discuss the general risk of the pathway to their company.

46 companies discuss the Hatch-Waxman Amendments with 22 generally stating the regulation without indication of its applicability. The other 24 discussed pursuing the patent term extension depending on their total development and approval time. Only 3 companies mentions a specific product in regard to the Amendments and these are all for Type 1 diseases.

Other Policies

Albireo Pharma, Inc. was granted to the Priority Medicines (PRIME) program for their product addressing Progressive familial intrahepatic cholestasis. The PRIME program is a European Medical Association initiative to address an unmet medical need and bring a major therapeutic advantage to patients. It is similar to the Orphan Drug Act in the US but confers different benefits including expedited review. PharmAthene, Inc is “considering applying for indemnification under the U.S. Support Anti-terrorism by Fostering Effective Technologies (SAFETY) Act of 2002 which preempts and modifies tort laws so as to limit the claims and damages potentially faced by companies who provide certain “qualified” anti-terrorism products” for their anthrax product (PharmAthene Inc., 2016, pg. 16).

Results: Mentions of Opportunities and Constraints by Hypothesized Barrier to R&D Investment

We look more closely at the nuances of investment decisions by examining the evidence for five specific disincentives to private sector investment: scientific uncertainty, weak policy environments, limited revenues and market uncertainty, high fixed costs, and imperfect markets. Though all five may affect estimates of net returns from an investment decision, they are worth examining separately as each calls for a different intervention or remediation to change behavior.

Mentions by Hypothesized Barrier: Company Level

Out of the five hypotheses, companies that researched any Type 2/3 disease mention fixed costs most often, while policy and regulatory uncertainty are mentioned least often. For companies that research only Type 1 diseases, limited revenues is mentioned most often and imperfect markets least often, however most companies mention all five hypotheses at least once in their 10-K filings.

Table 5. Count of companies mentioning each hypothesis, by company type

Factors hypothesized to affect company investment in R&D	Any Type 2 or 3 R&D (71 companies)		Type 1 R&D Only (61 companies)	
	Mentioned	Not Mentioned	Mentioned	Not Mentioned
1. Scientific Uncertainty	53 (75%)	18	55 (90%)	6
2. Policy and Regulatory Uncertainty	44 (62%)	27	53 (87%)	8
3. Limited Revenues / Market Risk	63 (89%)	8	59 (97%)	2
4. Fixed, Sunk, and Other Costs*	64 (90%)	7	58 (95%)	3
5. Imperfect Markets**	58 (86%)	13	50 (87%)	11

Note: A mention can be positive, negative, mixed, or neutral.
 *Includes manufacturing costs for products of R&D; **Includes licensing agreements

Mentions by Hypothesis: Disease Level

We find more variation of mentions for each hypothesis at the disease level as compared to the company level. For Type 1 diseases, the most frequently mentioned hypothesis - limited revenues - is mentioned more than twice as often as the least mentioned hypothesis, policy and regulatory uncertainty. This is similar for Type 2 diseases and Type 3 diseases, although the most frequently mentioned hypothesis for Type 3 diseases are fixed costs followed closely by limited revenues. Policy and regulatory uncertainties are the least mentioned hypothesis for all disease types.

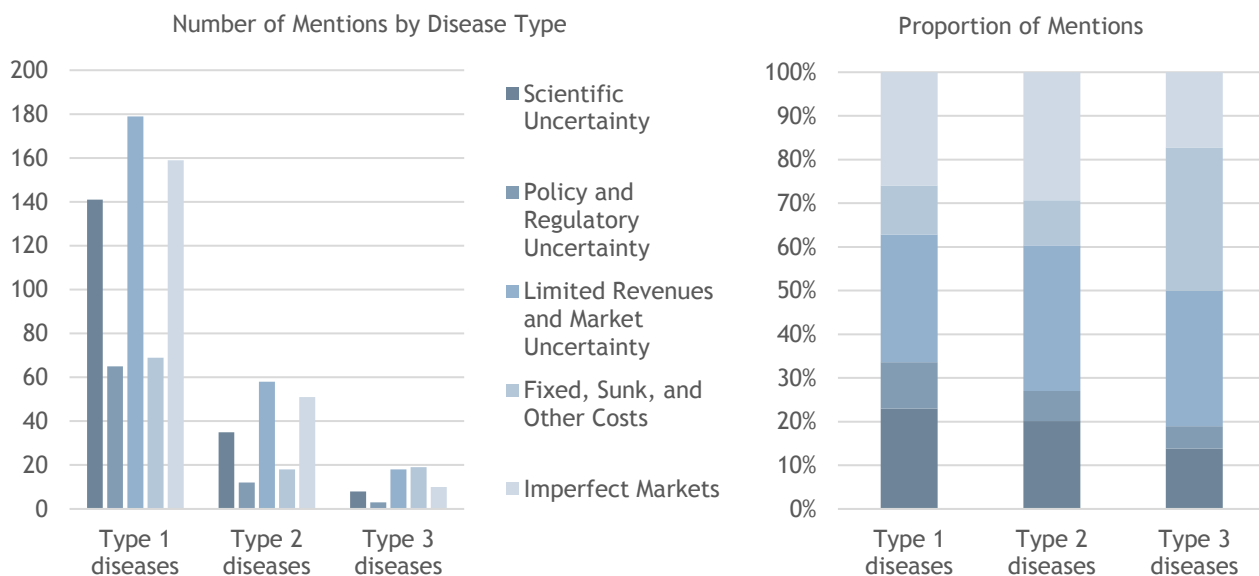
Table 6. Count of companies mentioning each hypothesis, by disease type

	Type 1 diseases (247)		Type 2 diseases (109)		Type 3 diseases (36)	
	Mentioned	Not Mentioned	Mentioned	Not Mentioned	Mentioned	Not Mentioned
1. Scientific Uncertainty	141 (57%)	106	35 (32%)	74	8 (22%)	28
2. Policy and Regulatory Uncertainty	65 (26%)	182	12 (11%)	97	3 (8%)	33
3. Limited Revenues / Market Risk	179 (72%)	68	58 (53%)	51	18 (50%)	18
4. Fixed, Sunk, and Other Costs*	69 (28%)	178	18 (17%)	91	19 (53%)	17
5. Imperfect Markets**	159 (64%)	88	51 (47%)	58	10 (28%)	26

Note: A discussion can be positive, negative, mixed, or neutral.

*Includes manufacturing costs for products of R&D

Figure 4. Count and proportion of times a company mentioned each hypothesis in reference to a disease type they are researching



Note:

Total Type 1 Diseases in Sample: 247

Total Type 2 Diseases in Sample: 109

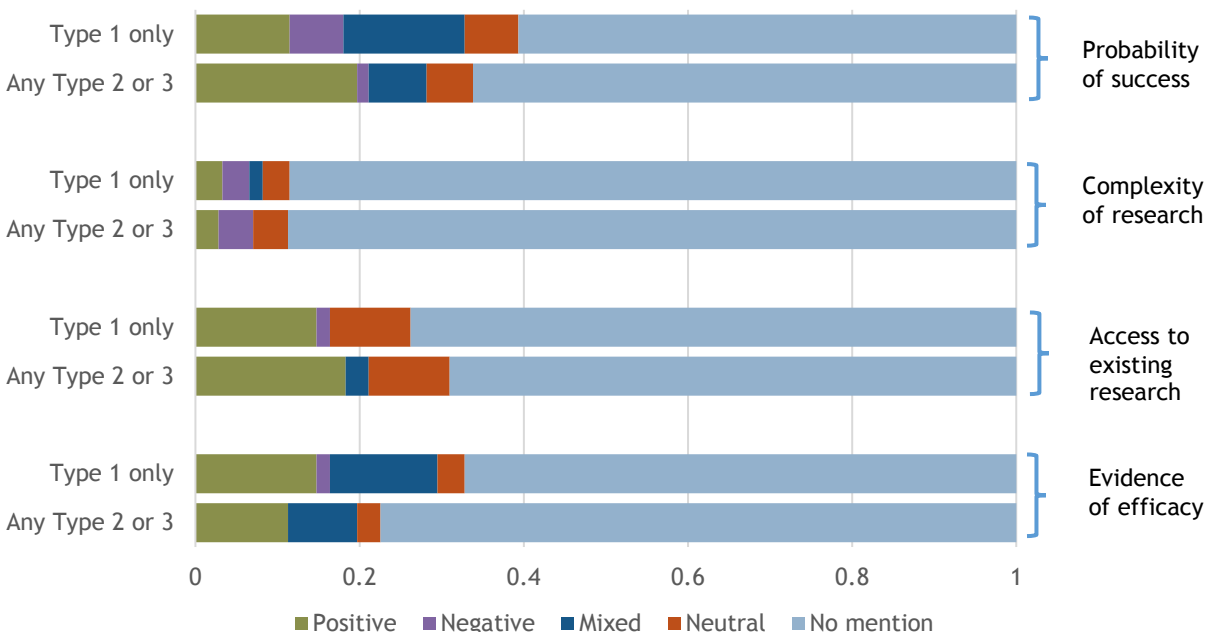
Total Type 3 Disease in Sample: 36

Hypothesis 1: Scientific Uncertainty

We review company mentions of scientific uncertainty in four broad - though related - categories, recognizing that, for example the probability of scientific success is related to the complexity of research and access to existing research.

1. **Probability of success** refers to perceptions of how likely a stream of research will yield a marketable product based on scientific considerations.
2. **Complexity of research** refers to the scientific and technical difficulties or uncertainties pertaining to a stream of research.
3. **Access to existing research** refers to a company's access to previous research related to their active research streams, through either purchases or partnerships.
4. **Evidence of efficacy** on reducing mortality or morbidity is the scientific evidence that a company has pertaining to its research stream that may improve perceptions of its probability of success.

Figure 5. Proportion of mentions for four aspects of scientific uncertainty comparing companies that work on Type 1 diseases only versus those that work on any Type 2 or 3 diseases



Note: These proportions are based on a sample size of 61 companies that work on Type 1 diseases only, and 71 companies that work on any Type 2 or 3 diseases.

Factors related to scientific uncertainty are mentioned by less than half of the companies. Probability of success and, to a lesser extent, access to existing research are mentioned positively relatively more often for companies that worked on any Type 2 or 3 diseases compared to those that worked on Type 1 only. Evidence of efficacy was mentioned positively relatively more often for Type 1 companies as compared to Type 2 / 3 companies. Few of these factors are discussed in negative terms, as creating particular challenges for companies' R&D investments. Neutral and mixed mentions not expressing any clear position on the impact of these factors on companies' ability to pursue particular R&D streams are relatively more common than negative mentions. Positive mentions are most common overall (except for complexity of research), indicating companies discussing these aspects of scientific uncertainty as enabling factors for their R&D investments.

Key Takeaways: Scientific Uncertainty

Eighty-two percent (108 out of 132) of companies make some reference to scientific uncertainty in the business or risk section of their 10-K filings in 2016, including 75% of companies conducting R&D on some Type 2 or Type 3 diseases (53 out of 71), and 90% of companies focusing exclusively on Type 1 diseases (55 out of 61).

- Some companies (3 in our sample) are developing companion diagnostics alongside their products to increase the chances of success. These diagnostics will lower the risk of clinical trials by allowing researchers to select patients that will better respond to their therapies.
- Three companies report using disease, project, or computer modeling to reduce scientific uncertainty.
- One company uses publicly available information to identify therapies that were pulled off the market for adverse side effects so that it can reevaluate them for its “drug rescue program”.
- Other companies note that novel compounds can lead to more efficacious therapies with fewer adverse side-effects, however, there is more uncertainty as to whether a novel mechanism will result in a marketable product because there is no proof of concept.
- Other mentions include reports that designing studies to evaluate the safety and efficacy of new treatments for rare diseases with no currently available treatment is more difficult because there are no examples of study endpoints to prove efficacy to regulatory agencies.
- Two companies report that complex manufacturing processes have the upside of limiting competition.

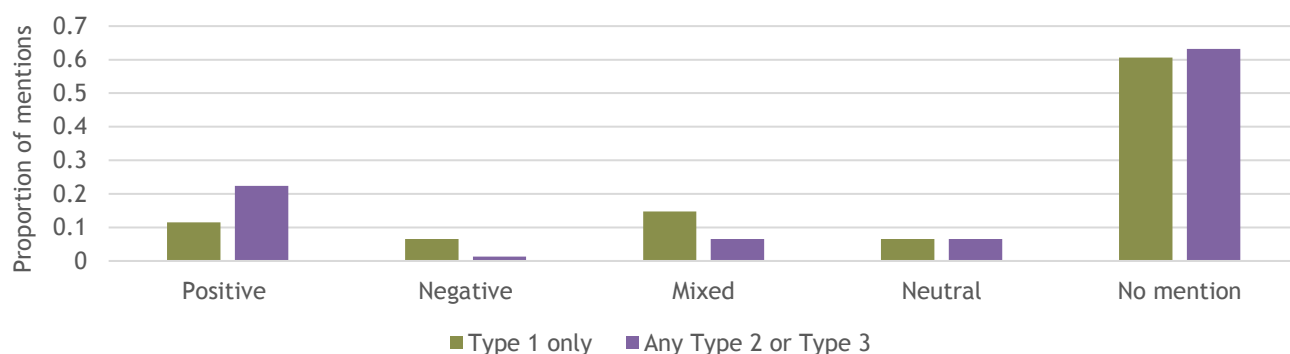
Mentions of scientific uncertainty are quite common in 10-K filings relative to expert interviews and the secondary literature. Science was rarely mentioned in West et al. (2017b) and Anderson et al. (2017) found only four of 285 studies emphasizing the complexity of research, access to existing research or the limited volume of existing knowledge as specific factors influencing private R&D investment decisions.

Scientific Enabling Factors

Probability of Success

Twenty-two companies report a positive probability of success, meaning that they indicate they are pursuing a product that they believe is likely to make it all the way through the development process. This includes 14 Type 2/3 companies, and eight companies that research Type 1 diseases only.

Figure 6. Proportion of companies that mention a probability of success by type of research



Note: There are 61 Type 1 only companies and 71 companies that research any Type 2 or 3 disease. This graph represents the proportion of the total number of companies in each category that discuss each kind of mention in their 10-K.

Nine of these companies mention that their drug discovery platforms and technologies will help them develop more novel drug candidates with a higher chance of success, including one Type 1 company, and eight Type 2/3 companies. Researching novel mechanisms of interaction can provide new therapies that are more efficacious and have fewer side effects, as well as produce a pipeline of differentiated products. Arrowhead Pharmaceuticals researches RNAi therapeutics with the target of addressing previously “undruggable” targets

(Arrowhead Pharmaceuticals, 2016, pg. 5). Another company, Respirex Pharmaceuticals, researches drug-induced respiratory depression and has developed ampakine technology, which has resulted in the production of multiple drugs with improved safety profiles over previous research.

Arbutus Biopharma Corporation also researches the use of RNAi therapy with the idea of creating novel therapies. “The development of RNA Interference (RNAi) drugs allows for a completely novel approach to treating disease, which is why RNAi is considered one of the most promising and rapidly advancing frontiers in drug discovery” (Arbutus Biopharma Corporation, 2016, pg. 6). As of the publication of their 10-K there were multiple companies researching this technology, however there have not been any approved drugs using RNAi technology yet. Arbutus Biopharma Corporation uses this technology to focus on developing drugs for Hepatitis B (a Type 2 disease). Their most advanced candidate is currently in Phase II trials.

Three companies (Endocyte, Inc., Agios Pharmaceuticals, Inc., and Regulus Therapeutics, Inc.) report the use of companion diagnostics they are developing alongside their products to increase the chances of successful drug development. The use of these diagnostics will lower the risks of clinical trials since the researchers can select for patients that will better respond to their therapies. Endocyte currently uses this technology to research and develop oncology and inflammation therapies. Their two most advanced candidates are both in Phase I trials for prostate cancer and lung cancer. Agios Pharmaceuticals researches oncology and rare genetic metabolic disorders. Their most advanced candidates are in Phase III clinical trials for acute myeloid leukemia and cholangiocarcinoma (both are cancers). Agios’ development strategy includes the use of targeted study populations “...enabling the potential for proof of concept early in clinical development, along with the potential for accelerated approval” (Agios Pharmaceuticals, 2016, pg. 2). Regulus Therapeutics uses microRNA biomarkers to select and monitor patients for three diseases, one of which is hepatitis C, a Type 2 disease.

Six companies report that they expect to successfully advance products to the next phase of research, or to develop a marketable product, including three companies that research Type 2/3 diseases. The lead product of Glycomimetics, Inc. is a therapy that treats a condition resulting from sickle-cell disease (Type 2), which the company is currently enrolling patients for a phase 3 trial in partnership with Pfizer. Glycomimetics believes that the positive results from the phase 2 trial provides evidence that their therapy has the potential to successfully complete phase 3 trials.

Three companies report less scientific uncertainty due to strategic disease, project, or computer modeling, including one company that researches Type 2/3 diseases. Omeros Corporation, which researches pneumonia (Type 2) along with multiple Type 1 diseases, uses “rigorous project management techniques to assist us in making disciplined strategic research and development programmatic decisions and to limit the risk profile of our product pipeline” (Omeros, 2017, pg. 29). Omeros notes that not relying on third parties to conduct the majority of their preclinical research and not depending on any one clinical trial site reduces their risk.

One company (Impax Laboratories) reports that their controlled release delivery technology may “improve drug efficacy, ensure greater patient compliance with the treatment regimen, reduce side effects or increase drug stability and be more patient friendly by reducing the number of times a drug must be taken” (Impax Laboratories, 2017, pg. 11).

Table 7. Companies mentioning a positive probability of success by different categories of success

Factors positively influencing perceived probability of success	Number of Companies	
	Type 1 only (61 companies)	Any Type 2 or 3 (71 companies)
Develop novel candidates	1	8
Use of companion diagnostics	2	1
Advancement along R&D pipeline	3	3
Strategic R&D technology	2	1
New delivery technology	0	1
Total	8	14

Complexity of Research

Four companies report positive strides reducing the complexity of the research they conduct including two companies that research only Type 1 diseases and two companies that research some Type 2 and 3 diseases. Positive mentions of complexity refer to companies that have managed to simplify their own R&D pathway or those that see their own complex research as conferring a market advantage.

Impax Laboratories researches novel therapies as well as produces generic drugs. Their focus is on producing generic pharmaceuticals that have “technically challenging drug-delivery mechanisms or unique product development formulations” (Impax Laboratories, 2017, pg. 6). The company reports that producing difficult to manufacture therapies provides a competitive advantage. “Due to our focus on relatively hard to replicate controlled-release products, competition in the generic pharmaceutical market is sometimes limited to those competitors who possess the appropriate drug delivery technology” (Impax Laboratories, 2017, pg. 6).

Only two specific diseases have positive effects associated with the complexity of research, both of which are Type 1 diseases (cancer and Lung-ARS), and in one case by the expectation that the complexity will slow competitors. Aeolus Pharmaceuticals is developing a therapy for Pulmonary Acute Radiation Syndrome (Lung-ARS) using the Animal Rule allowing them to show efficacy in animal models only - without testing on human subjects. They will still be required to show safety in human subjects. Bellicum Pharmaceuticals is developing multiple cancer therapies, which depend on a complex drug that is difficult to manufacture. The company “believe(s) that a competitor will face substantial obstacles with respect to time and cost in order to derive a clinically acceptable manufacturing process” (Bellicum Pharmaceuticals, 2017, pg. 10).

Access to Existing Research

Twenty-two companies report that access to existing research positively impacts their R&D efforts, meaning that they have substantial access to existing research and a scientific knowledge base, through purchases or agreements, that decreases uncertainty related to their own research. This includes 18% (13 out of 71) of the companies that research at least one Type 2 or Type 3 disease, and 15% (9 out of 61) companies that exclusively research Type 1 diseases.

Table 8. Companies mentioning positive access to existing research by different categories of access

Factors positively influencing access to existing research	Number of Companies	
	Type 1 only (61 companies)	Any Type 2 or 3 (71 companies)
Collaborations with other companies or organizations	3	6
Purchases of research products or other companies	5	3
Accessing publicly available information	1	1
Access to compound libraries	0	2
Free scientific advice from orphan drug status	0	1
Total	9	13

Nine of these companies report that they will gain access to existing research through collaborations with other companies, academic institutions, medical centers, or government agencies. The research gained may be used to advance their own research or to access technology useful for clinical trials. This includes six companies that research at least one Type 2 or 3 disease, and three companies that research Type 1 diseases exclusively.

Vertex Pharmaceuticals, Inc., which researches two Type 2 diseases (sickle cell disease and influenza), collaborates with other pharmaceutical companies, academic research institutions, government laboratories, and foundations in order to advance research and to access needed technologies. Their agreement with CRISPR Therapeutics to develop hemoglobinopathy treatments, including for sickle cell disease, includes shared development costs and revenues. Vertex has also outlicensed their influenza drug candidate to Janssen Pharmaceuticals for an upfront payment of \$35 million, and future milestone and royalty payments. Omeros Corporation develops antibodies that they believe will be useful for a wide range of diseases, including pneumonia (Type 2 disease). Omeros licenses the technology used to create these antibodies from the University of Washington.

Four companies discuss gaining access to existing research through purchases, including one company (Arrowhead Pharmaceuticals) that researches primarily Type 1 diseases, but also researches Type 2 or 3 diseases, and three companies that research Type 1 diseases only. Arrowhead Pharmaceuticals purchased the RNAi development arms of Roche and Novartis, which gave them access to scientists and technology. “We see the Roche and Novartis acquisitions as a powerful combination of intellectual property, R&D infrastructure, and RNAi delivery experts” (Arrowhead Pharmaceuticals Inc., 2016, pg. 4). Arrowhead plans to use this technology primarily to develop hepatitis B therapies.

One company discussed the benefits of having access to publicly available information on drugs that have been removed from the market due to safety concerns. VistaGen Therapeutics primarily develops therapies for major depressive disorders (Type 1 disease). The company plans to use proprietary technology to evaluate drugs that were approved but pulled off the market for toxicity. VistaGen plans to use pre-existing public domain knowledge on the therapeutic and commercial potential of their rescue drugs to gain a head-start on demonstrating proof of concept for their own NCEs.

“We believe the pre-existing public domain knowledge base supporting the therapeutic and commercial potential of NCEs we target for our drug rescue programs will provide us with a valuable head start as we launch each of our drug rescue programs. Leveraging the substantial prior investments by global pharmaceutical companies and others in discovery, optimization and efficacy validation of the NCEs we identify in the public domain is an essential component of our drug rescue strategy.” (VistaGen Therapeutics, Inc., 2016, pg. 15)

VistaGen believes that this will allow them to generate proof of concept for their therapies with considerably less investment than their competitors. While the company does not specify which kinds of diseases they will target with their drug rescue activities, they currently focus on research for major depressive disorders.

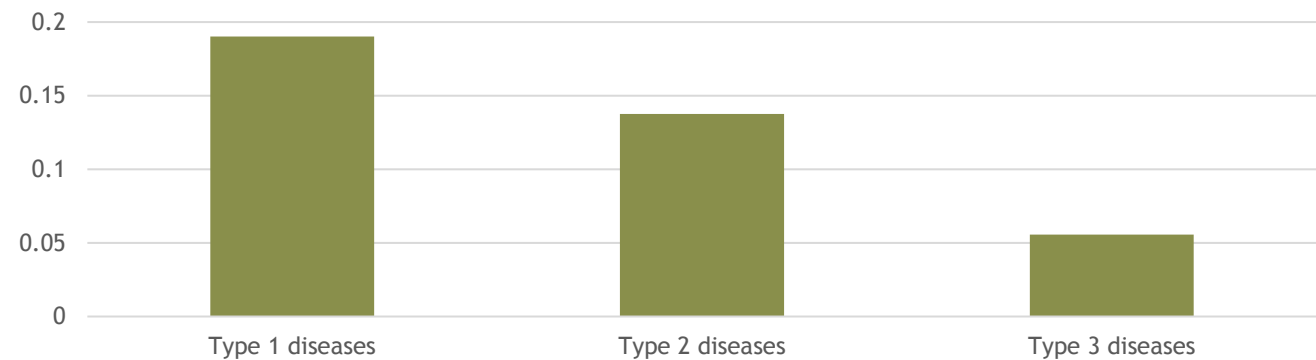
Two companies mention that they have access to large compound libraries, which allows for the discovery of novel therapies. Nabriva Therapeutics focuses only on Type 2 diseases, including bacterial pneumonia and acute bacterial skin and skin structure infections (ABSSSI). They are using their compound library to develop novel antibacterial therapies, including broad-spectrum antibiotics and those that target antibiotic resistant bacteria. Amarillo Biosciences focuses on developing therapies for several Type 2 diseases, influenza and hepatitis C, along with several Type 1 diseases. Amarillo Biosciences plans to use their compound library developed over the last 30 years to form partnerships with other pharmaceutical companies in order to develop and commercialize novel therapies.

Evidence of Efficacy

Forty-four companies report that products they are researching have demonstrated some evidence of efficacy on reducing mortality or morbidity in humans, decreasing uncertainty about the product making it all the way through clinical trials.

In total 65 products have demonstrated efficacy by these 44 companies. Evidence of efficacy is referenced in relationship to 6% of Type 3 diseases mentioned in the overall sample (2 out of 36 diseases mentioned), 15% of Type 2 diseases (16 out of 109 mentioned), and 19% of Type 1 diseases (47 out of 247 mentioned).

Figure 7. The proportion of specific diseases that companies report evidence of efficacy on reducing morbidity or mortality, by disease type



Note: This graph represents the total proportion of disease types that are reported as showing evidence of efficacy in a company 10-K.
Total Type 1 Diseases in Sample: 247
Total Type 2 Diseases in Sample: 109
Total Type 3 Disease in Sample: 36

Kalobios Pharmaceuticals is developing a drug for Chagas disease (a Type 2 disease) that has already undergone multiple clinical trials in other countries, and is approved for use in other countries. The company is pursuing FDA approval for this drug after purchasing the rights to develop and commercialize the drug worldwide, and plans to use previous research to show efficacy and safety for approval in the U.S. They are the only company in our sample that is currently developing a drug for Chagas disease. Kalobios focuses exclusively on neglected and rare diseases, which the company sees as a market opportunity.

"Our strategy also involves identifying, acquiring, developing and supporting the commercialization of additional treatments for neglected and rare diseases. We believe the treatment of neglected and rare diseases represents an opportunity to enter underserved patient populations and serve specialty markets." (Kalobios Pharmaceuticals, 2016, pg. 5)

VBI Vaccines, Inc. is applying for FDA approval for their hepatitis B vaccine that is already approved for use in 15 countries, although not in the U.S., Canada, or the European Union. This vaccine has already been distributed in the countries where it has gained approval and has "demonstrated safety and efficacy in over 300,000 patients in currently licensed markets" (VBI Vaccines, Inc., 2016, pg. 1).

Arbutus Biopharma has shown some success in developing therapies using RNAi technology. The company is using this technology to develop therapies for Hepatitis B (Type 2), and dropping development plans for other diseases including oncology (Type 1), Ebola and Marburg (Type 3). They do not state why they chose to pursue Hepatitis B over other diseases. Their oncology research showed some success in Phase 1/2 clinical trials, and is "available for partnership to enable further development" (Arbutus Biopharma Corporation, 2016, pg. 11). Their Ebola research was funded under a \$140 million U.S. DoD contract, which has since been suspended due

to the “unclear development path for TKM-Ebola” (Arbutus Biopharma Corporation, 2016, pg. 11). The Ebola program also showed success in early clinical trials as it demonstrated high efficacy and was well-tolerated in healthy volunteers. The company is also looking for partners to further develop this program.

Arbutus Biopharma holds what they describe as a “dominant intellectual property position” in the field of RNAi technology. Developing a therapy with a novel mechanism of action can also confer market advantages due to IP protections.

“The broad applicability of this platform to RNAi development has established Arbutus as a leader in this new area of innovative medicine...Our LNP technology represents the most widely adopted delivery technology in RNAi, which has enabled several clinical trials and has been administered to hundreds of human subjects. We are the leaders in LNP delivery and hold a dominant intellectual property position in this field.” (Arbutus Biopharma Corp., 2016, pg. 10)

Two other Type 2 drugs showed efficacy on reducing morbidity in clinical trials, including Cocystal Pharma’s Hepatitis C drug, and Nabriva Therapeutics’ Pneumonia drug. Additionally, two more companies reported preclinical efficacy, including Synthetic Biologics’ pertussis vaccine and ContraFect Corporation’s flu therapy.

The Animal Rule is an approval pathway that changes the scientific evidence needed to approve therapies. This rule applies to diseases where clinical trials are not possible due to ethical reasons, and are generally related to therapies to combat bioweapons. Four companies report using the Animal Rule for developing therapies, two companies are researching Anthrax, one is researching smallpox, and one is researching Pulmonary Acute Radiation Syndrome (Lung-ARS) which is due to exposure to high levels of radiation from a nuclear detonation. There is some uncertainty whether the animal models used will accurately predict the effects of the therapies in human subjects, with the ultimate decision being made by the FDA.

Challenges Arising from Scientific Uncertainty

There is little evidence that there are systematic differences in how companies discuss issues related to scientific uncertainty or complexity among Type 1, 2, and 3 diseases, though each disease has its own unique scientific challenges, making comparisons across disease types or individual diseases difficult. Eighty-two percent (108 out of 132) of companies make some reference to scientific uncertainty in the business or risk section of their 10-K filings in 2016, including 75% (53 out of 71) of companies conducting R&D on some Type 2 or Type 3 diseases, and 90% (55 out of 61) of companies focusing exclusively on Type 1 diseases.

While researching novel compounds can lead to more efficacious therapies, two companies (Cytokinetics Inc. and RA Pharmaceuticals) report that there is a tradeoff to this kind of research; there is no proof of concept and therefore more uncertainty as to whether a novel mechanism will ultimately result in an approved product.

“Because no currently approved drugs appear to operate via the same biochemical mechanisms as our compounds, we cannot be certain that our drug candidates will result in commercially viable drugs that safely and effectively treat the indications for which we intend to develop them.” (Cytokinetics, Inc., 2016, pg. 40)

Table 9. Anticipated risks related to scientific uncertainty reported by companies

	Type 1 only (61 companies)		Any Type 2 or 3 (71 companies)	
	Mentioned	Not mentioned	Mentioned	Not mentioned
Product candidates may be deemed inefficacious during any clinical phase	56	5	66	5
Research partners may fail in their responsibilities to develop a drug	39	22	59	12
Risks related to being able to enroll enough patients in clinical trials	46	15	46	25
Serious adverse events or other side effects could harm chances of product candidate successfully completing clinical trials	56	5	57	14

Many companies form research partnerships with other pharmaceutical companies, or hope to form research partnerships in the future. 74% (102 out of 137) of the companies in our sample reported the anticipated risk that their research partners may fail in their responsibilities to develop a drug. This includes 83% (63 out of 76) of firms conducting R&D on any Type 2 or Type 3 diseases, and 64% (39 out of 61) of firms focusing exclusively on Type 1 diseases. Pharmaceutical companies also often rely on third parties, called contract research organizations (CROs), to conduct research, including clinical trials, however, the company is still responsible for the conduct and outcome of clinical trials and for the performance of the CROs. The number of CROs that pharmaceutical companies rely on to complete clinical trials has been increasing in recent years (Dimachkie Masri, Ramirez, & Popescu, 2012). No company mentions if the reliance specifically on CROs changes scientific uncertainty or incentives.

Much of the scientific uncertainty and scientific incentives around drug discovery and development may be confronted during the earliest basic science research, and therefore not mentioned in the 10-Ks. At the point that a company is discussing clinical research or commercialization in their 10-K report, there may already some evidence of the efficacy of their therapy.

Another anticipated risk expressed by companies is that research streams may not result in marketable products due to a failure to show efficacy or to adverse side effects. Many drugs that show promise in preclinical and early clinical phases are not ultimately approved due to these reasons.

"The failure of a number of Phase 3 clinical trials evaluating other compounds as potential treatments for patients with ALS may suggest an increased risk that our planned Phase 3 clinical development program of tirasemtiv in patients with ALS will also fail" (Cytokinetics, 2016, pg. 31)

The number of companies that mention their product candidates may be deemed inefficacious during any phase of clinical trials is 92% (122 out of 132), including 93% of companies that focus on any Type 2 or Type 3 diseases (66 out of 71 companies), and 92% of companies that focus solely on Type 1 diseases (56 out of 61). Eighty-six percent of companies mention that serious adverse events or other harmful side-effects could harm the chances of successfully developing their candidates (113 out of 132), including 80% of companies that focus on any Type 2 or Type 3 diseases (57 out of 71), and 92% of companies that focus solely on Type 1 diseases (56 out of 61).

Additionally, Achillion Pharmaceuticals, Inc. asserts that undesirable side-effects may cause the company to "abandon development or limit development to sub-populations in which the adverse side-effects are less prevalent, less-severe, or more acceptable from a risk-benefit perspective" (Achillion Pharmaceuticals, Inc., 2016, pg. 35). This same company mentions that designing studies for rare diseases are more difficult because there are no examples of study endpoints:

“In addition, our interest in developing potential therapies for rare diseases for which there is no currently available treatment, such as C3G, makes the difficulty in study design and outcome more challenging, as the appropriate endpoints for obtaining approval from regulatory authorities have not been previously defined.” (Achillion Pharmaceuticals, Inc., 2016, pg. 34)

Another company (Cymabay Therapeutics) reports that not all therapies are for a single disease, which may complicate clinical trials and development.

“Recognizing that SHTG [Severe Hypertriglyceridemia] is a heterogeneous collection of diseases, we are continuing our assessment of the best patient populations to study in a small Phase 2 clinical trial.” (Cymabay Therapeutics, Inc., 2016, pg. 11)

There may be a limited number of clinical trial sites and patients available for some diseases. Seventy percent (92 out of 132) mentioned the risk of not being able to enroll enough patients in clinical trials as a general risk, including 65% (46 out of 71) of firms conducting R&D on any Type 2 or Type 3 diseases, and 75% (46 out of 61) of firms focusing exclusively on Type 1 diseases.

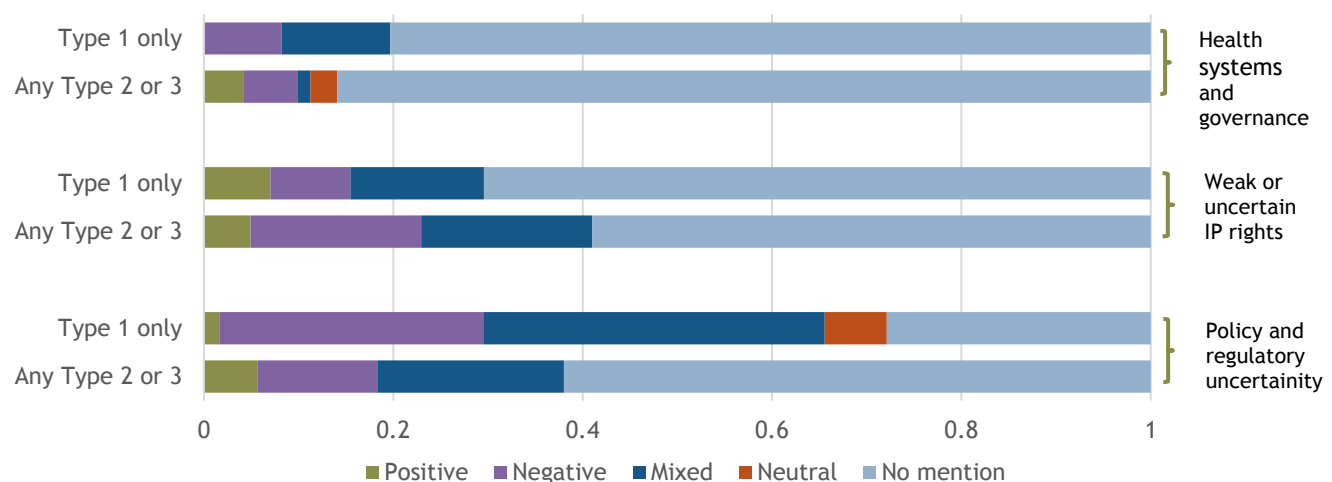
Hypothesis 2: Policy and Regulatory Environment

We review company mentions of perceived risks related to policy and regulatory environments in three broad categories.

1. **Policy or regulatory uncertainty** refers to companies’ uncertainty regarding policies or regulations in approval processes such as data requested by regulating agencies or possibility of gaining approval.
2. **Weak or uncertain IP protections** refers to limited or variable intellectual property systems including issuing or protecting patent regulations, trade secrets, and other IP policies.
3. **Health systems and governance** refers the health infrastructure, health policy, and other associated policies in countries’ that the company operates such as makeup of regulatory agencies.

We also review mentions regarding **regulatory costs**, **development time**, and **approval time**. These categories provide supplemental information to the broad categories. Discussion of specific policy incentives tools is reported separately.

Figure 8. Proportion of mentions of policy and regulatory environment by company and aspect of environment



Note: These proportions are based on a sample size of 61 companies that work on Type 1 diseases only, and 71 companies that work on any Type 2 or 3 diseases.

Mentions of regulatory uncertainty are relatively more frequent among companies focusing only on Type 1 diseases versus companies working on Type 2 or 3 diseases. Health systems and governance is mentioned least among the three categories of regulatory uncertainty while more general policy and regulatory uncertainty is mentioned by a majority of companies. Among companies mentioning regulatory uncertainty, there are generally more negative mentions than positive mentions across all three categories. However, all three categories of regulatory uncertainty are mentioned positively more by companies working on Type 2 and 3 diseases than by those working on Type 1 disease only, i.e., Type 2/3 firms are more like to reference efforts speeding up approval pathways, reducing regulatory costs or uncertainty, or otherwise lowering barriers and incentivizing investment as influencing their investment decisions.

Key Takeaways: Policy and Regulatory Uncertainty

Seventy percent (92 out of 132) of companies in the sample reference policy or regulatory uncertainty in the business or risk section of their 10-K filing, including 62% of companies conducting R&D on Type 2 or Type 3 diseases (44 out of 71) and 87% of companies focusing solely on Type 1 diseases (53 out of 61).

- 86.4% of companies mention the uncertainty of patent and intellectual property rights in boilerplate statements. All five companies that develop products for Type 2/3 diseases and discuss specific negative impacts of weak IP protections, discuss their response to weaker IP systems in markets outside North America and Europe.
- The four companies which discuss health systems and health governance outside the US in detail focus on barriers associated with restrictive health policies or weak regulatory systems.
- One company mentions using Nigeria's regulatory and approval process as a model for submission in other African countries that do not have formal processes.
- Much of the discussion of policy and regulatory uncertainty occurs in general boilerplate language regarding risks and policy pathways open to companies.
- Companies that work on Type 2 and Type 3 diseases are relatively more likely to take advantage of US policies that have larger global reach such as priority review vouchers (PRVs) and fast track pathways. Policies which mainly target Type 1 diseases or products meant for US domestic markets such as Hatch-Waxman Act (dealing with IP rights) are not as widely used for Type 2 and Type 3 diseases or products.

Policy and regulatory environments likewise featured heavily in both expert interviews and the secondary literature review, though with varying specifics. Geo-political risks and unstable macroeconomic and policy environments are widely cited in industry reports as deterrents to private sector investment in global health R&D in West et al. (2017b). In Anderson et al. (2017) uncertainty in returns stemming from the regulatory environment, regulatory costs, and weak or uncertain intellectual property protections are among the more commonly cited policy challenges for private health R&D, rather than general macroeconomic volatility.

Policy and Regulatory Incentives

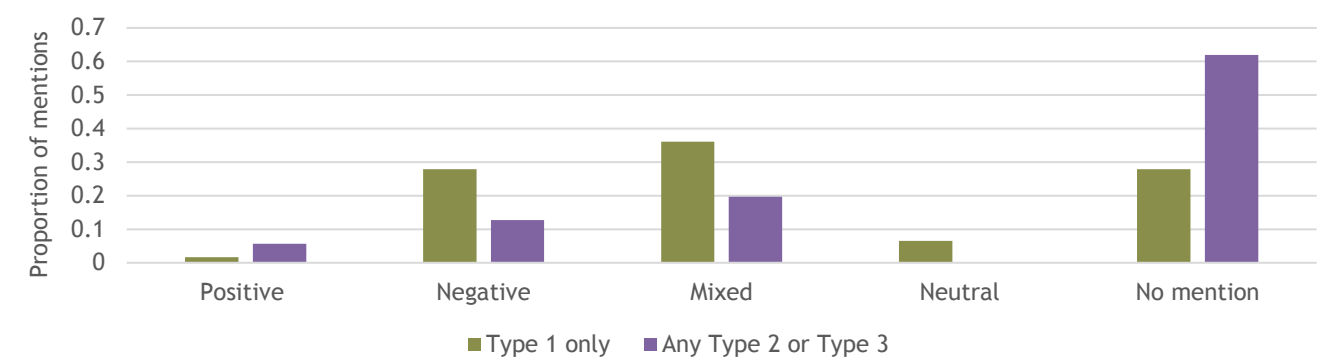
Policy or Regulatory Uncertainty

Twenty companies (ten working on Type 2 and 3 diseases) mention policy or regulatory uncertainty negatively, in that uncertainty regarding policies or regulatory issues are negatively affecting their R&D process. Most companies (34) mention policy or regulatory uncertainty in a mixed fashion. This appears logical since companies face many regulations and policies and will have varying experiences with them. There are only eight positive company-level mentions, meaning there is uncertainty around policies or regulations that will positively affect the R&D process and investment.

Nine companies with positive or mixed statements stated that they believed their product was eligible for more expedient regulatory pathway due their products' composition or previous regulatory history. Mylan NV stated that the approval pathways from generic products are faster and less burdensome. Five of the twenty-six

companies who mentioned negative effects stopped development of some of their products. Two Type 1 companies (Jazz Pharmaceuticals Public Limited Company and Adamis Pharmaceuticals Corporation) due to regulation of their suppliers. The other two companies, Arrowhead Pharmaceuticals Inc, Clovis Oncology, Inc, and Horizon Pharma Public Limited Company, stopped the development and approval process due to delays and lack of efficacy.

Figure 9. Proportion of companies that mention policy or regulatory uncertainty by type of disease research



Weak or Uncertain IP Rights

IP protections are theorized to incentivize investment and when IP are uncertain or weak, investment incentive may decrease because there is less likelihood of recouping investment costs. All nine companies that mention specific positive effects of IP protections claim they have strong IP rights over their products. However, Vital Therapies, Inc., which mainly develops platform technologies, states that they did not pursue patenting of their intermediary products and its production process because they “prefer to avoid the disclosure requirements inherent in the patenting process, as such disclosure could provide competitors with insights that allow them to invent around any granted patents. We believe that this concern is particularly appropriate since C3A cells are now publicly available, and have been available for research purposes for more than twenty years” (Vital Therapies, Inc., 2016, pg. 49). Of the twenty-two companies that have mixed statements regarding IP (they mention different IP rights issues positively and negatively affecting R&D investment), 16 mention the possibility of non-exclusivity or generics eroding their patent’s value.

5 companies mention the weak IP protections in markets outside North America and Europe. RA Pharmaceuticals mentions the risk of their work outside these markets:

“The legal systems of some countries, including India, China and other developing countries, do not favor the enforcement of patents and other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties.” (RA Pharmaceuticals, 20106, pg. 83)

Bioverativ Inc. states issues regarding the enforcement of international regulations:

“Although the World Trade Organization’s agreement on trade-related aspects of intellectual property rights requires signatory countries to provide regulatory exclusivity to innovative pharmaceutical products, implementation and enforcement varies widely from country to country.” (Bioverativ Inc., 2016, pg.14)

Aptevo Therapeutics does “not seek patent protection in countries where we have reason to believe we would not be able to enforce patents” based on the Office of the United States Trade Representative’s Priority Watch List of the Special 301 Report (Aptevo Therapeutics, 2016, pg. 15). They do file patents in China, Russia, and

India even though they are on this list. Aptevo also does not file for IP protections in countries on the United Nations' list of Least Developed Countries.

At the disease level, of the fourteen mentions of IP, only 1 is for a Type 2/3 disease. Aptevo Therapeutics relies on trade secret law to protect their Hepatis B drug and its manufacturing process and does not have a patent on it. These trade secrets and IP protections are also held by Emergent Biosolutions since Aptevo was a subsidiary of it until August of 2016.

Health Systems and Governance

Of the twenty-two companies that mention health systems and governance, eighteen discuss the Affordable Care Act and the impact of the US health system. Of those that discuss non-US governance, SciClone Pharmaceuticals mentions the price controls that regional Chinese government have in place, Biostar Pharmaceuticals, Inc. mentions the inclusion of many of their drugs in China's National Essential Medicines list, iBio, Inc. mentions the lagging Brazilian health governance system, and Immune Therapeutics, Inc. discusses the lack of drug regulation in African countries. Immune "plans to use the NAFDAC [regulating body of Nigeria] Registration as the guideline for submission in Africa for countries that do not have their own application and approval procedures" and present their drugs directly to the minister of health in Equatorial Guinea (Immune Therapeutics, Inc., 2016, pg. 38).

At the disease level, health system and governance statements regarding twelve Type 1 diseases all focus on US governance systems while statements regarding three Type 2/3 diseases discussed international governance systems. Both Immune Therapeutics, Inc. and Pfenex Inc. pursued approval in Nigeria for specific drugs while Genex Biotechnology Corporation gained approval from USAID for their HIV diagnostic test

General Challenges and Anticipated Risks from Policy and Regulatory Uncertainty

Most companies discuss policy and regulatory challenges as they affect their entire business model rather than specific products, limiting the ability to disaggregate statements by disease type. These statements are referenced in Appendix C. For example 86.4% use the generic language "The degree of future protection for our proprietary rights is uncertain because legal means afford only limited protection and may not adequately protect our rights or permit us to gain or keep our competitive advantage" in the business or risk section of their 10-K filings, including 90.2% of firms focusing exclusively on Type 1 diseases and 88.8% of companies working on Type 2 and 3 diseases. An additional 91.7% use the generic language "Our commercial success depends significantly on our ability to operate without infringing the patents and other proprietary rights of third parties" including 85.2% of firms focusing only on Type 1 diseases and 97.2% of companies working on Type 2 and 3 diseases. See Appendix C for other boilerplate language on policy and regulatory uncertainty.

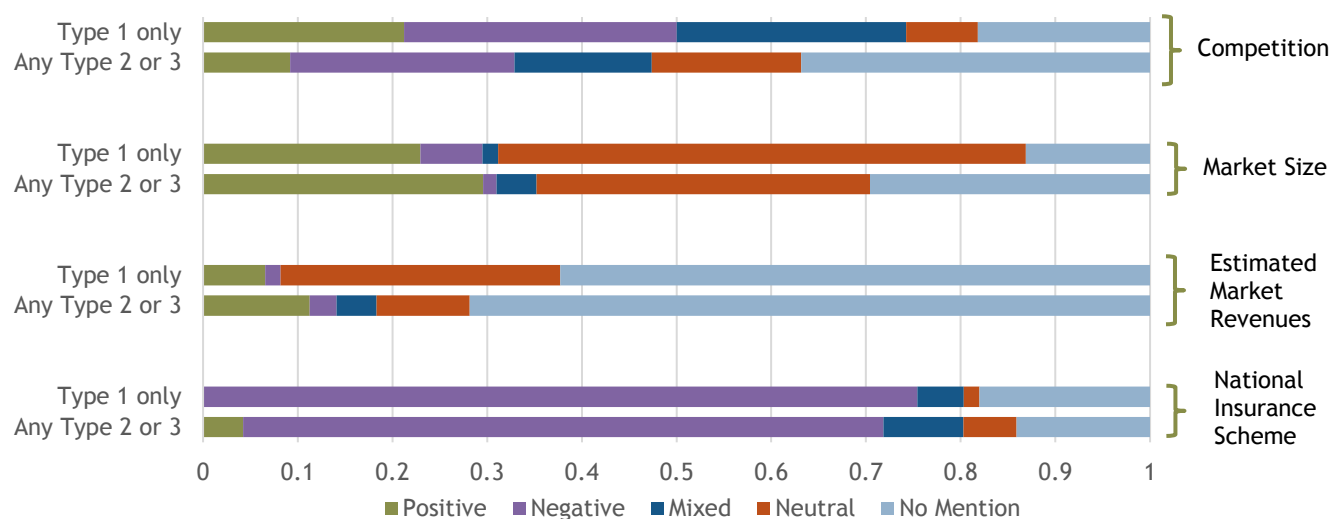
Hypothesis 3: Limited Revenues and Market Uncertainty

To assess the incentives and challenges posed by revenues and market uncertainty, we review company mentions of four categories related to limited revenues and market uncertainty:

- 1) **Competition** with other firms in the market both generally and in relation to specific diseases.
- 2) **Estimated market size** for disease-specific products, including the annual incidence of specific diseases and other factors affecting market size such as geography and market trends.
- 3) **Estimated market revenue** in terms of expected revenue for disease-specific products.

4) Existence of a national insurance scheme, including potential for reimbursement by government.¹⁴

Figure 10. Proportion of limited revenues and market uncertainty mentions by company type



Note: These proportions are based on a sample size of 61 companies that work on Type 1 diseases only, and 71 companies that work on any Type 2 or 3 diseases.

Companies that research Type 1 diseases only mention market size and competition as negative more often than companies that research Type 2 and 3 diseases. Market size is primarily mentioned naturally, while mentions of competition include more negative than positive discussion, suggesting constraints related to competition. Mentions of national insurance schemes are primarily negative across both company types.

¹⁴ Additional categories were coded that relate to limited revenues and market uncertainty, however, they have been excluded from this section due to very limited information for these columns.

Key Takeaways: Limited Revenues and Market Uncertainty

Ninety-two percent (122 out of 132) of companies in the sample reference market potential or uncertainty in the business or risk section of their 10-K filing, including 89% of companies conducting R&D on Type 2 or Type 3 diseases (63 out of 71) and 97% of companies focusing solely on Type 1 diseases (59 out of 61).

- Companies (both those targeting Type 1 and Type 2 diseases) strive to differentiate their product candidates from existing products and products in development by other companies as a way of gaining competitive market advantage.
- Two companies describe strategies to create barriers to competition through IP rights and pursuing R&D for diseases with high barriers to entry.
- Companies that research Type 2 and 3 diseases mention market advantages from expanding to markets outside of the United States more often than companies that research Type 1 diseases only.
- Companies that receive reimbursement for their products from national insurance programs, private insurance companies, and other third party payers are not only able to charge higher prices and recover more of their R&D costs but also enjoy a larger market for their products.
- Most companies (both those targeting Type 1 and Type 2 diseases) describe cost containment measures and downward pricing pressure on healthcare expenditures as significant threats to profitability.
- Specific challenges from market competition that both types of companies list are other companies developing drugs for similar indications (33 companies), increasing competition from “biosimilar” drugs (9 companies), the introduction of cheaper generic or OTC drugs (8 companies), well-established existing treatments (3 companies), disease specific competition increasing (4), and competition for government contracts (1 company).

Industry experts, secondary authors, and firm filings all discuss low or uncertain revenues as stifling investment in diseases affecting LMICs. However only two sources cite small market size as the deterrent - most highlight pricing (low and/or uncertain LMIC prices). Incentives to invest in R&D targeting diseases prevalent in the U.S. and other high-income countries are higher given the ability to set prices at what the market will bear, relative to prices in LMICs which may be lower, regulated, or unknown.

Incentives Related to Revenues and Market Size

Market Competition Incentives

Table 10. Types of positive mention of market competition, by company type associated with the mention

Factors influencing perceived positive market advantage	Number of Companies	
	Type 1 only (61 companies)	Any Type 2 or 3 (71 companies)
Limited competition	6	7
Differentiated product candidate/unmet medical need	13	11
Strong brand recognition	0	1
Product used in combination with other therapies	1	0
IP creates barriers to competition	1	0
Total	21	19

In total 40 companies report that their product candidates are positively positioned in the market in relation to existing products or product candidates in development by other pharmaceutical companies. No substantial differences are observed in the types of incentives related to market competition discussed by companies that research Type 1 diseases only compared to companies that research Type 2 and 3 diseases.

The most commonly discussed positive mention of market competition by companies that work on Type 1 diseases as well as Type 2 and 3 diseases is in relation to differentiated product candidates. 24 companies state that their product candidate has demonstrated superior efficacy, uses a different dosing method that will increase its market appeal, or is associated with fewer adverse side effects than existing marketed products.

Product candidates that are unique from existing marketed products have the potential to fill an unmet medical need, giving them a competitive advantage in the market. These mentions are associated with 36 specific diseases—27 Type 1 diseases, four Type 2 diseases, and five Type 3 diseases. For example, Chembio Diagnostics, Inc. describes the competitive advantages of their diagnostic test for the treatment of a variety of tropical diseases (Malaria, Ebola, Marburg, Lassa, Dengue Fever, and Chikungunya) over existing products due to its ability to test for multiple types of the same pathogen.

“The multiplex assay is planned to be designed to include a quality control test band and seven tests bands with specific antibodies to detect different pathogens, including multiple serotypes of the same pathogen.... Currently available POC diagnostics lack the ability to test for multiple diseases simultaneously. Further, existing POC diagnostics may lack the sensitivity and specificity required to detect infected but asymptomatic patients - information that is critical for preventing the spread of disease.” (Chembio Diagnostics, Inc., p. 5).

Positive Impact of Market Size in Terms of Potential Patient Population

Table 11. Types of positive mention of market size, by company type associated with the mention

Factors positively influencing market size	Number of Companies	
	Type 1 only (61 companies)	Any Type 2 or 3 (71 companies)
Large or increasing incidence of disease	13	11
Market potential outside the United States	1	5
Differentiated dosing methods	1	1
Changing perception of disease	1	2
Total	16	19

37 companies report positively on the size of the potential patient population in reference to their R&D investments including 22 companies that research at least one Type 2 or 3 disease and 15 companies that research Type 1 diseases only. Of these, 22 discuss Type 1 disease specific markets, 13 discuss Type 2 disease markets, and three discuss Type 3 disease markets.

24 companies discuss a large or increasing incidence of disease as increasing the potential market size for products of their R&D. For example, Synthetic Biologics, Inc. notes that Pertussis (a Type 2 disease) affects 50 million people worldwide and that incidence rates are increasing due to declining effectiveness of an acellular vaccine introduced in the 1990s (Synthetic Biologics, Inc., 2016, p. 10). Increasing rates of disease in the U.S. and worldwide provide a general incentive for companies to invest in certain diseases, however, companies do not discuss characteristics like the geography of certain markets as being more advantageous than others.

Three companies note that trends in the market and perception of disease present growing opportunities for their products, or could in the future. For example, Chembio Diagnostics, Inc. describes the increased availability and reduced costs of treatments for HIV (a Type 2 disease) as lessening the stigma associated with the disease and increasing market demand for HIV diagnostic tests (Chembio Diagnostics, Inc., 2016, p. 10).

Companies that research Type 2 or 3 diseases report market advantages from expanding to markets outside of the United States relatively more often than companies that research Type 1 diseases only, although rarely in relation to specific diseases. For example, Amarillo Biosciences reports, “The Company also has the opportunity to capitalize on its new access to the Far Eastern markets to explore sources of raw materials, capital, production facilities, and new customers” (Amarillo Biosciences, 2016, p. 4). Biostar Pharmaceuticals, which develops drug candidates for Hepatitis B, reports, “With approximately one-fifth of the world’s population and a fast-growing gross domestic product, the PRC (People’s Republic of China) presents significant potential for the pharmaceutical industry. We believe that the burgeoning market provides business opportunities for us” (BioStar Pharmaceuticals, 2016, p. 11).

62 companies mention market size (typically as the annual incidence of disease) without specifying whether it has a positive or negative impact on their company's operations or R&D investment. For example, Vital Therapies states, "40,000 patients annually in the United States, or U.S., experience the acute forms of liver failure that may be addressed by the ELAD System" (Vital Therapies, Inc., 2016, p. 62).

Eight companies report positive expectations about revenue from their R&D investments due to a large or increasing market size. For example, one company (iBio, Inc.) which is developing a technological platform to produce vaccines and therapeutics for a broad range of diseases (including Type 1, 2, and 3 diseases) lists growing economies and populations of foreign countries (Brazil, China, India) as a driver for higher potential revenue:

"In other geographic regions, such as Brazil, India and China where the economies and middle classes are growing rapidly and decision-makers are building domestic biologics infrastructures, we anticipate entering into and deriving revenues from licenses that may include multiple product categories to which our technology applies" (iBio, Inc., 2016, p. 8)

Twelve companies speak positively of market potential in terms of sales revenue, including eight that research Type 2 and 3 diseases. Of these, seven companies listed Type 1 disease specific markets, four listed Type 2 disease specific markets, and two listed Type 3 disease specific markets (some companies mention multiple disease specific markets).

54 companies mention market potential with reference to a particular disease in their 10-K filings without specifying whether it had a positive or negative effect on their operations or R&D investment. In general, these companies simply state an estimated market revenue, but do not characterize it as small, large, encouraging, or discouraging. For example, Biostar Pharmaceuticals states, "Currently, the U.S. market for adult hepatitis B vaccines is approximately \$270 million annually" (Biostar Pharmaceuticals, Inc., 2016, p. 7).

Incentives Related to Insurance Markets

Companies that receive reimbursement for their products from national insurance programs, private insurance companies, and other third party payers are not only able to charge higher prices and recover more of their R&D costs but also enjoy a larger market for their products. Three companies (Chembio Diagnostics, Inc., Inc., China Pharma Holdings, and Biostar Pharmaceuticals, Inc.) report a positive impact of a national health insurance scheme, noting that they have either secured reimbursement, or that they are likely to receive reimbursement for their product candidates in the future. For example, Chembio Diagnostics, a company that is developing a diagnostic test for HIV (a Type 2 disease) describes the market advantages to securing reimbursement for their product candidate:

"Finally, in 2013, the United States Preventive Services Task Force ("USPSTF") fully embraced these CDC routine HIV testing recommendations. This USPSTF recommendation, which was given an A grade under their recommendation grading system based on the benefits of this practice and the nearly 600,000 AIDS-related deaths in the United States, requires insurance coverage under the Affordable Care Act (the "ACA") as a preventive screening test without any co-payment required... Assuming that new legislation does not modify this requirement, of which there is no assurance, we expect this requirement to result in an increase in HIV testing in the United States in the coming years, which we believe will include point-of-care HIV testing utilizing our products. Although as stated above, currently most public health testing in the United States is funded by grants allocated to high prevalence areas by the CDC, we believe this will shift to an insurance-funded model under the ACA in the years to come, increasing the amount of testing done in doctor's offices and community health centers," (Chembio Diagnostics, Inc., 2016, p. 9).

Eight companies report a mixed impact of a national health insurance scheme and reimbursement. Seven of these note that they expect their products to be reimbursed, but also describe downward pricing trends as a threat. Dynavax Technologies Corporation expects that their vaccine for the treatment of Hepatitis B will be reimbursed due to favorable pricing and reimbursement for Hepatitis B vaccines in the U.S., but also describes the process of obtaining reimbursement approval for a product as unpredictable and notes that they may not be able to charge high enough prices for their product to recoup their R&D expenses if they don't receive adequate reimbursement (Dynavax Technologies Corporation, 2016, p. 17).

Challenges from Limited Revenues and Market Uncertainty

Market Competition Challenges

Table 12. Types of negative mentions of market competition, by company type associated with the mention

Factors negatively influencing perceived market position	Number of Companies	
	Type 1 only (61 companies)	Any Type 2 or 3 (71 companies)
Other companies developing drugs for similar indications	16	17
Current treatments well-established in market	2	1
Increasing competition of “biosimilars”	3	6
Cheaper over-the-counter or generic products	5	3
Disease specific competition increasing	3	1
Competition for government contracts	0	1
Total	29	29

40 companies report risks of market competition to the successful commercialization of their product candidates including 20 companies that research Type 1 diseases only and 20 companies that research Type 2 and 3 diseases. 20 companies report that other pharmaceutical companies are developing drugs for the same diseases that the company’s product candidate targets, referring to their R&D efforts targeting 16 Type 1 diseases, 4 Type 2 diseases, and 1 Type 3 disease (one company references multiple diseases). Arbutus Biopharma Corporation states, “We are aware of several companies that are working to develop drugs that would compete against our drug candidates for HBV treatment. As a significant unmet medical need exists for HBV, there are several large and small pharmaceutical companies focused on delivering therapeutics for treatment of HBV. We anticipate significant competition in the HBV market with several early phase product candidates announced. We will also face competition for other product candidates that we expect to develop in the future,” (Arbutus Biopharma Corporation, 2016, p. 32).

Three companies (Ophthotech Corporation, Agios Pharmaceuticals, and Nabriva Therapeutics) describe market uncertainty because existing alternative products are already well-established in the medical community, making it more difficult for their products to gain market share. Nabriva Pharmaceuticals reports, “Current treatments for pneumonia, including generic options, are well established in the medical community, and doctors may continue to rely on these treatments without lefamulin. In addition, our efforts to effectively communicate lefamulin’s differentiating characteristics and key attributes to clinicians and hospital pharmacies with the goal of establishing favorable formulary status for lefamulin may fail or may be less successful than we expect” (Nabriva Pharmaceuticals, Inc., 2016, p. 63).

Nine companies report increasing competition of “biosimilars”, drugs that are nearly identical to an existing product, as a risk to market exclusivity for firms engaging in R&D of new products. Regeneron Pharmaceuticals, Inc. reports, “Due to this risk, and uncertainties regarding patent protection, if our late-stage product candidates or other clinical candidates are approved for marketing, it is not possible to predict the length of market exclusivity for any particular product with certainty based solely on the expiration of the relevant patent(s) or the current forms of regulatory exclusivity,” (Regeneron Pharmaceuticals, Inc., 2016, p. 39).

Eight companies report disease specific risks from the existence or introduction of cheaper over the counter (OTC) or generic products due to lower pricing potentially negatively affecting customers' willingness to pay for more expensive prescription versions. Five of these companies reference Type 1 diseases and three reference Type 2 diseases. For example, Nabriva Therapeutics AG reports that generics pose a threat to their drug candidate for community-acquired bacterial pneumonia (a Type 2 disease) as their drug would be priced higher than a generic product, lowering its chances of reimbursement by third parties.

Negative Impacts of Limited Market Size

Five companies report limited potential market size due to small targeted patient populations for particular disease R&D efforts, two of which describe the specific challenges this poses to their company. BioMarin, a company that develops products targeting rare diseases and medical conditions (for example, late infantile neuronal ceroid lipofuscinosis (CLN2), a form of Batten disease, phenylketonuria (PKU), and hemophilia A) describes limited target patient populations as a risk, as the company may not be able to recoup their development and manufacturing costs of producing the drug:

“All of our products target diseases with small patient populations. As a result, our per-patient prices must be relatively high in order to recover our development and manufacturing costs and achieve profitability. For Naglazyme and Vimizim in particular, we must market worldwide to achieve significant market penetration of the product. In addition, because the number of potential patients in each disease population is small, it is not only important to find patients who begin therapy to achieve significant market penetration of the product, but we also need to be able to maintain these patients on therapy for an extended period of time. Due to the expected costs of treatment for our products, we may be unable to maintain or obtain sufficient market share at a price high enough to justify our product development efforts and manufacturing expenses” (BioMarin Pharmaceuticals, Inc., 2016, p. 36).

Negative Impacts of Potential Market Revenue

Four companies report a decline in disease specific revenues, all in relation to Type 2 diseases. Three of these companies (Johnson & Johnson, Merck & Co., and Kadmon Holdings) describe a decline in revenues compared to previous years from products targeting Hepatitis C due to the introduction of new competing products. Two companies (Abbvie and Merck & Co.) report decreased revenues for HIV drugs due to increased competition, although Merck & Co. notes that while the decline was caused by lower sales volumes and lower demand in Europe, it was “partially offset by higher volumes in Latin America and higher pricing in the United States” (Merck & Co., 2016, p. 40). One company specifically reports a risk related to potential market revenue due to potential low willingness to pay. Xbiotech Inc., a company that develops products to treat Type 1 diseases, states that “disease indications, such as those in our pipeline, might become sufficiently rare, or victims might be sufficiently impoverished, that commercial production is uneconomic” (Xbiotech, Inc, 2016, p. 29).

Challenges Related to National Health Insurance

119 companies (89%) include boilerplate language describing risks related to the potential inability to obtain adequate reimbursement rates from government programs, insurance companies, managed healthcare organizations or other third party payers for product candidates as a risk with the potential to impact drug pricing and company revenues. Of these, 86 companies discuss the increasing trend toward cost containment in government healthcare policies and insurance markets as a risk, citing limited coverage and reimbursement by third party payers including Medicare as a threat to product pricing and revenues. Innoviva, Inc. reports a realized loss in revenues from their marketed products treating chronic obstructive pulmonary disease (COPD) and asthma as a result of the trend toward cost containment:

“The continuing efforts of governments, pharmaceutical benefit management organizations (PBMs), insurance companies, managed care organizations and other payors of health care costs to contain or reduce costs of health care has adversely affected the price, market access, and total revenues of RELVAR®/BREO® ELLIPTA® and ANORO® ELLIPTA® and may continue to adversely affect them in the future. In addition, we have experienced and expect to continue to experience increased competitive activity which has resulted in lower overall prices for our products.” (Innoviva, Inc., 2016, p. 12)

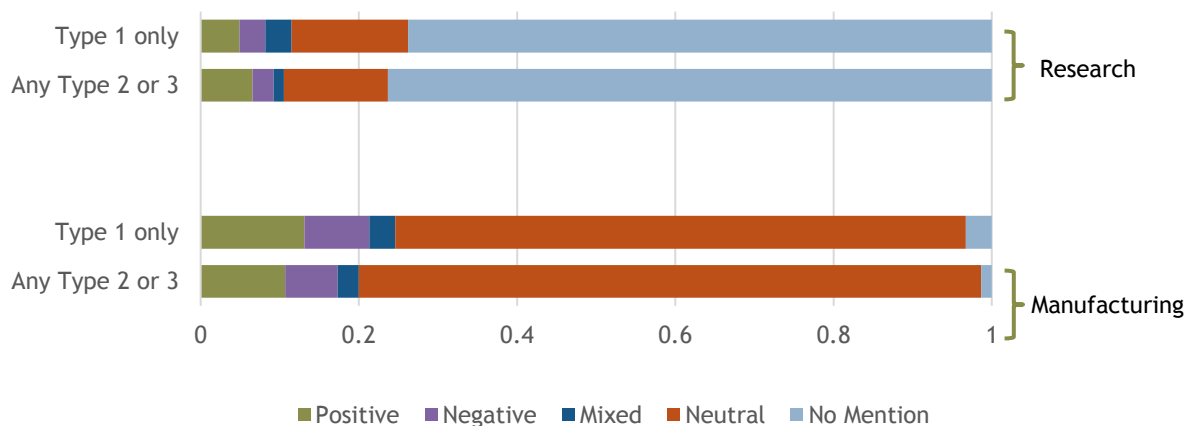
Two companies (Bellicum Pharmaceuticals, Inc. and BioMarin Pharmaceutical, Inc.) report low patient populations or expensive product candidates putting additional pressure on the ability of the company to obtain reimbursement by third-party and government payers. One company (Adamis Pharmaceuticals Corporation) states that a small percentage of their products are reimbursed. Three companies (Cocrystal Pharma, Inc., Vertex Pharmaceuticals, Inc., Global Blood Therapeutics, Inc.) report that foreign governments typically reimburse at lower rates than the United States.

Hypothesis 4: High Costs of Research and Manufacturing

We review company mentions related to funding of research and manufacturing efforts fixed costs, with a particular focus on fixed costs which include up-front capital investment and sunk costs arising from investments that cannot be repurposed or expenditures that cannot be recouped. Both the size of upfront investments, and the degree to which they are specialized, can deter investment - particularly in products with a long and uncertain timeline to market.

- 1) **Research funding** refers to companies’ efforts to find funding for R&D activities, particularly upfront investments in facilities or equipment or specialized “sunk” costs.
- 2) **Manufacturing** refers to a company’s in-house versus outsourcing arrangements for producing outputs stemming from the R&D process.

Figure 11. Proportion of companies referencing fixed costs and manufacturing process by company type



Note: These proportions are based on a sample size of 61 companies that work on Type 1 diseases only, and 71 companies that work on any Type 2 or 3 diseases.

Nearly all 10-Ks include general boilerplate language on concerns related to costs and funding for R&D activities (Appendix C), but few companies mention specific fixed costs that they incur in the R&D process. More frequently, companies discuss the need to attract additional funding to support the costs of the R&D process, including fixed and other sunk costs. On the other hand, nearly all companies discuss costs associated

with the manufacturing process for the products of R&D. Companies incur these costs either through outsourcing or in-house production, but there are potentially trade-offs between specialization efficiencies, risk, and process control.

Key Takeaways: High Costs of Research and Manufacturing

Specific concerns related to fixed costs for R&D are mentioned by less than one quarter of the companies in our sample (30 out of 132) and mostly relate to the need to seek out additional sources of funding, but costs and approaches to the manufacturing process for R&D products are mentioned by 98% of companies (129 out of 132). We find that comparable proportions of companies that research Type 1 diseases and Type 2 or 3 diseases discuss positive, negative, and mixed effects of manufacturing costs on research and development.

- Most companies (82%, or 108 out of 132 companies) including both those targeting Type 1 and Type 2/3 diseases in relatively equal numbers, include boilerplate 10-K language reporting the need to ensure additional funding to continue R&D activities.
- Companies report that additional funding from outside sources helps to offset expenditures related to research and development/commercialization of product candidates - additional funding sources discussed are public/philanthropic and other collaborative.
- More companies that research any Type 2/3 diseases reported receiving public funding compared to companies that research Type 1 diseases only.
- Companies that work primarily on diseases that are classified as bio-threats as well as certain Type 3 diseases (especially hemorrhagic fevers) report the U.S. government as the primary purchaser of their product.
- Some companies possess the ability to manufacture small amounts of product, however, scaling up production of products to commercial scale is difficult and comes with risks.
- Outsourcing manufacturing allows companies to avoid expending resources on fixed costs like facilities and instead focus resources on research and development, but problems can arise from limited manufacturers who are able to produce a specific product.
- Manufacturing products internally allows companies to maintain control over processes, “know how” and intellectual property, but facilities can be difficult to finance and use to their full potential.

Similar to scientific uncertainty, cost considerations (as opposed to revenues or local policy environments) are unique to global health R&D only to the extent that Type 2 and 3 diseases are associated with more specific up-front costs than Type 1 diseases. High initial investment costs with difficult to re-purpose capital are often cited as barriers to all health R&D, not particular to global health, reflected in a range of cost estimates for bringing a drug to market between \$802 million and \$2.2 billion (Anderson et al., 2017). In firm filings, however, costs associated with the manufacturing process for R&D outputs are mentioned more than concerns over upfront specific investments for the R&D process, perhaps because those filing had already incurred such costs.

Incentives and Challenges Related to Research Funding

Recent research compiled by DiMasi et al. (2016) estimates the cost of producing a pharmaceutical product at between \$802 million (DiMasi, 2003) and \$2.2 billion (O’Hagan & Farkas, 2009). DiMasi et al. (2016) estimate that the out-of-pocket cost per approved new compound is \$1.4 billion. When factoring-in the costs of capital, including opportunity costs, the total cost for pre-approval reaches \$2.6 billion.

Most companies (107 of 132) note that unforeseeable risks and changes in the future could negatively affect their ability to survive. Companies discuss the need to fund operations through debt financing, the risks of losing funding, the need for additional funding, and expansion costs. The predominant concern for all companies (Type 1 and Type 2/3) was their ability to secure funding in order to continue operations, develop products, and remain functional enough to see a return on investment.

When discussing the need for more financial resources, 85 companies include boilerplate language saying that they are in need of additional funding to continue their R&D activities, including 51 companies that research any Type 2 or 3 diseases compared to 56 companies that research Type 1 diseases only. When discussing

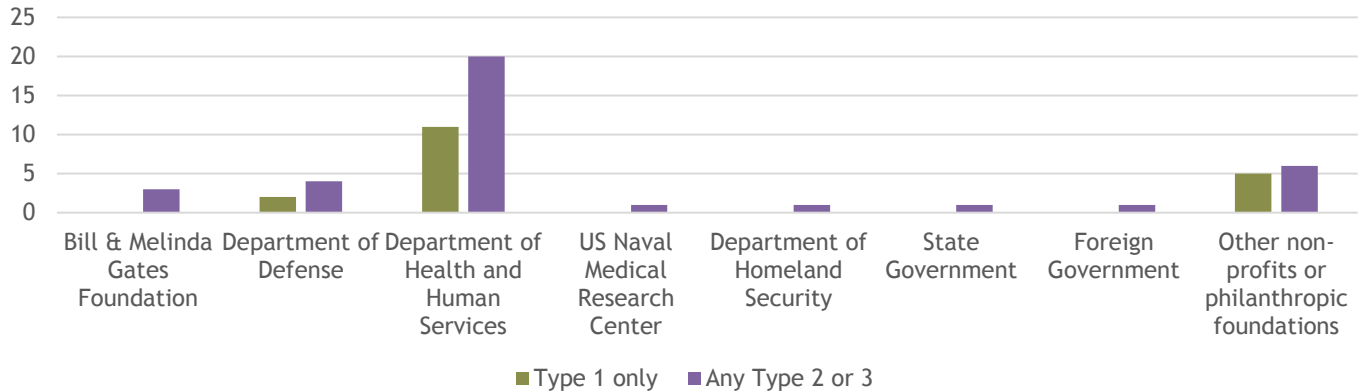
sources of funding, companies primarily discuss public/philanthropic funding (44 companies), private funding (15) and other collaborative funding (18).

The most common sources of public/philanthropic funding (mentioned by 45 or 34% of companies) are the U.S. government and foundations such as the Bill & Melinda Gates Foundation. Most government sources except for the Department of Health and Human Services (which includes a large number of varied departments) seem to primarily support companies that do at least some research on Type 2 and 3 diseases and rather than companies that research Type 1 diseases only. Emergent Biosolutions, a company that researches both Type 1 and Type 2 and 3 diseases, reports:

Our company is engaged in research and development and has incurred substantial expenses for these activities. These expenses generally include the cost of acquiring or inventing new technologies and products, as well as development work on new product candidates (or label expansions of existing marketed products). To offset these expenditures, we actively seek, and historically have been successful in obtaining, contract and grant awards for development funding from a variety of U.S. government sub-agencies within both HHS and DoD (Emergent Biosolutions, 2016, n.pg.).

Seven companies report that government contracts account for their primary source of annual revenues. These companies tend to work on diseases that are considered “biothreats” (e.g. anthrax), or certain Type 3 diseases, especially hemorrhagic fevers. Despite the benefits, these companies note that strong competition and funding uncertainty raise the risks of solely relying on this source. For example, Sarepta Therapeutics, Inc. reports that they are discontinuing their development for product candidates to treat Ebola and Marburg because their government contract to fund the R&D for these diseases has expired (Sarepta Therapeutics, Inc., 2016, p. 36).

Figure 12. Mentions of public or philanthropic sources of funding by company type



Note: This graph is based on a sample size of 61 companies that work on Type 1 diseases only, and 71 companies that work on any Type 2 or 3 diseases.

Some companies discuss collaborative funding partnerships with other pharmaceutical companies that don’t fall under the category of license agreements. Array Biopharma reports, “We entered into a Drug Discovery Collaboration Agreement with InterMune in 2002, which resulted in the joint discovery of ASC08 / danoprevir, a novel small molecule inhibitor of the Hepatitis C Virus NS3/4A protease. Roche Holding AG acquired ASC08 from InterMune in 2010 and partnered with Ascleitis in 2013 to advance the program in greater China” (Array Biopharma, 2016, p. 10). Other mentions of collaborative funding include additional funding sources that fall into multiple categories. For example, GenereX Biotechnologies reports that they plan to submit all of their gene cassettes to the Global Fund, “a partnership between governments, civil society, the private sector and

people affected by infectious diseases specifically HIV/AIDs, tuberculosis, and malaria” (Generex Biotechnologies, 2016, p. 14).

Incentives and Challenges Related to Manufacturing R&D Products

In addition to the costs of R&D, companies also discuss costs of manufacturing outputs of the R&D process as influencing their R&D investments. 92 companies mention that they contract with third-party contract manufacturing organizations (CMOs) instead of investing in their own manufacturing infrastructure for R&D. Companies that choose not to invest in manufacturing avoid the high costs of building and maintaining their own facilities. Since product development can be costly, any savings in capital and the reduction and outsourcing of risk associated with operating a manufacturing facility remains attractive to many companies. For example, Xencor, Inc. discuss their rationale for choosing to partner with a CMO:

We have adopted a manufacturing strategy of contracting with third parties in accordance with current good manufacturing practices (cGMPs) for the manufacture of drug substance and product [...]. Additional contract manufacturers are used to fill, label, package and distribute investigational drug products. This allows us to maintain a more flexible infrastructure while focusing our expertise on developing our products (Xencor, Inc., p. 16).

One company (Emergent Biosolutions, Inc.) describes providing contract manufacturing services to other pharmaceutical companies, and cites these services as a growing source of company revenue (\$49.1 million in 2016), but also reports risks related to uncertainty that they will be able to use the full manufacturing capacity of one of their facilities.

22 companies discuss owning and operating their own manufacturing facilities as the primary means of manufacturing their products, including 15 companies that research Type 2 or 3 diseases and seven companies that research only Type 1 diseases. Although two companies discuss the benefits of owning their own manufacturing facilities, citing increased control over expertise and intellectual property as well as increased production capacity, three companies mention that they also contract with third party CMOs to mitigate the risk of not being able to produce enough product to meet demand.

Companies also cite product-specific risks of engaging in the manufacturing process. United Therapeutics, a company that researches Type 1 and 2 diseases, discusses negative risks of manufacturing their own products due to the complex nature of their commercialized drugs:

In addition, our internal manufacturing process also subjects us to risks as we engage in increasingly complex manufacturing processes. For example, Remodulin, Tyvaso and Unituxin are sterile solutions that must be prepared under highly-controlled environmental conditions, which are challenging to maintain on a commercial scale...Finally, we have limited experience producing Orenitram and Unituxin on a commercial scale...and currently all Orenitram and Unituxin manufacturing is performed internally. It could take substantial time to establish an FDA-approved contract manufacturer as a back-up supplier of Orenitram, or this process may not be successful at all. Our limited internal manufacturing capacity has restricted our ability to supply Unituxin outside the United States. We are constructing a new facility to expand our manufacturing capacity for dinutuximab, the active ingredient in Unituxin, but this process will take several years and may not be successful at all (United Therapeutics, 2016, p. 37).

Eight companies discuss new construction to meet the needs of their operations, including three companies that work on Type 2 and 3 diseases, and five companies that research Type 1 diseases only. Expanding R&D manufacturing facilities carries potential benefits such as an increased ability to meet increased product demand and product-specific customization of the manufacturing process, however, problems include the need to secure more funding before completing capital projects and the possibility of underutilizing a newly completed facility:

To provide for capacity expansion beyond the initial few years following potential launch of rocapuldencel-T, we had planned for the build-out and equip a second facility, which we refer to as the Centerpoint facility. In August 2014, we entered into a ten-year lease agreement with renewal options...The shell of the new facility was constructed on a build-to-suit basis in accordance with agreed upon specifications and plans and was completed in June 2015. However, the build-out and equipping of the interior of the facility was suspended as we pursued financing arrangements. (Argos Therapeutics, Inc., 2017, pg. 19)

In addition, the difficulty of scaling up to commercial production levels can also be unique to drug/disease manufacturing specifications. For example, Nektar Therapeutics reports the impact of difficulties in scaling up the production of its drug for pneumonia on its research and development process:

In the past we have encountered challenges in scaling up manufacturing to meet the requirements of large scale clinical trials without making modifications to the drug formulation, which may cause significant delays in clinical development. We experienced repeated significant delays in starting the Phase 3 clinical development program for Amikacin Inhale as we sought to finalize and validate the device design with a demonstrated capability to be manufactured at commercial scale (Nektar Therapeutics, 2016, p. 36).

92 companies mention relying on contract manufacturing organizations for manufacturing operations. Many companies report that they have the capacity for small-scale manufacturing capabilities but rely on CMOs for bulk manufacturing services due to the difficulty of scaling up to produce at a commercial scale. Collaborating with third-party manufacturers can reduce costs, but problems can also arise when there is too much dependence on one partner. 12 companies discuss problems with supplies and a limited number of contract manufacturing operators available to produce specific products. Amarillo Biosciences, a company that develops drugs for Type 1 diseases as well as Type 2 diseases (influenza and Hepatitis C) discuss their reliance on a CMO and the consequences they now face as a result of the partner no longer being able to produce a product essential to their R&D efforts:

The Company's long-time human interferon producer is no longer able to provide the essential supply of interferon. Without the interferon, the Company is unable to continue its research, conduct clinical trials, and ultimately unable to commercialize a product. Options available to ABI to find a suitable interferon source include: (1) locating a laboratory/production facility that could follow the same path and development model for natural human interferon which was viable for the Company in the past; (2) restart the process from the original cell line and develop the natural human interferon in the laboratory on a commercial level; or (3) select the best source of recombinant interferon which can be developed for the Company's goals. The Company is exploring its options to determine the optimal choice of interferon supplies to commercialize the products. (Amarillo Biosciences, Inc., 2016, p. 4).

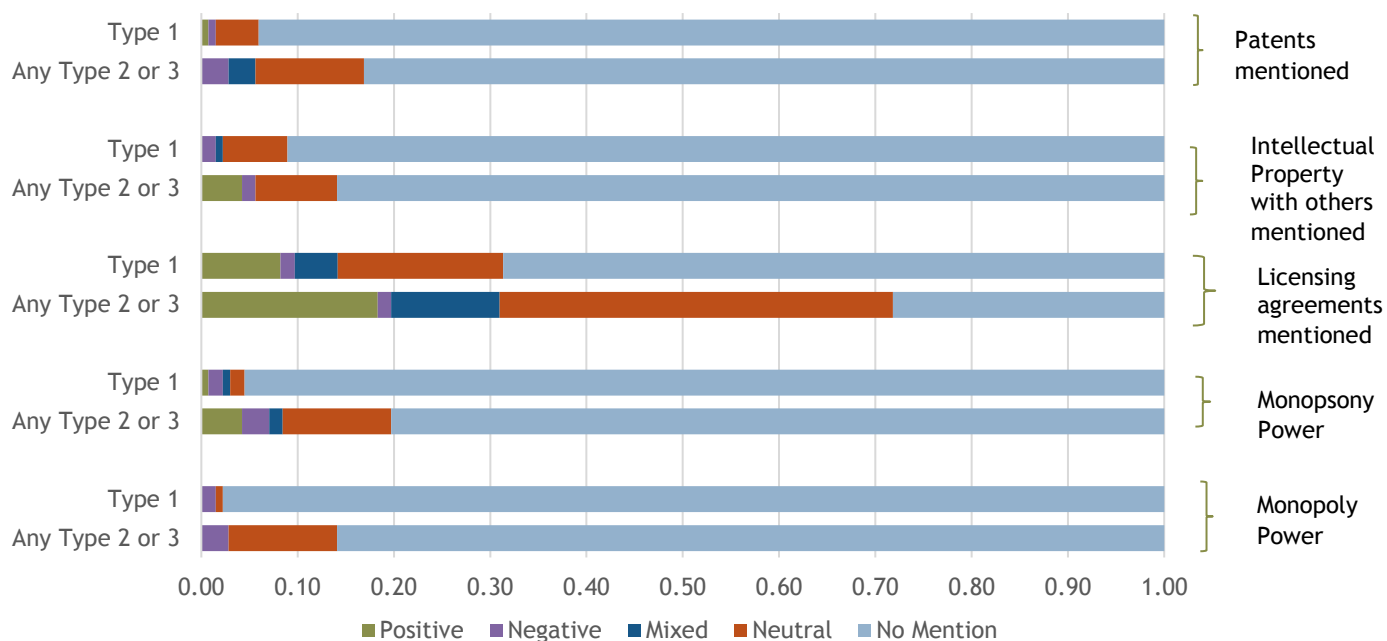
Hypothesis 5: Imperfect Markets

We review several aspects of imperfect competition in health R&D: company mentions of patents, licenses, and other intellectual property mechanisms that affect the benefits and costs of R&D and the entry and exit of firms, and the market structure that affects the buying and selling price and quantity of R&D inputs:

1. **Patents with others** refers to mentions of patent transactions
2. **Intellectual Property with others** refers to mentions of other IP transactions
3. **Licensing agreements with others** refers to mentions of other in- or out-licensing agreements
4. **Market power due to monopoly** refers to evidence of certain companies controlling a large share of the market for a particular disease or product

5. **Market power due to monopsony** refers to evidence of certain diseases or products having only one or few buyers

Figure 13. Proportion of companies reporting imperfect markets by company type



Note: These proportions are based on a sample size of 61 companies that work on Type 1 diseases only, and 71 companies that work on any Type 2 or 3 diseases.

Licensing agreements are mentioned by 90 out of 134 companies in the sample, and particularly by companies with any Type 2 or 3 disease R&D investments. Licensing agreements are more frequently mentioned as having a positive effect compared to a negative effect for all companies. Other concerns related to imperfect markets are less frequently mentioned, but are mentioned more frequently by Any Type 2 or 3 companies than Type 1 only companies. These mentions are primarily neutral rather than positive or negative.

Key Takeaways: Imperfect Markets

Opportunities or constraints related to imperfect markets are mentioned by less than half of all companies for every category of evidence, except for licensing agreements, which are mentioned by 90 out of 134 companies in the sample.

- Type 1 companies in our sample report out-licensing their products more frequently than in-licensing. Type 2/3 companies reported out-licensing their products as frequently as they reported in-licensing. Companies use in-licensing agreements to fill gaps in their research during clinical development, or to gain access to the rights to commercialization and development of a product at the end of (and dependent on the success of) clinical trials.
- Companies most frequently use out-licensing agreements to access global markets, gain revenues to support their R&D base, reduce risks and costs associated with commercialization and marketing, shift disease or product focus, and assist partner companies and organizations in advancing their research.
- Several companies discuss the uncertainties related to their business practice of out-licensing commercialization of their products, noting the risks of giving up rights to a product that would have been more valuable had the company developed it in-house as well as the potential to in-license a product that was riskier than anticipated and does not generate the desired revenue.
- Two companies describe leveraging patent expirations to develop and commercialize biosimilars and generics, allowing them to avoid the risky process of clinical trials.
- Three companies report the market for product candidates is dominated by one or a few companies.

Theory predicts that the nature of the pharma R&D industry and current regulatory structure create incentives for large firms with downstream capacity to increasingly move resources out of upstream R&D, especially in the U.S., if they are able to purchase rights to the results of upstream R&D at lower cost than producing those R&D outputs themselves. Upstream competition can make it more profitable for large firms with a downstream presence to purchase patent rights rather than invest in their own upstream R&D, which Roy & King (2016) note is a common industry practice. Nonetheless, these hypothesized disincentives to R&D were seldom mentioned by industry experts (West et al., 2017b) or in the secondary literature (Anderson et al., 2017) or directly by firms. Five secondary sources (compared to one firm filing) describe private R&D efforts to improve the efficacy or effectiveness of existing treatments – so-called “me-too” drugs – as examples of private investors’ preference to secure downstream rents rather than invest in new health R&D ventures. The suggestion repeated in the literature that limited patent windows may encourage private firms to divert resources towards marketing rather than additional R&D in order to maximize profits during the period of exclusivity (Love, 2005) is not referenced in the 10-Ks.

Intellectual Property Protections

Two companies (Marinus Pharmaceuticals, Inc. and IntelGenx Technologies Corp.) describe strategies that create barriers to competition. Marinus Pharmaceuticals, Inc. reports a market advantage from the possession of intellectual property creating barriers to competition from other firms. “We believe that our intellectual property around nanotechnology and other formulation know-how creates significant barriers to competition. We have developed most of our technology internally which provides us with greater control and flexibility and reduces expense” (Marinus Pharmaceuticals, Inc., 2016, p. 9). IntelGenx Technologies Corp. states that they plan to pursue the development of generic drugs that have “certain barriers to entry, e.g., where product development and manufacturing is complex” to limit their firm’s competition (IntelGenx Technologies Corp., 2016, p. 12).

Intellectual Property Transactions

Licensing agreements, patent agreements and other IP transactions are sometimes used to overcome the inherently public good nature of ideas and knowledge (create the ability to exclude non-payers), with firms purchasing IP upstream or downstream based on their production specialties, process of drug development, or cost.

Twenty four out of 90 (27%) companies mentioning licensing agreement describe these as having a positive effect on their R&D investments, conferring some benefit to the company. Benefits the companies describe

include revenues and royalty payments from licensing out a patent, access to “know-how” including resources such as compound libraries and technological platforms, access to compounds in clinical trials for development and commercialization, access to a particular regional market, and third-party commercialization experience. For example, Vertex Pharmaceuticals, states that they enter into collaborations and licensing agreements with “other companies and organizations that provide...financial and other resources, including capabilities in research, development, manufacturing and sales and marketing, and licenses to intellectual property. These collaborations have provided us with drug candidates and/or important financial and non-financial resources that have contributed to our products and a number of the drug candidates in our current development pipeline” (Vertex Pharmaceuticals, 2016, pg. 5). Companies access these benefits either by in-licensing the rights to a drug, compound or other proprietary product from another firm, or by out-licensing the rights to their own products to another firm.

Table 13. License agreement type by disease categorization

License Agreement Type	Number of Companies	
	Type 1 only (61 companies)	Any Type 2 or 3 (71 companies)
In-Licenses	27	15
Out-Licenses	7	16
Both	9	14
Total	43	45

Note: Two companies do not specify whether their licensing agreements involve in-licenses or out-licenses

As seen in Table 13, forty-two companies (27 Type 1 and 15 Type 2 or 3) describe their licensing agreements as “in-licenses,” while twenty-three describe them as “out-licenses”. Twenty-three companies have employed both in-licenses, and out-licenses. For Type 1 companies, in-licenses are significantly more common than out-licenses, but Type 2/3 companies report in-licensing agreements about equally as frequently as out-licenses, and as having both in-licenses and out-licenses.

The licensing agreements for the evaluated companies are largely “in-licenses,” meaning the company acquires intellectual property or patent licenses for a drug, compound, or other proprietary product from another firm. In-licenses, in general, provide a company with a compound, technology, “know-how,” or expertise that somehow helps to advance the company’s research. In-licensing occurs in all stages throughout the research and development process. Some companies use in-licensing to fill gaps in their research during clinical development. For example, VBI Vaccines “identified the need for a vaccine antigen discovery and design platform” for their hepatitis B and cancer research, and entered into an agreement with private company ePixis to “obtain access to its exclusive rights to key IP covering its “enveloped Virus Like Particle” or “eVLP” vaccine platform (VBI Vaccines, 2016, pg. 4).

Other companies in-license rights to commercialization and development at the end of (and dependent on the success of) clinical trials. These types of agreements are lower risk because the company purchases the license downstream of clinical trials, but also likely come at higher costs for the company. As an example, Synthetic Biologics (Type 2/3), has an “Exclusive Channel Collaboration” license with pharmaceutical company Intrexon, allowing the company to “use Intrexon’s technology relating to the identification, design and production of human antibodies and DNA vectors for the development and commercialization of a series of monoclonal antibody therapies for the treatment of pertussis” (Synthetic Biologics, 2016, pg. 4). Through the license agreement, Synthetic Biologics acquires the rights to Intrexon’s technology, and then is responsible for “the development, commercialization and manufacturing of products” (ibid).

Aytu Bioscience (Type 1 only) also plans to develop and commercialize products that are already far along in the development phase (Aytu Bioscience, 2016)

"We intend to seek assets that are near commercial stage or already generating revenues. Further, we intend to seek to acquire products through asset purchases, licensing, co-development, or collaborative commercial arrangements (co-promotions, co-marketing, etc.)" (Aytu Biosciences, 2016, pg. 39)

Companies without out-licensing agreements discuss a wider variety of reasons for entering into these types of agreements. For example, Achillion Pharmaceuticals strategically chooses compounds to out-license commercialization based on the geographical market, and what they could expect to receive in terms of compensation: "Outside of North America, and in situations or markets where a more favorable return may be realized through licensing commercial rights to a third party, we may license a portion or all of our commercial rights in a territory to a third party in exchange for one or more of the following: up-front payments, research funding, development funding, milestone payments and royalties on drug sales... We generally plan to collaborate with third parties for commercialization in the United States of any products that we cannot commercialize with a small sales force and that require a large sales, marketing and product distribution infrastructure." (Achillion Pharmaceuticals, 2016, pg. 13)." Achillion's hepatitis C drug is licensed to Janssen Pharmaceuticals, with whom they sought a licensing agreement with "in order to access the worldwide development and commercialization expertise of a major pharmaceutical organization. (Achillion Pharmaceuticals, 2016, pg. 3)."

Ionis Pharmaceuticals, a Type 2/3 company, states that revenues from out-licensing supports their R&D base: "Through our partnerships, we have created a broad and sustaining base of potential research and development, or R&D, revenue in the form of license fees, upfront payments and milestone payments while spending prudently to advance our pipeline and technology (Ionis Pharmaceuticals, 2016, Pg. 21)."

Several companies mention that they frequently evaluate their late-stage products to determine whether it is more valuable for the company to commercialize and market the product in-house, or out-license them. For example, Merck & Co., Inc, "reviews its pipeline to examine candidates which may provide more value through out-licensing. The Company continues to evaluate certain late-stage clinical development and platform technology assets to determine their out-licensing or sale potential (Merck & Co. Inc, 2016, pg. 11)."

Similarly, Nektar Therapeutics (Type 2/3) evaluates each of their drug candidates to determine whether they should be out-licensed or developed internally:

We decide on a drug candidate-by-drug candidate basis how far to advance clinical development (e.g. Phase 1, 2 or 3) and whether to commercialize products on our own, or seek a partner, or pursue a combination of these approaches. When we determine to seek a partner, our strategy is to enter into collaborations with leading pharmaceutical and biotechnology companies to fund further clinical development, manage the global regulatory filing process, and market and sell drugs in one or more geographies. The options for future collaboration arrangements range from comprehensive licensing and commercialization arrangements to co-promotion and co-development agreements with the structure of the collaboration depending on factors such as the structure of economic risk sharing, the cost and complexity of development, marketing and commercialization needs, therapeutic area and geographic capabilities. (Nektar Therapeutics, 2016, pg. 9)

Two Type 1 companies describe developing their business strategy around the use of out-licensing: Cannabics Pharmaceutical's "business model is solely based on technology development and IP out-licensing to licensed and certified producers for marketing...Within the US, Cannabics Pharmaceuticals Inc. itself does not manufacture, distribute, dispense or possess any controlled substances, including cannabis or cannabis based preparations, it merely licenses its IP (Cannabics Pharmaceuticals, 2016, pg. 6)."

Skinvisible also employs the use of out-licensing as a business strategy: “Our business model will continue to out-license our patented prescription and over-the-counter (“OTC”) products featuring Invisicare to established manufacturers and marketers of brands internationally and to maximize profits from the products we have already out-licensed. The opportunity for us to license our products continues to be a viable model as the need for pharmaceutical companies to access external R&D companies for new products due to their own down-sizing or elimination of internal R&D departments (Skinvisible, 2016 pg. 3).”

One Type 2/3 company - iBio -outsources all their research and development activities as a business strategy, stating that “Outsourcing our research and development work allows us to develop our product candidates, and thereby promote the value of such product candidates and our technology platforms for licensing and product development purposes, without bearing the full risk and expense of establishing and maintaining our own research and development staff and facilities (iBio, 2016, pg. 12).” They choose to out-license as a business strategy not only because of financial benefit, but also because they “believe that successful development by third party licensees of iBio technology-enhanced product candidates will further validate [their] technologies, increase awareness of the advantages that may be realized by the use of such platforms and promote broader adoption of [their] technologies by additional third parties (iBio, 2016, pg.5)”

Seventeen (Nine Type 2/3 companies and eight Type 1) companies mention that out-licenses allow them to access new regional markets, by developing licensing agreements with companies in target countries for distribution - as in the case of Generex, who is seeking out-license opportunities to distribute one of their products in South America and the EU (Generex, 2016). Additionally, Argos Therapeutics entered into an agreement for two of its products (an immunotherapy platform used to develop treatments for HIV, and a cancer treatment) and out-licensing commercialization rights to other global pharmaceutical companies to gain access to Eastern Europe and Central Asia, and to China, Hong Kong, Taiwan, and Macau (Argos Therapeutics, 2016).

An additional benefit is the ability for companies to use out-licensing to as a means to shift disease or product focus, though no Type 2 or 3 companies mentioned this as a benefit. RespireRx Pharmaceuticals reports that their early research showed that a compound they work on for the treatment of mental disorders has potential to benefit respiratory disorders as well. The company has decided to focus its research on breathing disorders, and may “seek to partner, out-license or sell [their] rights to the use of ampakine compounds as for the treatment of neurological and psychiatric indications (RespireRx Pharmaceuticals, 2018, pg. 10).

Patents

Twenty-eight companies mention patents distinct from licensing agreements. Ten mentions come from Type 1 companies, with six mentioning patents for products that are owned or co-owned by universities. In comparison, of the eighteen Type 2/3 companies mentioning patents, only three are for products owned by universities. For example, Contrafect Corporation licenses patents from Rockefeller University.

Two Type 2/3 companies (Pfenex, Inc. and Impax Laboratories), describe leveraging patent expirations to develop and commercialize biosimilars and generics: “We generally focus our generic product development on brand-name products as to which the patents covering the active pharmaceutical ingredient have expired or are near expiration, and we employ our experience to develop bioequivalent versions of such brand-name products (Pfenex, Inc., 2016, Pg. 6).” Doing so lessens the company’s downstream risk by expediting the pathway through clinical trials.

Mergers and Acquisitions

Six companies mention acquiring patents or licenses through an acquisition or merger. A summary of these cases is provided below, in Figure 14.

Figure 14. Cases of intellectual property acquired through mergers or acquisitions

PharmAthene (Type 1) - Filed a complaint against SIGA in the Delaware Court of Chancery that alleged that PharmAthene has the right to license exclusively the development and marketing rights for SIGA's drug candidate, Tecovirimat pursuant to a merger agreement between the parties that was terminated in 2006.
Matinas Biopharmaceuticals (Type 1) - Acquired a license from Rutgers University for a cochleate delivery technology through the acquisition of Aquarius Biotechnologies
RespireRX (Type 1) - Through a merger with Pier Pharmaceuticals, gained access to an Exclusive License Agreement, that Pier had entered into with the University of Illinois on October 10, 2007.
Contravir Pharmaceuticals (Type 2/3) - Merged with Ciclofilin Pharmaceuticals, Inc. in 2016, and acquired their lead asset, which is in development against hepatitis B virus (HBV).
Mylan (Type 2/3) - Has significantly bolstered global R&D capabilities over the past several years, particularly in injectables and respiratory therapies, through several acquisitions.
Minerva Neurosciences (Type 1) - In 2013, Cyrenaic Pharmaceuticals, Inc. And Sonkei Pharmaceuticals, Inc., merged and the new company, acquired the rights to develop and commercialize two drugs in clinical trials, for schizophrenia and Major Depressive Disorder.

Royalties

Table 14. Companies paying and collecting royalties by company type

Mentions of royalties	Number of Companies	
	Type 1 only (61 companies)	Any Type 2 or 3 (71 companies)
Collecting royalties	4	5
Paying royalties	12	12
Both collecting and paying royalties	1	0
No mention	44	54
Total	61	71

Thirty-four out of 132 companies (26%) mention paying or receiving royalties. Of the nine companies that collect royalties, 14 (23%) mention collecting royalties on products for Type 1 diseases, and 11(16%) company mention royalties on products for Type 2/3 diseases. Twenty-four out of 132 companies report paying royalties to other pharmaceutical companies or organizations, 12 of which work only on Type 1 diseases and 12 of which reference work on any Type 2 or 3 diseases.

There are 19 different disease specific mentions of paying royalties to other pharmaceutical companies, and 11 disease specific mentions of paying royalties to public or philanthropic organizations (public and philanthropic organizations mentioned include foundations, hospitals, and universities). Products addressing Type 1 diseases involve paying royalties to pharmaceutical and public/philanthropic organizations more frequently than products addressing Type 2 and 3 diseases. There were no Type 3 disease-specific mentions of paying royalties to pharmaceutical companies and philanthropic/public organizations.

Challenges from IP Protection

85 out of 132 companies (64%) anticipate that the company's inability to obtain favorable licensing agreements may be detrimental to the company - 43 of these companies are work on Type 1 diseases only, and 42 work on Type any Type 2 or 3 diseases.

One company, Contrafect Corporation (a Type 2/3 company), reports negative effects of licensing agreements in regards to the timing of milestone payments for products they've in-licensed: "The timing of milestone payments under our licenses and sponsored research agreements is subject to factors relating to the clinical and regulatory development and commercialization of products, many of which are beyond our control. We may become obligated to make a milestone payment when we do not have the cash on hand to make such payment, which could require us to delay our clinical trials, curtail our operations, scale back our commercialization and marketing efforts or seek funds to meet these obligations on terms unfavorable to us" (Contrafect Corporation, 2016, pg. 33).

Two companies discuss compliance difficulties and litigation threats as uncertainties related to IP-protections. Two companies - PharmAthene (Type 1) and Rich Pharmaceuticals (Type 2/3) - mention ongoing litigation regarding their license, arguing they have the rights to another pharmaceutical company's drug candidate due to a merger. The complaint against Rich Pharmaceuticals includes allegations of patent and copyright infringement, misappropriation of trade secrets, breach of fiduciary duty, unfair competition and other causes of actions against the Company" (Rich Pharmaceuticals, 2016, pg. 10)

One Type 2/3 company discusses the uncertainties related to their business practice of out-licensing commercialization of their products: "As a result of entering into arrangements with third parties to perform sales, marketing and distribution services, our product revenues or the profitability of these product revenues may be lower, perhaps substantially lower, than if we were to directly market and sell products in those markets" (Achillion, 2016, p. 39).

Companies also mentioned the risks of giving up rights to a product that would have been more valuable had the company developed it in-house. Conversely, others mention the risks of in-licensing a product that was riskier than anticipated and did not generate the desired revenue. For example, Newlink Genetics, a Type 2/3 company, notes that "If we enter into collaborations, licensing or other royalty arrangements to develop or commercialize a particular product candidate, we may relinquish valuable rights to that product candidate in situations where it would have been more advantageous for us to retain sole rights to development and commercialization" (Newlink Genetics, 2016, pg. X).

Vertex further notes:

Acquisitions and licensing arrangements are inherently risky, and ultimately, if we do not complete an announced acquisition or license transaction or integrate an acquired business, or an acquired or licensed drug, drug candidate or other technology successfully and in a timely manner, we may not realize the benefits of the acquisition or license to the extent anticipated and the perception of the effectiveness of our management team and our company may suffer in the marketplace. Additionally, we may later incur impairment charges related to assets acquired in any such transaction. For example, we acquired or licensed several drug candidates for the treatment of HCV infection, but due to adverse clinical data regarding these drug candidates and competitive pressures, we incurred significant costs and impairment charges but did not realize the expected benefits from these transactions.

Monopoly Power

40 out of 132 companies (35%) mention potential mergers or acquisitions of other pharmaceutical companies as a risk to their company operations and ability to compete in the marketplace. Additionally, 55 companies anticipate that their dependence on technology owned or licensed to the company by third parties could pose a risk to the company. One company, Macrogenics, Inc. (Type 2/3), describes mergers and acquisitions that have already occurred in the pharmaceutical industry resulting in a reduced number of potential future collaborators" (Macrogenics, Inc., 2016, p. 29).

Three companies report that the market for their product candidates is dominated by one or a few companies. Cocystal Pharma, Inc. states that "Gilead dominates the market for Hepatitis C with an estimated share greater than 70% of the market" (Cocystal Pharma, Inc., 2016, p. 8). Azurix Biopharma, Inc. (Type 1) reports that its product candidate for Pancreatitis will compete directly with porcine pancreatic enzymes, the market for which is "well-established" and dominated by "a few large pharmaceutical companies, including Abbvie, Johnson & Johnson, and Allergan" (Azurix Biopharma, Inc., 2016, p. 9).

Conversely, Arrowhead Pharmaceuticals, Inc., describes a positive effect of its acquisitions of two companies, allowing them to access to critical intellectual property, extensive resources, and a corner on the RNAi market:

"The last five years have brought substantial change to Arrowhead's research and development (R&D) capabilities and strategy. We are now an integrated RNAi therapeutics company, developing novel drugs that silence disease-causing genes based on our broad RNAi technology platform. The most significant step in this transition was our 2011 acquisition of the RNAi therapeutics business of Hoffmann-La Roche, Inc. and F. Hoffmann-La Roche Ltd. (collectively, "Roche"). Roche built this business unit in a manner that only a large pharmaceutical company is capable of: backed by expansive capital resources, Roche systematically acquired technologies, licensed expansive intellectual property rights, attracted leading scientists, and developed new technologies internally. At a time when the markets were questioning whether RNAi could become a viable therapeutic modality, we saw great promise in the technology broadly and the quality of what Roche built specifically" (Arrowhead Pharmaceuticals, Inc., 2016, p. 3).

Monopsony Power

Four companies report that the United States government is the sole customer for their products. Emergent Biosolutions, Inc. (Type 2/3) and PharmAthene, Inc. (Type 1), both of which primarily develop biodefense anthrax vaccine candidates, and Newlink Genetics and Vertex Pharmaceuticals, Inc. which develop products for a variety of Type 1 and 2 diseases, describe the risks that the United States government's monopsony power in the market poses for their companies, including loss of government contracts, loss of IP rights, and government control of product exports.

Six additional companies report that the majority of their revenues come from a limited number of customers, but do not mention specific risks that this poses to their companies (Biostar Pharmaceuticals, Inc., Abbvie Impax Laboratories, Mylan NV (Type 2/3) and BioMarin Pharmaceutical Inc., IntelGenx Technologies (Type 1 only).

Discussion: Triangulating 10-Ks with Expert Interviews and Literature Findings

We find some corroboration between expert opinion as reported in West et al. (2017b) and in the review of literature undertaken by Anderson et al. (2017). West et al. (2017b) found six main factors reported by industry experts to explain limited global health private sector R&D: *Limited Markets for Certain Diseases* (illnesses

that affect small numbers), the *Cost of Drug Development* (long development cycle), *Geo-political Risks* (risks to long-term investments and revenue streams), *Macroeconomic Difficulties* (recession, exchange rate, and interest rate risks), *Poor Health Governance* (difficulty in products reaching intended beneficiaries), and a *Lack of Systematic Data* (evidence on what works). Anderson et al.'s (2017) review of literature as well as the current review of industry 10-Ks suggest that in the revenue calculation, LMIC pricing is the primary disincentive (even in cases where the LMIC market size is large), especially relative to drug pricing in the U.S. and other HICs. Limited market size was seldom mentioned as a deterrent among the 10-Ks we reviewed (9 out of 132 companies). Rather, company 10-Ks were more likely to cite challenges related to market competition, which were mentioned by 27 companies. Another common problem cited in company 10-Ks references downward pricing pressure and cost-containment from governments and other third-party payers in high income countries. Other factors cited by experts in West et al. (2017b) including *Geopolitical Risks*, *Macroeconomic Difficulties*, *Poor Health Governance*, and a *Lack of Systematic Data* are less frequently cited in the literature or 10-Ks as key determinants of private sector investment decisions - although all broadly relate to private firms' perceptions of risks and potential revenues associated with R&D investments.

Largely absent from factors highlighted in expert consultations but frequently mentioned in the literature is the effect of an imperfectly competitive market structure. This potentially grants larger pharmaceutical firms sufficient market power to buy or license R&D below a competitive market price (rather than conduct their own R&D) and enough market and regulatory influence to sell final products above a competitive market price. Patents, licensing, and royalties were mentioned by a majority of firms in the 10-K filings, with approximately half (65 out of 132) specifically mentioning purchasing licenses for R&D. Companies in the 10-K sample report that in-licensing occurs through all stages of drug development, with companies acquiring R&D to either fill gaps in their research during clinical development, or to commercialize and market after clinical trials have been completed. We find evidence that the current health R&D market structure is characterized - and likely constrained - by specialization, high entry costs, regulatory rents and privately held information; a result of both the nature of disease research and the policy environment.

Though a variety of policy tools exist to promote private sector investment in R&D, including push mechanisms (public research funding, R&D tax credits) and pull mechanisms (advance purchase commitments, orphan drug programs, priority review vouchers, wild-card patent extensions), evidence of effectiveness is mixed. Advanced purchase or market commitments (AMC) guarantee markets for new, viable products that can incentivize developing products for diseases with limited markets, but are mentioned by very few companies in our sample (four). Orphan drug status is most commonly applied by companies to Type 1 disease R&D. Expedited review policies mentioned include several aimed specifically at Type 2 or 3 diseases, though others such as "Fast Track" designation may also be applied to Type 1 disease R&D. The attractiveness of licensing upstream research rather than conducting it internally is likely to increase as more computing and data-based aspects of R&D occur in biotech companies relative to the physical science labs of traditional pharmaceutical companies.

Lastly, to the extent that health data are more limited for global health diseases, there is reason to speculate that as the industry shifts more R&D to biotechnology even less will be directed at diseases prevalent in LMICs. Both industry experts and the literature lament the limited market data available to assess potential market outcomes - yet despite potential industry-wide gains, there is no incentive for any individual firm to either fund or contribute to such a data service. We found some evidence in our review of 10-Ks that point to collaborations between companies, academic institutions, medical centers, or government agencies, although this was mentioned by only a relatively few (6 out of 71) companies that research Type 2 or 3 diseases.

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Appendix A. Preliminary Landscape of R&D Pipeline for Type 2 & 3 Diseases

The information in this spreadsheet is drawn from a review of private company 10-K filings for fiscal years ending in 2016. Companies with more than \$10 million in assets and a class of equity securities that is held by more than 2,000 owners must file annual and other periodic 10-K reports, regardless of whether the securities are publicly or privately traded. We retrieved 10-K filings from the SEC's EDGAR database following keyword searches targeting individual Type 2 and 3 diseases, as classified by the WHO and IHME.

Table A1. Type 2 & 3 Diseases Mentioned in 2016-2017 Company 10-K Filings, by Company, Disease, and Modality.

Company	SIC Code	Type	Category of Disease	Infectious Disease?	Infection Specification	Disease	Vaccine	Drug	Diagnostic	Other
Aptevo Therapeutics	2834	2	Birth disorders	N		hemolytic disease of the newborn		marketed product		
Shire PLC	2834	2	Birth disorders	N		hemolytic disease of the newborn		marketed product		
Vitality Biopharma	8731	2	Birth disorders	N		neonatal hypoxic-eschemic encephalopathy		preclinical		
Alexion Pharmaceuticals	2834	2	Blood disorders	N		hemolytic anemia		phase 3		
ChemoCentryx, Inc	2834	2	Blood disorders	N		hemolytic anemia		phase 3		
Rigel Pharmaceuticals	2834	2	Blood disorders	N		hemolytic anemia		phase 2		
Bioverativ Inc	2834	2	Blood disorders	N		sickle cell disease		preclinical		
bluebird bio, Inc.	2836	2	Blood disorders	N		sickle cell disease		phase 1 / phase 2		
Crispr Therapeutics Ag	2836	2	Blood disorders	N		sickle cell disease		preclinical		
Editas Medicines Inc.	2836	2	Blood disorders	N		sickle cell disease		preclinical		
Global Blood Therapeutics, Inc.	2834	2	Blood disorders	N		sickle cell disease		phase 3		
GlycoMimetics, Inc.	2834	2	Blood disorders	N		sickle cell disease		phase 3		
Icagen, Inc.	8731	2	Blood disorders	N		sickle cell disease				modality unknown
La Jolla Pharmaceutical Company	2836	2	Blood disorders	N		sickle cell disease		phase 1		
Mast Therapeutics	2834	2	Blood disorders	N		sickle cell disease		phase 3 ¹⁶		
Vertex Pharmaceuticals Inc.	2834	2	Blood disorders	N		sickle cell disease		phase unknown		
Sangamo Therapeutics, Inc.	2836	2	Blood disorders	N		sickle cell disorders		phase 1/2		
United Therapeutics	2834	2	Blood disorders	N		sickle cell disorders		phase 2/3		
Accelaron Pharma Inc.	2836	2	Blood disorders	N		thalassemias (beta-thalassemia)		phase 3		
bluebird bio, Inc.	2836	2	Blood disorders	N		thalassemias (beta-thalassemia)		phase 1 / phase 2		
Crispr Therapeutics Ag	2836	2	Blood disorders	N		thalassemias (beta-thalassemia)		preclinical		
Editas Medicines Inc.	2836	2	Blood disorders	N		thalassemias (beta-thalassemia)		preclinical		

La Jolla Pharmaceutical Company	2836	2	Blood disorders	N		thalassemias (beta-thalassemia)		phase 1		
Sangamo Therapeutics, Inc.	2836	2	Blood disorders	N		thalassemias (beta-thalassemia)		phase 1/2		
Nanoviricides, Inc.	8731	2	Brain tissue infections	Y	viral	encephalitis		phase unknown		
Sage Therapeutics	2834	2	Brain tissue infections	Y	viral	encephalitis		phase 1		
Pacira Pharmaceuticals	2834	2	Brain tissue infections	Y	bacterial	meningitis		marketed product		
Quidel Corporation	2835	2	Brain tissue infections	Y	bacterial	meningitis			marketed product	
Alere, Inc.	2835	2	Respiratory infection	Y	bacterial	tuberculosis			marketed product	
Oxford Immunotec Global PLC	2835	2	Respiratory infection	Y	bacterial	tuberculosis			marketed product	
Generex Biotechnology Corporation	2834	2	Respiratory infection	Y	bacterial	tuberculosis			phase unknown	
Genocea Biosciences, Inc.	2836	2	Respiratory infection	Y	bacterial	tuberculosis	phase unknown			
Medical International Technology, Inc.	3841	2	Respiratory infection	Y	bacterial	tuberculosis				phase 1 ¹¹
Nantkwest, Inc.	2836	2	Respiratory infection	Y	bacterial	tuberculosis		phase unknown		
Nu-Med Plus, Inc.	3841	2	Respiratory infection	Y	bacterial	tuberculosis	phase not specified			
Taxus Cardium Pharmaceuticals Group Inc.	2836	2	Respiratory infection	Y	bacterial	tuberculosis		FDA approved		
Biopix Inc.	2835	2	Intestinal disorders	N		appendicitis			completed clinical trials ¹⁸	
Albireo Pharma Inc	2834	2	Intestinal disorders	Y		diarrheal diseases		phase 2		
Seres Therapeutics, Inc.	2834	2	Intestinal disorders	Y	bacterial	diarrheal diseases		phase 2		
Chimerix, Inc.	2834	2	Intestinal disorders	Y	viral	norovirus	preclinical			
Chimerix, Inc.	2834	2	Intestinal disorders	Y	viral	norovirus		preclinical		
Cocrystal Pharma, Inc.	2834	2	Intestinal disorders	Y	viral	norovirus		preclinical		
Orasure Technologies, Inc.	3841	2	Liver infections	Y	viral	hepatitis			marketed product	
Protalix Biotherapeutics, Inc.	2836	2	Liver infections	Y	viral	hepatitis		preclinical		
Inovio Pharmaceuticals	3841	2	Liver infections	Y	viral	hepatitis	phase 1			
Alere, Inc.	2835	2	Liver infections	Y	viral	hepatitis B			marketed product	
Adma Biologics, Inc.	2836	2	Liver infections	Y	viral	hepatitis B		FDA approved		
Alnylam Pharmaceuticals, Inc.	2834	2	Liver infections	Y	viral	hepatitis B		phase 1/2		
Aptevo Therapeutics Inc	2834	2	Liver infections	Y	viral	hepatitis B		marketed product		
Arbutus Biopharma Corporation	2834	2	Liver infections	Y	viral	hepatitis B		phase 1		
Arbutus Biopharma Corporation	2834	2	Liver infections	Y	viral	hepatitis B		phase 2		
Arbutus Biopharma Corporation	2834	2	Liver infections	Y	viral	hepatitis B		phase 2		

Arrowhead Pharmaceuticals Inc	2834	2	Liver infections	Y	viral	hepatitis B		preclinical		
Assembly Biosciences	2834	2	Liver infections	Y	viral	hepatitis B		phase 1		
Biostar Pharmaceuticals, Inc.	2834	2	Liver infections	Y	viral	hepatitis B		marketed product		
Cerus Corporation	3841	2	Liver infections	Y	viral	hepatitis B			marketed product	
Chimerix, Inc.	2834	2	Liver infections	Y	viral	hepatitis B		phase unknown ⁴		
China Biologic Products, Inc.	2836	2	Liver infections	Y	viral	hepatitis B	FDA approved			
China Pharma Holdings	2834	2	Liver infections	Y	viral	hepatitis B		marketed product		
Cocrystal Pharma, Inc.	2834	2	Liver infections	Y	viral	hepatitis B		phase unknown		
Contravir Pharmaceuticals	2834	2	Liver infections	Y	viral	hepatitis B		preclinical		
Contravir Pharmaceuticals	2834	2	Liver infections	Y	viral	hepatitis B		phase 2		
Dynavax Technologies Corporation	2834	2	Liver infections	Y	viral	hepatitis B	phase 3			
Enanta Pharmaceuticals, Inc.	2834	2	Liver infections	Y	viral	hepatitis B		preclinical		
Generex Biotechnology Corporation	2834	2	Liver infections	Y	viral	hepatitis B			phase unknown	
Geovax Labs, Inc.	2834	2	Liver infections	Y	viral	hepatitis B	preclinical			
Gilead Sciences, Inc.	2834	2	Liver infections	Y	viral	hepatitis B		FDA approved		
Hemispherx Biopharma, Inc.	2836	2	Liver infections	Y	viral	hepatitis B		phase 3		
Ionis Pharmaceuticals, Inc.	2834	2	Liver infections	Y	viral	hepatitis B		phase 2		
Kadmon Holdings	2834	2	Liver infections	Y	viral	hepatitis B		marketed product		
Nanoviricides, Inc.	8731	2	Liver infections	Y	viral	hepatitis B		phase unknown		
SciClone Pharmaceuticals	2834	2	Liver infections	Y	viral	hepatitis B		marketed product		
Spring Bank Pharmaceuticals, Inc.	2834	2	Liver infections	Y	viral	hepatitis B		phase 2		
VBI Vaccines Inc.	2834	2	Liver infections	Y	viral	hepatitis B	phase unknown ⁵			
Intellia Therapeutics	2835	2	Liver infections	Y	viral	hepatitis B				phase unknown ⁶
Quotient Limited	2835	2	Liver infections	Y	viral	hepatitis B			beginning clinical trials ¹⁷	
Alere, Inc.	2835	2	Liver infections	Y	viral	hepatitis C			marketed product	
Achillion Pharmaceuticals, Inc.	2834	2	Liver infections	Y	viral	hepatitis C		phase 2		
Alnylam Pharmaceuticals, Inc.	2834	2	Liver infections	Y	viral	hepatitis C		phase unknown		
Amarillo Biosciences, Inc.	2834	2	Liver infections	Y	viral	hepatitis C		research		
Array BioPharma, Inc.	2834	2	Liver infections	Y	viral	hepatitis C		phase 3		

Cerus Corporation	2834	2	Liver infections	Y	viral	hepatitis C			marketed product	
Cocrystal Pharma, Inc.	2834	2	Liver infections	Y	viral	hepatitis C		phase 1		
Cocrystal Pharma, Inc.	2834	2	Liver infections	Y	viral	hepatitis C		preclinical		
Enanta Pharmaceuticals, Inc.	2834	2	Liver infections	Y	viral	hepatitis C		FDA approved		
Enzon Pharmaceuticals, Inc.	2836	2	Liver infections	Y	viral	hepatitis C		FDA approved		
Generex Biotechnology Corporation	2834	2	Liver infections	Y	viral	hepatitis C			phase unknown	
GenMark Diagnostics, Inc.	2834	2	Liver infections	Y	viral	hepatitis C			marketed product	
Gilead Sciences, Inc.	2834	2	Liver infections	Y	viral	hepatitis C		FDA approved		
Hemispherx Biopharma, Inc.	2836	2	Liver infections	Y	viral	hepatitis C		phase unknown ⁷		
Idera Pharmaceuticals, Inc.	2836	2	Liver infections	Y	viral	hepatitis C		phase 2		
Johnson & Johnson	2834	2	Liver infections	Y	viral	hepatitis C		marketed product		
Kadmon Holdings	2834	2	Liver infections	Y	viral	hepatitis C		marketed product		
Merck & Co., Inc.	2834	2	Liver infections	Y	viral	hepatitis C		FDA approved		
Mylan N.V.	2834	2	Liver infections	Y	viral	hepatitis C		marketed product		
Nanoviricides, Inc.	8731	2	Liver infections	Y	viral	hepatitis C		phase unknown ⁸		
Nektar Therapeutics	2834	2	Liver infections	Y	viral	hepatitis C		marketed product		
Regulus Therapeutics, Inc.	2834	2	Liver infections	Y	viral	hepatitis C		phase 1/2		
SciClone Pharmaceuticals	2834	2	Liver infections	Y	viral	hepatitis C		marketed product		
Spring Bank Pharmaceuticals, Inc.	2834	2	Liver infections	Y	viral	hepatitis C		phase 2		
Theravance Biopharma, Inc.	2834	2	Liver infections	Y	viral	hepatitis C		phase 2		
AbbVie Inc.	2834	2	Liver infections	Y	viral	hepatitis C		phase 2		
AbbVie Inc.	2834	2	Liver infections	Y	viral	hepatitis C		phase 3		
Quotient Limited	2835	2	Liver infections	Y	viral	hepatitis C			beginning clinical trials ¹⁷	
Eiger Biopharmaceuticals, Inc.	2836	2	Liver infections	Y	viral	hepatitis delta virus		phase 2		
Accelaron Pharma Inc.	2836	2	Micronutrient deficiency	N		anemia		phase 3		
Cerus Corporation	2834	2	Micronutrient deficiency	N		anemia			phase 3 ¹	
Entia Biosciences	2833	2	Micronutrient deficiency	N		anemia		phase unknown		
Pieris Pharmaceuticals	8731	2	Micronutrient deficiency	N		anemia		phase 1		
Kalabios Pharmaceuticals, Inc.	2834	2	Neglected tropical diseases	Y	parasitic	chagas disease		phase unknown		

Quotient Limited	2835	3	Neglected tropical diseases	Y	parasitic	chagas disease			beginning clinical ¹⁷	
Chembio Diagnostics, Inc.	2834	3	Neglected tropical diseases	Y	viral, vector	Chikungunya Virus			phase unknown	
Mymetics Corporation	2836	3	Neglected tropical diseases	Y	viral, vector	Chikungunya Virus	preclinical			
Alere, Inc.	2835	3	Neglected tropical diseases	Y	viral, vector	dengue			marketed product	
Cerus Corporation	3841	3	Neglected tropical diseases	Y	viral, vector	dengue			phase not specified	
Chembio Diagnostics, Inc.	2834	3	Neglected tropical diseases	Y	viral, vector	dengue			preclinical	
Emergent Biosolutions Inc.	2834	3	Neglected tropical diseases	Y	viral, vector	dengue		phase 1		
Heat Biologics, Inc.	2834	3	Neglected tropical diseases	Y	viral, vector	dengue	preclinical			
Inovio Pharmaceuticals	3841	3	Neglected tropical diseases	Y	viral, vector	dengue	marketed product			
Nanoviricides, Inc.	8731	3	Neglected tropical diseases	Y	viral, vector	dengue		preclinical		
Vical Incorporated	2836	3	Neglected tropical diseases	Y	viral, vector	dengue	phase 1			
Navidea Biopharmaceuticals	2835	3	Neglected tropical diseases	Y	viral, vector	dengue			preclinical	
Gilead Sciences, Inc.	2834	3	Neglected tropical diseases	Y	parasitic	leishmaniasis		marketed product		
Navidea Biopharmaceuticals	2835	3	Neglected tropical diseases	Y	parasitic	leishmaniasis			Preclinical	
Celgene Corporation	2834	3	Neglected tropical diseases	Y	bacterial	leprosy		marketed product		
China Biologic Products, Inc.	2836	3	Neglected tropical diseases	Y	viral	rabies	FDA approved			
Nanoviricides, Inc.	8731	3	Neglected tropical diseases	Y	viral	rabies		phase unknown		
OncBioMune Pharmaceuticals, Inc.	2834	3	Neglected tropical diseases	Y	viral	rabies		marketed product		
BioTime, Inc.	2836	2	Opportunistic infections	N		HIV/AIDS resulting in other diseases		phase 3		
Cel-Sci Corporation	2836	2	Opportunistic infections	N		HIV/AIDS resulting in other diseases		phase 1		
Relmada Therapeutics	2834	2	Opportunistic infections	N		HIV/AIDS resulting in other diseases		preclinical		
Navidea Biopharmaceuticals	2835	2	Opportunistic infections	N		HIV/AIDS resulting in other diseases			phase unknown	
iBio, Inc.	2834	2	Parasitic infections	Y	parasitic	hookworm	research			
Impax Laboratories, Inc.	2834	2	Parasitic infections	Y	parasitic	hookworm		marketed product		
Alere, Inc.	2835	3	Parasitic infections	Y	parasitic	malaria			marketed product	

Meridian Bioscience	2835	3	Parasitic infections	Y	parasitic	malaria			marketed product	
Agenus Inc.	2836	3	Parasitic infections	Y	parasitic	malaria	phase 3			
Amyris, Inc	2860	3	Parasitic infections	Y	parasitic	malaria		phase unknown		
Artemis Therapeutics, Inc.	2890	3	Parasitic infections	Y	parasitic	malaria		clinical		
Chembio Diagnostics, Inc.	2834	3	Parasitic infections	Y	parasitic	malaria			phase unknown	
Genex Biotechnology Corporation	2834	3	Parasitic infections	Y	parasitic	malaria			phase unknown	
Genocoe Biosciences, Inc.	2836	3	Parasitic infections	Y	parasitic	malaria	phase 2			
Genvec, Inc	2834	3	Parasitic infections	Y	parasitic	malaria	phase 1/2			
Geovax Labs, Inc.	2834	3	Parasitic infections	Y	parasitic	malaria	preclinical			
iBio, Inc.	2834	3	Parasitic infections	Y	parasitic	malaria	phase 1			
Inovio Pharmaceuticals	3841	3	Parasitic infections	Y	parasitic	malaria	anticipated			
Medical International Technology, Inc.	3841	3	Parasitic infections	Y	parasitic	malaria				phase 1 ¹¹
Mymetics Corporation	2836	3	Parasitic infections	Y	parasitic	malaria	phase 1			
Pfenex Inc.	2834	3	Parasitic infections	Y	parasitic	malaria	phase unknown			
Selecta BioScience Inc.	2834	3	Parasitic infections	Y	parasitic	malaria	research			
Vical Incorporated	2836	3	Parasitic infections	Y	parasitic	malaria	phase unknown			
China Biologic Products, Inc.	2836	3	Nervous system infection	Y	bacterial	tetanus	FDA approved			
Merck & Co., Inc.	2834	3	Nervous system infection	Y	bacterial	tetanus	phase 2/3			
China Biologic Products, Inc.	2836	3	Viral infection	Y	viral	measles	FDA approved			
Merck & Co., Inc.	2834	3	Viral infection	Y	viral	measles, mumps, rubella (MMR)	marketed product			
Meridian Bioscience	2835	3	respiratory infection	Y	bacterial	pertussis			marketed product	
Great Basin Scientific	3841	3	respiratory infection	Y	bacterial	pertussis			approval pending ¹⁴	
Merck & Co., Inc.	2834	3	respiratory infection	Y	bacterial	pertussis	phase 2/3			
Synthetic Biologics, Inc.	2834	3	respiratory infection	Y	bacterial	pertussis	preclinical			
Quidel Corporation	2835	3	respiratory infection	Y	bacterial	pertussis			FDA approved	
Parallax Health Sciences, Inc.	2834	3	Viral infection	Y	viral	rubella			FDA	
Anthera Pharmaceuticals, Inc.	2834	2	Renal diseases	N		glomerulonephritis		phase 2		
Rigel Pharmaceuticals	2834	2	Renal diseases	N		glomerulonephritis		phase 2		
Merck & Co., Inc.	2834	3	Respiratory infections	Y	bacterial	diphtheria	phase 2/3			
Alnylam Pharmaceuticals, Inc	2834	2	Respiratory infections	Y	viral	influenza		phase unknown		
Amarillo Biosciences, Inc.	2834	2	Respiratory infections	Y	viral	influenza		research		
Biocryst Pharmaceuticals, Inc.	2834	2	Respiratory infections	Y	viral	influenza		FDA approved		

Chembio Diagnostics, Inc.	2834	2	Respiratory infections	Y	viral	influenza			phase unknown	
Cocrystal Pharma, Inc.	2834	2	Respiratory infections	Y	viral	influenza		preclinical		
ContraFect Corporation	2834	2	Respiratory infections	Y	viral	influenza		phase 1		
Emergent Biosolutions Inc.	2834	2	Respiratory infections	Y	viral	influenza		phase 1		
Generex Biotechnology Corporation	2834	2	Respiratory infections	Y	viral	influenza	phase unknown			
Generex Biotechnology Corporation	2834	2	Respiratory infections	Y	viral	influenza	phase 1			
iBio, Inc.	2834	2	Respiratory infections	Y	viral	influenza	phase 1			
Karyopharm Therapeutics, Inc.	2834	2	Respiratory infections	Y	viral	influenza		preclinical		
Nanoviricides, Inc.	8731	2	Respiratory infections	Y	viral	influenza		phase unknown		
Novavax, Inc.	2834	2	Respiratory infections	Y	viral	influenza	preclinical			
Vertex Pharmaceuticals Inc.	2834	2	Respiratory infections	Y	viral	influenza		phase unknown		
Merck & Co., Inc.	2834	2	Respiratory infections	Y	bacterial	pneumococcal disease	marketed product			
Alnylam Pharmaceuticals, Inc	2834	2	Respiratory infections	Y	viral	respiratory syncytial virus		phase unknown		
Enanta Pharmaceuticals, Inc.	2834	2	Respiratory infections	Y	viral	respiratory syncytial virus		preclinical		
Genvec, Inc	2834	2	Respiratory infections	Y	viral	respiratory syncytial virus	phase unknown			
Karyopharm Therapeutics, Inc.	2834	2	Respiratory infections	Y	viral	respiratory syncytial virus		preclinical		
Novavax, Inc.	2834	2	Respiratory infections	Y	viral	respiratory syncytial virus	phase 1			
Novavax, Inc.	2834	2	Respiratory infections	Y	viral	respiratory syncytial virus	phase 2			
Novavax, Inc.	2834	2	Respiratory infections	Y	viral	respiratory syncytial virus	phase 3			
Spring Bank Pharmaceuticals, Inc.	2834	2	Respiratory infections	Y	viral	respiratory syncytial virus		investigatory ¹⁵		
Akers Bioscience	2835	2	Sexually transmitted diseases	Y	bacterial	chlamydia			phase unknown ¹⁹	
China Pharma Holdings	2834	2	Sexually transmitted diseases	Y	bacterial	chlamydia		marketed product		
Genocea Biosciences, Inc.	2836	2	Sexually transmitted diseases	Y	bacterial	chlamydia	phase 2			
Great Basin Scientific	3841	2	Sexually transmitted diseases	Y	bacterial	chlamydia			preclinical	
Alere, Inc.	2835	2	Sexually transmitted diseases	Y	viral	HIV			prequalification	
AbbVie Inc.	2834	2	Sexually transmitted diseases	Y	viral	HIV		marketed product		
AbbVie Inc.	2834	2	Sexually transmitted diseases	Y	viral	HIV		marketed product		
Alnylam Pharmaceuticals, Inc	2834	2	Sexually transmitted diseases	Y	viral	HIV		phase unknown		
Argos Therapeutics, Inc.	2834	2	Sexually transmitted diseases	Y	viral	HIV		preclinical		

Argos Therapeutics, Inc.	2834	2	Sexually transmitted diseases	Y	viral	HIV		phase 2		
Atara Biotherapeutics, Inc.	2836	2	Sexually transmitted diseases	Y	viral	HIV		phase 2		
Becton, Dickinson and Company	3841	2	Sexually transmitted diseases	Y	viral	HIV			marketed product	
Bristol-Meyers-Squibb	2834	2	Sexually transmitted diseases	Y	viral	HIV		marketed product		
Cerus Corporation	3841	2	Sexually transmitted diseases	Y	viral	HIV			marketed product	
Chembio Diagnostics, Inc.	2834	2	Sexually transmitted diseases	Y	viral	HIV			preclinical	
Chimerix, Inc.	2834	2	Sexually transmitted diseases	Y	viral	HIV		phase unknown ⁹		
CytoDyn, Inc.	2834	2	Sexually transmitted diseases	Y	viral	HIV		phase 2		
CytoDyn, Inc.	2834	2	Sexually transmitted diseases	Y	viral	HIV		phase 3		
Generex Biotechnology Corporation	2834	2	Sexually transmitted diseases	Y	viral	HIV	phase unknown			
Generex Biotechnology Corporation	2834	2	Sexually transmitted diseases	Y	viral	HIV			phase unknown	
Geovax Labs, Inc.	2834	2	Sexually transmitted diseases	Y	viral	HIV	preclinical			
Geovax Labs, Inc.	2834	2	Sexually transmitted diseases	Y	viral	HIV	phase 1			
Geovax Labs, Inc.	2834	2	Sexually transmitted diseases	Y	viral	HIV	phase 2			
Gilead Sciences, Inc.	2834	2	Sexually transmitted diseases	Y	viral	HIV		FDA approved		
Heat Biologics, Inc.	2834	2	Sexually transmitted diseases	Y	viral	HIV	preclinical			
Hemispherx Biopharma, Inc.	2836	2	Sexually transmitted diseases	Y	viral	HIV		phase 3		
Hoverink	2834	2	Sexually transmitted diseases	Y	viral	HIV		preclinical		
Immune Therapeutics, Inc.	2834	2	Sexually transmitted diseases	Y	viral	HIV		phase unknown		
Inovio Pharmaceuticals	3841	2	Sexually transmitted diseases	Y	viral	HIV	phase 1			
Johnson & Johnson	2834	2	Sexually transmitted diseases	Y	viral	HIV		marketed product		
Johnson & Johnson	2834	2	Sexually transmitted diseases	Y	viral	HIV		marketed product		
Kadmon Holdings	2834	2	Sexually transmitted diseases	Y	viral	HIV		marketed product		
Karyopharm Therapeutics, Inc.	2834	2	Sexually transmitted diseases	Y	viral	HIV		preclinical		

Macrogenics, Inc.	2834	2	Sexually transmitted diseases	Y	viral	HIV		phase 1		
Medical International Technology, Inc.	3841	2	Sexually transmitted diseases	Y	viral	HIV				phase 1 ¹¹
Merck & Co., Inc.	2834	2	Sexually transmitted diseases	Y	viral	HIV		phase 3		
Merck & Co., Inc.	2834	2	Sexually transmitted diseases	Y	viral	HIV		marketed product		
Mylan N.V.	2834	2	Sexually transmitted diseases	Y	viral	HIV		marketed product		
Mymetics Corporation	2836	2	Sexually transmitted diseases	Y	viral	HIV	phase 1			
Nanoviricides, Inc.	8731	2	Sexually transmitted diseases	Y	viral	HIV		preclinical		
Nantkwest, Inc.	2836	2	Sexually transmitted diseases	Y	viral	HIV		phase unknown		
Nutra Pharma Corp.	2833	2	Sexually transmitted diseases	Y	viral	HIV		phase 1/2		
Orasure Technologies, Inc.	3841	2	Sexually transmitted diseases	Y	viral	HIV			marketed product	
Parallax Health Sciences, Inc.	2834	2	Sexually transmitted diseases	Y	viral	HIV			FDA approved	
Parallax Health Sciences, Inc.	2834	2	Sexually transmitted diseases	Y	viral	HIV			phase unknown	
Quantix Biomedical Corporation	3841	2	Sexually transmitted diseases	Y	viral	HIV			phase unknown	
Sangamo Therapeutics, Inc.	2836	2	Sexually transmitted diseases	Y	viral	HIV		phase 1		
Sangamo Therapeutics, Inc.	2836	2	Sexually transmitted diseases	Y	viral	HIV		phase 1/2		
Sangamo Therapeutics, Inc.	2836	2	Sexually transmitted diseases	Y	viral	HIV		phase 2		
Spring Bank Pharmaceuticals, Inc.	2834	2	Sexually transmitted diseases	Y	viral	HIV		investigatory ¹⁰		
Xencor, Inc.	2834	2	Sexually transmitted diseases	Y	viral	HIV		phase 1		
Quotient Limited	2835	2	Sexually transmitted diseases	Y	viral	HIV			beginning clinical trials ¹⁷	
Aviragen Therapeutics, Inc.	2836	2	Sexually transmitted diseases	Y	viral	HPV (cervical cancer)		phase 2		
Cocrystal Pharma, Inc.	2834	2	Sexually transmitted diseases	Y	viral	HPV (cervical cancer)		phase unknown		
Generex Biotechnology Corporation	2834	2	Sexually transmitted diseases	Y	viral	HPV (cervical cancer)	phase unknown			
Hemispherx Biopharma, Inc.	2836	2	Sexually transmitted diseases	Y	viral	HPV (cervical cancer)		phase unknown ¹²		
iBio, Inc.	2834	2	Sexually transmitted diseases	Y	viral	HPV (cervical cancer)	research			

Merck & Co., Inc.	2834	2	Sexually transmitted diseases	Y	viral	HPV (cervical cancer)	marketed product			
Meridian Bioscience	2835	2	Sexually transmitted diseases	Y		sexually transmitted diseases			marketed product	
Chembio Diagnostics, Inc.	2834	2	Sexually transmitted diseases	Y		sexually transmitted diseases			phase unknown	
Alere, Inc.	2835	3	Sexually transmitted diseases	Y	bacterial	syphilis			prequalification	
Chembio Diagnostics, Inc.	2834	3	Sexually transmitted diseases	Y	bacterial	syphilis			preclinical	
Generex Biotechnology Corporation	2834	3	Sexually transmitted diseases	Y	bacterial	syphilis			phase unknown	
Quotient Limited	2835	3	Sexually transmitted diseases	Y	bacterial	syphilis			beginning clinical trials ¹⁷	
Arbutus Biopharma Corporation	2834	3	Viral hemorrhagic fevers	Y	viral	Ebola		phase 2 ²		
Biocryst Pharmaceuticals, Inc.	2834	3	Viral hemorrhagic fevers	Y	viral	Ebola		phase 1		
Cerus Corporation	3841	3	Viral hemorrhagic fevers	Y	viral	Ebola			phase 1	
Chembio Diagnostics, Inc.	2834	3	Viral hemorrhagic fevers	Y	viral	Ebola			phase unknown	
Gilead Sciences, Inc.	2834	3	Viral hemorrhagic fevers	Y	viral	Ebola		phase 3		
Hemispherx Biopharma, Inc.	2836	3	Viral hemorrhagic fevers	Y	viral	Ebola		research		
Inovio Pharmaceuticals	3841	3	Viral hemorrhagic fevers	Y	viral	Ebola	phase 1			
Medical International Technology, Inc.	3841	3	Viral hemorrhagic fevers	Y	viral	Ebola				phase 1 ³
Merck & Co., Inc.	2834	3	Viral hemorrhagic fevers	Y	viral	Ebola	phase 2/3			
Nanoviricides, Inc.	8731	3	Viral hemorrhagic fevers	Y	viral	Ebola		phase unknown		
Nantkwest, Inc.	2836	3	Viral hemorrhagic fevers	Y	viral	Ebola		preclinical		
Newlink Genetics Corporation	2834	3	Viral hemorrhagic fevers	Y	viral	Ebola	phase 3			
Novavax, Inc.	2834	3	Viral hemorrhagic fevers	Y	viral	Ebola	phase 1			
Novavax, Inc.	2836	3	Viral hemorrhagic fevers	Y	viral	Ebola	phase 1			
Orasure Technologies, Inc.	3841	3	Viral hemorrhagic fevers	Y	viral	Ebola			marketed product	
Regeneron Pharmaceuticals, Inc.	2834	3	Viral hemorrhagic fevers	Y	viral	Ebola		phase 1		
Sarepta Therapeutics, Inc.	2834	3	Viral hemorrhagic fevers	Y	viral	Ebola		phase 1		

Soligenix, Inc.	2834	3	Viral hemorrhagic fevers	Y	viral	Ebola	phase unknown			
Vical Incorporated	2836	3	Viral hemorrhagic fevers	Y	viral	Ebola	phase 1			
Chembio Diagnostics, Inc.	2834	3	Viral hemorrhagic fevers	Y	viral	hemorrhagic fever viruses				phase unknown
Emergent Biosolutions Inc.	2834	3	Viral hemorrhagic fevers	Y	viral	hemorrhagic fever viruses		preclinical		
Geovax Labs, Inc.	2834	3	Viral hemorrhagic fevers	Y	viral	hemorrhagic fever viruses	preclinical			
Chembio Diagnostics, Inc.	2834	3	Viral hemorrhagic fevers	Y	viral	Lassa virus				phase unknown
Chembio Diagnostics, Inc.	2834	3	Viral hemorrhagic fevers	Y	viral	Marburg virus				phase unknown
Heat Biologics, Inc.	2834	3	Viral hemorrhagic fevers	Y	viral, vector	yellow fever	preclinical			
iBio, Inc.	2834	2	Viral hemorrhagic fevers	Y	viral, vector	yellow fever	preclinical			

¹ In Phase 1 trials in Europe. Diagnostic is commercialized for other diseases, company has completed a study testing efficacy in HIV/AIDS patients.

² Phase 2 trials suspended

³ Medical International Technology, Inc. is developing a new needle-free technology for administering vaccines, meant to prevent the spread of infectious disease through unintentional needle sticks and can deliver vaccines quickly and accurately; Particularly intended for use in pandemics.

⁴ Product is in "clinical" stages

⁵ U.S. phase unknown, product is in phase 4 in Israel

⁶ Intellia Therapeutics is developing a gene editing therapy addressing Hepatitis B, which is going through in-vitro guide evaluations

⁷ Phase unknown for U.S. approval (marketed product in Argentina)

⁸ "Early stages of R&D"

⁹ "Clinical" stage

¹⁰ "May explore"

¹¹ Medical International Technology, Inc. is developing a new needle-free technology for administering vaccines that is meant to prevent the spread of infectious disease through unintentional needle sticks and can deliver vaccines quickly and accurately, particularly for use in pandemics.

¹² Phase unknown for U.S. approval, company has a marketed drug in Argentina

¹³ "QS-21 Stimulon is a key component included in certain of GSK's proprietary adjuvant systems, and we believe that a number of GSK's vaccine candidates currently in development are formulated using adjuvant systems containing QS-21 Stimulon, including its shingles and malaria vaccine candidates which have successfully completed Phase 3 clinical trials."

¹⁴ Completed clinical trials and submitted 510(k) application to FDA

¹⁵ "May explore"

¹⁶ Phase 3 trials canceled

¹⁷ Product is a donor blood screening tool (screens donor blood for chagas, hepatitis, HIV, etc.)

¹⁸ Did not receive FDA approval, canceled further trials

¹⁹ Awaiting FDA approval

SIC Codes Included:

-2833 MEDICINAL CHEMICALS & BOTANICAL PRODUCTS (2 companies)

-2834 PHARMACEUTICAL PREPARATIONS (136 companies)

-2835 IN VITRO & IN VIVO DIAGNOSTIC SUBSTANCES (9 companies)

-2836 BIOLOGICAL PRODUCTS (NO DIAGNOSTIC SUBSTANCES) (26 companies)

-2860 INDUSTRIAL ORGANIC CHEMICALS (1 company)

-
- 2890 MISCELLANEOUS CHEMICAL PRODUCTS (1 company)
 - 3841 SURGICAL & MEDICAL INSTRUMENTS & APPARATUS (9 companies)
 - 8731 SERVICES - COMMERICAL PHYSICAL AND BIOLOGICAL RESEARCH (5 companies)
 - 5912 RETAIL-DRUG STORES AND PROPRIETARY STORES (1 company)

Appendix B. Review Coding Framework.

General

- Coding at company or Disease?
- Type 1 only or any Type 2 or 3 Diseases
- Document #
- Year of filing (year of content is previous year)
- Company name
- SIC code
- Link to online 10-K filing
- Currently or formerly (performing R&D)
- New or adapted product

Company Characteristics

- Location of Headquarters (Country Only)
- # of employees
- Company size category
- Multinational Company? (Y/N)
- Total Assets (\$)
- Net Income (\$)
- Total Revenues (\$)
- Total Operating Expenses (\$)
- Operating Expense size category
- Operating Expenses: Research and Development (\$)
- Operating Expense: R&D size category
- Ratio of Operating Expenses: Research and Development to Total operating expenses
- Ratio of Operating Expenses: Research and Development to Total revenues
- Primary Stage Focus (stated)
- Stages involved in
- Country of R&D Operations (includes countries of clinical trials)
 - If multiple, list

Product and Phase Information

- Vaccine(s)? (Y/N)
 - Describe (diseases targeted and phase of development)
 - Phase of development
 - Describe (relative importance of product to company)
- Drug(s)? (Y/N)
 - Describe (diseases targeted and phase of development)
 - Phase of development
 - Describe (relative importance of product to company)
- Diagnostic tool(s)? (Y/N)
 - Describe (diseases targeted and phase of development)
 - Phase of development
 - Describe (relative importance of product to company)
- Other products (Y/N)
 - Describe (diseases targeted and phase of development)
 - Phase of development
 - Describe (relative importance of product to company)

Diseases

- Type 1 Diseases (Y/N)
 - List (separated by comma)
- Type 2 Diseases (Y/N)
 - List (separated by comma)
- Type 3 Diseases (Y/N)
 - List (separated by comma)
- Other diseases (Y/N)
 - List (separated by comma)
- Type of Diseases Researched

Hypothesis 1

- Discusses any effect of scientific uncertainty on R&D investment (Y/N)?

- Discusses any effect of scientific uncertainty on R&D investment: (Mention, Mixed, Positive, Negative)
 - Discusses any effect of scientific uncertainty on R&D investment: Describe
- Probability of success: (Mention, Mixed, Positive, Negative)
 - Probability of success: Describe
- Complexity of research: (Mention, Mixed, Positive, Negative)
 - Complexity of research: Describe
- Access to existing research: (Mention, Mixed, Positive, Negative)
 - Access to existing research: Describe
- Evidence of efficacy on reducing mortality or morbidity?: (Mention, Mixed, Positive, Negative)
 - Evidence of efficacy on reducing mortality or morbidity?: Describe

Hypothesis 1, Anticipated Risks

- Product candidates may be deemed inefficacious during any clinical phase (Y/N)
- Research partners may fail in their responsibilities to develop a drug (Y/N)
- Risks related to being able to enroll enough patients in clinical trials (Y/N)
- Serious adverse events or other side effects could harm chances of product candidate successfully completing clinical trials (Y/N)

Hypothesis 2

- Discusses any effect of policy or regulatory environment on R&D investment (Y/N)?
- Discusses any effect of policy or regulatory uncertainty on R&D investment: (Mention, Mixed, Positive, Negative)
 - Discusses any effect of policy or regulatory uncertainty on R&D investment: Describe
- Weak or uncertain IP protections?: (Mention, Mixed, Positive, Negative)
 - Weak or uncertain IP protections?: Describe
- Health delivery systems and health governance (state of health delivery systems and state of government regulation): (Mention, Mixed, Positive, Negative)
 - Health delivery systems and health governance (state of health delivery systems and state of government regulation): Describe
- Regulatory Costs: Describe
- Development Time: Describe
- Approval Time: Describe

Hypothesis 2, Anticipated Risks

- Issues with enforcement of IP protection including in foreign markets (Y/N)
- May need to engage in litigation to protect IP (Y/N)
- Failure in obtaining regulatory approval including in foreign markets (Y/N)
- Risks related to healthcare legislation such as insurance markets (Y/N)
- Other policy changes in trade (restrictions around generics) or advertising (Y/N)
- Unforeseen and increased costs due to meeting regulatory obligations such as changes in safety or efficacy thresholds (Y/N)
- Product candidates may infringe the intellectual property rights of others (Y/N)

Hypothesis 3

- Discusses any effect of limited revenues and market uncertainty on R&D investment (Y/N)?
 - Discusses any effect of limited revenues and market uncertainty on R&D investment: (Mention, Mixed, Positive, Negative)
 - Discusses any effect of limited revenues and market uncertainty on R&D investment: Describe
- Discusses "competition" for product?: (Mention, Mixed, Positive, Negative)
 - Discusses "competition" for product?: Describe
- What is the expected ROI for R&D in progress?
- Is actual ROI more or less than expected?
- Market size? (number of potential customers): (Mention, Mixed, Positive, Negative)
- What is the burden of the disease?
- What is the projected burden of disease? (Increasing or Decreasing)
- What is the geographical distribution of the disease?
- What is the number of individuals (worldwide) affected per year?
 - Market size: Describe
- What is the estimated market potential (total sales revenue): (Mention, Mixed, Positive, Negative)
 - What is the estimated market potential (total sales revenue): Describe

- WTP in target markets (effect on final market price): (Mention, Mixed, Positive, Negative)
 - WTP in target markets (effect on final market price): Describe
- What is the ability/willingness to pay in HIC?: (Mention, Mixed, Positive, Negative)
 - What is the ability/willingness to pay in HIC?: Describe
- What is the ability/willingness to pay in LIC?: (Mention, Mixed, Positive, Negative)
 - What is the ability/willingness to pay in LIC?: Describe
- Are target beneficiaries expected to bear the full costs of the product: (Mention, Mixed, Positive, Negative)
- Is there a differential pricing option? (Y/N)
 - Are target beneficiaries expected to bear the full costs of the product: Describe
- Will subsidies be needed to provide the drug/vaccine to those most in need: (Mention, Mixed, Positive, Negative)
 - Will subsidies be needed to provide the drug/vaccine to those most in need: Describe
- Is there a national health insurance scheme that would affect this product: (Mention, Mixed, Positive, Negative)
 - Is there a national health insurance scheme that would affect this product: Describe
- Market uncertainty (lack of market data for forecasting), challenges estimating future market demand: (Mention, Mixed, Positive, Negative)
 - Market uncertainty (lack of market data for forecasting), challenges estimating future market demand: Describe

Hypothesis 3, Anticipated Risks

- Product may not be accepted by medical community including physicians, patients, hospitals (including pharmacy directors) and third-party payers (Y/N)
- Third-party coverage and reimbursement for product may not be available or adequate (Y/N)
- Other firms may create a superior product and/or the superior product may be created faster and/or cheaper (Y/N)
- External market factors including changes in economic conditions (Y/N)
- Risks related to healthcare legislation such as insurance markets (Y/N)

Hypothesis 4

- Discusses any effect of fixed and other costs on R&D investment (Y/N)?
 - Discusses effect (increases or decreases) of capital, fixed or sunk costs on R&D investment: (Mention, Mixed, Positive, Negative)
 - Discusses effect (increases or decreases) of capital, fixed or sunk costs on R&D investment: Describe
- Investments in manufacturing infrastructure? (Mention, Mixed, Positive, Negative)
 - Investments in manufacturing infrastructure?: Describe
- Disease specific cost of development: Describe
- Public/philanthropic research funding? (Y/N)
 - Describe
- Private/private research funding? (Y/N)
 - Describe
- University research funding? (Y/N)
 - Describe
- Other collaborative funding? (Y/N)
 - Describe

Hypothesis 4, Anticipated Risks

- Loss of public or private funding (Y/N)
- Need for additional funding (most companies operate at a financial loss) (Y/N)
- Incurring any financial losses due to unanticipated or unforeseen circumstances (this is the predominant concern of these companies) (Y/N)
- Increase investment in infrastructure, operations and R&D with expansion (Y/N)
- Raising additional capital (through debt financing or collaborations) may restrict operations, or require the company to relinquish rights to technologies or product candidates (Y/N)

Hypothesis 5

- Discusses any effect of downstream rents from imperfect markets on R&D investment (Y/N)?
 - Discusses any effect of downstream rents from imperfect markets on R&D investment?: (Mention, Mixed, Positive, Negative)
 - Discusses any effect of downstream rents from imperfect markets on R&D investment?: Describe

- Number of NCE (new chemical entities) Approved for the Disease
- Is there already a similar drug? (Y/N)
- Number of Existing Treatments: Describe
- Patents (only patents with others NOT company's own patents): (Mention, Mixed, Positive, Negative)
 - Patents (only patents with others NOT company's own patents): Describe
- IP (only IP in relation to others, not company's own IP): (Mention, Mixed, Positive, Negative)
 - IP (only IP in relation to others, not company's own IP): Describe
- Collecting Royalties: (Mention, Mixed, Positive, Negative)
 - Collecting Royalties: Describe
- Paying Royalties: (Mention, Mixed, Positive, Negative)
 - Paying Royalties: Describe
- License agreements (only if it changes the potential risk of the company) (Y/N)
 - License agreements (only if it changes the potential risk of the company): (Mention, Mixed, Positive, Negative)
 - License agreements (only if it changes the potential risk of the company) Describe
 - In-licensing or Out-licensing?
- Investment in "me too" drugs (drugs that offer relatively minimal benefits over existing treatments): (Mention, Mixed, Positive, Negative)
 - Investment in "me too" drugs (drugs that offer relatively minimal benefits over existing treatments): Describe
- Asymmetric market power: Monopoly (Mention, Mixed, Positive, Negative)
 - Any asymmetric market power? Monopoly: Describe
- Asymmetric market power: Monopsony (Mention, Mixed, Positive, Negative)
 - Any asymmetric market power? Monopsony: Describe

Hypothesis 5, Anticipated Risks

- Inability to obtain license agreements (Y/N)
- Mergers, acquisitions or other market structure changes that increase monopsony or monopoly power (Y/N)
- New products, patent expiration, or other product changes that affect firm's market power (Y/N)
- Dependence on technology owned or licensed to the company by third parties (Y/N)

Unspecified

- Unspecified Uncertainty? (Y/N)
 - Describe
- Other investment barriers/drivers? (Y/N)
 - Describe

Policy Incentives for R&D

- Policy Incentives for R&D?: (Mention, Mixed, Positive, Negative)
 - Policy Incentives for R&D?: Describe
- R&D tax credits? (Y/N) : (Mention, Mixed, Positive, Negative)
 - R&D tax credits?: Describe
- Advanced purchase commitments? (Y/N): (Mention, Mixed, Positive, Negative)
 - Advanced purchase commitments: Describe
- Orphan drug programs? (Y/N): (Mention, Mixed, Positive, Negative)
 - Orphan drug programs?: Describe
- Priority review vouchers? (Y/N): (Mention, Mixed, Positive, Negative)
 - Priority review vouchers?: Describe
- Wild-card patent extensions? (Y/N): (Mention, Mixed, Positive, Negative)
 - Wild-card patent extensions?: Describe
- Fast Track? (Y/N): (Mention, Mixed, Positive, Negative)
 - Fast Track?: Describe
- Breakthrough Therapy? (Y/N): (Mention, Mixed, Positive, Negative)
 - Breakthrough Therapy? Describe
- Other investment drivers?: (Mention, Mixed, Positive, Negative)
 - Other investment drivers?: Describe

Risk Factors Discussed

- For Scientific Uncertainty did the company mention: complexity or uncertainty? (Y/N)
- For policy and regulatory uncertainty, did the company mention: regulatory delays? (Y/N)

- For limited revenues & market uncertainty, did the company mention: small markets or low prices for products? (Y/N)
- For Fixed & Other Costs, did the company mention: specialized, fixed, sunk, initial or setup costs? (Y/N)
- Downstream Rents from Imperfect Markets did the company mention: excess or too much competition? (Y/N)

What's New?

- Opportunities: Describe
- New Models: Describe

Appendix C. Boilerplate Language on General Risk and Uncertainty

Table C1. Table of General Risks at Company Level. This table refers to general risks mentioned by companies in the *Risk Factors* section of the 10-K. These risks are not associated with any specific product or research the company is engaging in. They reflect the general risks perceived by the company as associated with carrying out R&D research in the pharmaceutical industry.

Risk	Mention	No Mention	Example Language
Scientific Risks			
1. Product candidates may be deemed inefficacious during any clinical phase	122	10	Interim results of a clinical trial do not necessarily predict final results, and interim results may result in early stoppage of our clinical trials for futility (Axsome Therapeutics, Inc., 2016, pg. 55).
2. Research partners may fail in their responsibilities to develop a drug	99	33	We rely on third parties to conduct our preclinical studies and our clinical trials. If these third parties do not perform as contractually required or expected, we may not be able to obtain regulatory approval for our product candidates, or we may be delayed in doing so. (Newlink Genetics Corporation, 2016, pg. 44)
3. Risks related to being able to enroll enough patients in clinical trials	92	40	Clinical trials can be delayed or halted for many reasons, including: delays in patient enrollment, variability in the number and types of patients available for clinical trials, poor accrual, or high drop-out rates of patients in our clinical trials; (Stemline Therapeutics, Inc., 2016. Pg. 31).
4. Serious adverse events or other side effects could harm chances of product candidate successfully completing clinical trials	114	18	Our product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following marketing approval, if any (RA Pharmaceuticals, Inc., 2016, pg. 52).
Policy and Regulatory Risks			
1. Issues with enforcement of IP protection including in foreign markets	118	14	The degree of future protection for our proprietary rights is uncertain because legal means afford only limited protection and may not adequately protect our rights or permit us to gain or keep our competitive advantage (RA Pharmaceuticals, Inc., 2016, pg. 81).
2. May need to engage in litigation to protect IP	116	16	Litigation regarding patents, patent applications and other proprietary rights may be expensive and time consuming. If we are involved in such litigation, it could cause delays in bringing drug candidates to market and harm our ability to operate (Prothena Corporation Public Limited Company, 2016, pg. 33).
3. Failure to obtain regulatory approval including in foreign markets	124	8	Our failure to obtain regulatory approval in international jurisdictions would prevent us from marketing our product candidates outside the United States (Five Prime Therapeutics, Inc., 2016, pg. 43).
4. Other policy changes in trade (restrictions around generics) or advertising	108	24	Approvals for our new generic drug products may be delayed or become more difficult to obtain if the FDA institutes changes to its approval requirements. (Impax Laboratories, 2016, pg. 28)

5. Unforeseen and increased costs due to meeting regulatory obligations such as changes in safety or efficacy thresholds	123	9	Changes in regulatory requirements or FDA guidance or unanticipated events during our non-clinical studies and clinical trials may force us to amend non-clinical studies and clinical trial protocols or the FDA or applicable regulatory authorities outside the U.S. may impose additional non-clinical studies and clinical trial requirements. (Sage Therapeutics, 2016, pg. 35)
6. Product candidates may infringe the intellectual property rights of others	78	54	Our success depends in significant part on our ability and the ability of our licensors and collaborators to obtain, maintain and defend patents and other intellectual property rights and to operate without infringing the intellectual property rights of others (Five Prime Therapeutics, Inc., 2016, pg. 52).
Limited Revenues and Market Risks			
1. Product may not be accepted by medical community including physicians, patients, hospitals (including pharmacy directors) and third-party payers	100	32	Any of our product candidates that receive regulatory approval may fail to achieve the degree of market acceptance by physicians, patients, healthcare payors and others in the medical community necessary for commercial success (Merrimack Pharmaceuticals, Inc., 2016, pg. 48).
2. Third-party coverage and reimbursement for product may not be available or adequate	116	16	If we or our partners are unable to achieve and maintain adequate levels of coverage and reimbursement for our products, or any future products we may seek to commercialize, their commercial success may be severely hindered (Corium International, Inc., 2016, pg. 29).
3. Other firms may create a superior product and/or the superior product may be created faster and/or cheaper	86	46	Our competitors' drugs or product candidates may be more effective, have fewer negative side effects, be more convenient to administer, have a more favorable resistance profile, or be more effectively marketed and sold than any drug we, or our potential collaborators, may develop or commercialize. (Contravir Pharmaceuticals, Inc., 2016, pg. 29)
4. External market factors including changes in economic conditions	53	79	The risks associated with its operations outside the United States include: political and economic instability, including sovereign debt issues (AbbVie Inc., 2016, pg. 20).
5. Risks related to healthcare legislation such as insurance markets	92	40	Healthcare reform measures could hinder or prevent the commercial success of our products and product candidates (Corium International, Inc., 2016, pg. 49).
High Costs of Research and Manufacturing Risks			
1. Loss of public or private funding	108	24	Even though we have received governmental support in the past, we may not continue to receive support at the same level or at all...We have also received significant financial assistance, primarily in the form of grants and contracts, from federal agencies to support our infectious disease research. There can be no assurance that we will continue to receive the same level of assistance from these or other government agencies, if at all. (Newlink Genetics Corporation, 2016, pg. 42)
2. Need for additional funding (most companies operate at a financial loss)*	123	9	We will be required to raise additional capital within the next year to continue the development and commercialization of current product candidates and to continue to fund operations at the current cash expenditure

			levels. We cannot be certain that additional funding will be available on acceptable terms, or at all. (Contravir Pharmaceuticals, Inc., 2016, pg. 51)
3. Incurring any financial losses due to unanticipated or unforeseen circumstances	78	54	Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to generate any revenues or achieve profitability. (Seres Therapeutics, Inc., 2016, pg. 34)
4. Increase investment in infrastructure, operations and R&D with expansion	82	50	Our success will depend upon the expansion of our operations and the effective management of our growth, which will place a significant strain on our current and future management and other administrative and operational resources. To manage this growth, we may need to expand our facilities, augment our operational, financial and management systems and hire and train additional qualified personnel. If we are unable to manage our growth effectively, our business would be harmed. (Assembly Biosciences, Inc., 2016, pg. 23)
5. Raising additional capital (through debt financing or collaborations) may restrict operations, or require the company to relinquish rights to technologies or product candidates	100	32	Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights (Stemline Therapeutics, Inc., 2016. pg. 39).
Imperfect Market Risks			
1. Inability to obtain license agreements	86	46	We may not be able to execute our business strategy if we are unable to enter into alliances with other companies that can provide business and scientific capabilities and funds for the development and commercialization of our product candidates. (Alnylam Pharmaceuticals, Inc., 2016, pg. 42)
2. Mergers, acquisitions or other market structure changes that increase monopsony or monopoly power	53	79	Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors (Axsome Therapeutics, Inc., 2016, pg. 31).
3. Patent expiration	92	40	Patents have a limited lifespan. In the United States, the natural expiration of a patent is 20 years after it is filed, although various extensions may be available. However the life of a patent, and the protection it affords, is limited. Once the patent life has expired for a product, we may be open to competition from generic medications.(Cocrystal Pharma, Inc., 2016, pg. 18)
4. Dependence on technology owned or licensed to the company by third parties	71	51	Our business depends, in part, on our ability to use the technology that we have licensed or will in the future license from third parties...and, if these licenses were terminated or if we were unable to license additional technology we may need in the future, our business will be adversely affected. (Arbutus Biopharma Corporation, 2016, pg. 31)

* 86.2% of companies in our sample operated at a financial loss as reported by net income for the year of filing.

Appendix D. Results from Automated Analyses of 10-K Forms

C. Leigh Anderson, Travis Reynolds, Pierre Biscaye, Adam Hayes

Systematically measuring topics emphasized by Type 1 and Type 2 or 3 disease R&D companies

This summary appendix examines the risk factors and stated incentives emerging from an exploratory automated analysis of all private sector pharmaceutical companies required to file 10-K forms with the U.S. Securities and Exchange Commission (SEC). 10-K reports from pharmaceutical companies are rich repositories, with information on risk factors (scientific, market, and regulatory), financial performance, investment options, lines of research, and promising acquisitions. Risks and challenges include scientific and financial uncertainty, regulations, and competition from R&D companies overseas, while opportunities include promising new forms of R&D (e.g., data driven and biologics), regulatory reforms, and emerging markets. Using data from 10-K reports allows us to analyze the same information across the full population of public pharmaceutical companies.

The SEC requires public companies file 10-K reports each year. Since 2005, 10-K filings have included a risk factors section, and since 2011, companies have been submitting financial statements that generally include line items associated with revenue and research and development spending. A small number of recent studies have drawn on 10-K data to analyze trends in risk factors facing public companies and resultant effects on investment in R&D spending across various industries (Baker et al., 2016; Koijen et al., 2016). Koijen et al. (2016) used the risk factors section of a large sample of 10-K forms across a range of industries to show that private firms in the health care sector overall tend to reference government-related risk significantly more frequently than firms in other sectors, but they do not distinguish R&D for LICs from HICs, nor do they look at opportunities or incentives.

As described in the main body of the report, we draw on a WHO typology to categorize disease research efforts according to the ratio of disease burden (measured by DALYs) for populations in low-income countries (LICs) over the disease burden for populations high-income countries (HICs). Type 1 diseases have a DALYs ratio of less than 3, and represent diseases that do not burden LIC populations much more than high-income countries HIC populations, such as cancers. Type 3 diseases are those that burden LICs overwhelmingly more than HICs with a DALYs ratio of greater than 35 (e.g., African trypanosomiasis (sleeping sickness), dengue fever). Type 2 diseases are those with DALYs ratios between these two extremes (e.g., HIV/AIDS).

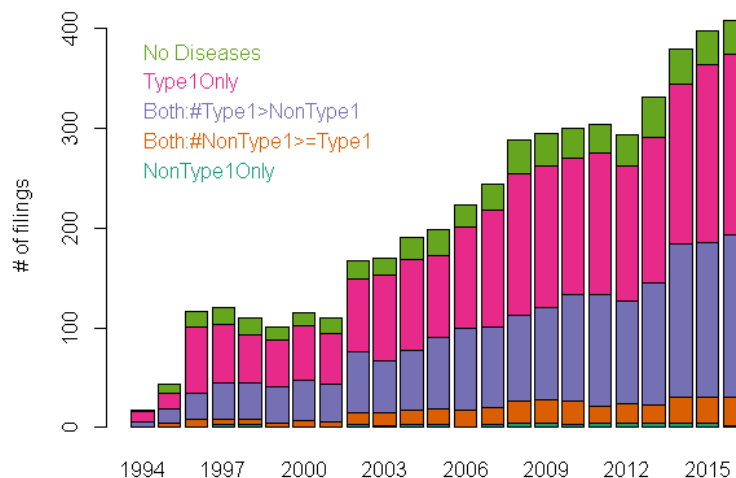
In this appendix we use text mining to examine what proportion of companies discuss particular diseases, particularly Type 1, 2 and 3 disease classifications, and illustrate how this changes over time. We further test whether reported risk/opportunity factors change according to the composition of diseases/conditions reported by each company's 10-K filing.

Automated analyses of 10-K data

Each company 10-K is filed as a text document on the SEC Edgar database. We created a program using R to check the SIC code for each 10-K filing listed in the file directory, retrieving all 10-K filings under SIC 2834 "Pharmaceutical

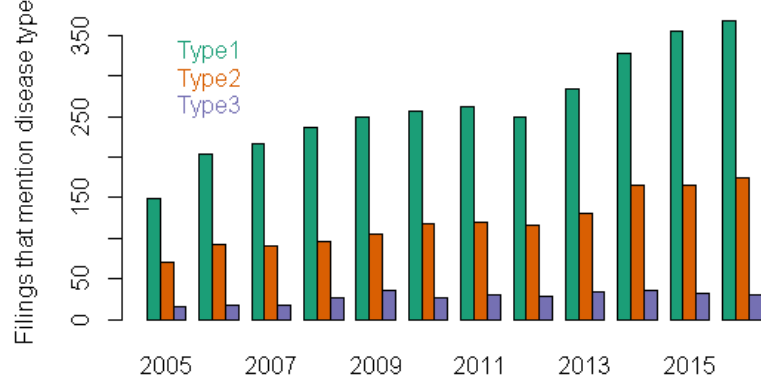
Preparations" since 1994. Using text analysis tools in R, we generate counts of mentions of Type 1, 2, and 3 diseases in each 10-K filing. Based on these counts, we initially categorize the Pharma 10-K filings as mentioning no diseases, Type 1 diseases only, Type 2 or 3 diseases (non-Type 1) only, both Type 1 and non-Type 1 diseases but more Type 1 mentions, and both Type 1 and non-Type 1 diseases but more non-Type 1 mentions. Figure D1 summarizes the company types included in the full sample of all filings under SIC 2834 since 1994.

Figure D1. 10-K filings (Pharmaceutical Preparations) by predominant disease type within companies



Since 1994, we can see that the number of pharmaceutical firms filing 10-Ks has increased by a factor of more than four - far greater than the rate of population or market growth. R&D in firms only engaged in Type 2 or 3 R&D (involving LIC diseases) has been very low over the past two decades, however, and as recently as 2016, has fallen to a few firms. While the number of firms mentioning Type 2 or 3 diseases more frequently than Type 1 diseases in their 10-K filings each year increased in the early 2000s, this number has not increased as much as firms focusing more or only on Type 1 diseases with more prevalence in HICs. This suggests that firms may be reluctant to engage in R&D that does not have a HIC market, and perhaps are becoming increasingly so over time.

Figure D2. 10-K filings (Pharmaceutical Preparations) by predominant disease type within Item 1a Risk Factors text 2005-2016



For machine-based automated analysis of the 10-K filings, we limited the sample to all filings under SIC 2834 from 2005-2016 (as these are the years for which 10-Ks included the Item 1a risk factors section). The combined business and risk sections for all SIC 2834 10-K filings between 2005 and 2016 that reached at least 8000 characters and mention at least one disease resulted in a sample of 3,287 company 10-Ks. Figure D2 presents a count of Pharma 10-K filings each year from 2005-2016 year by the Type of disease with the most frequent number of mentions in the Risk

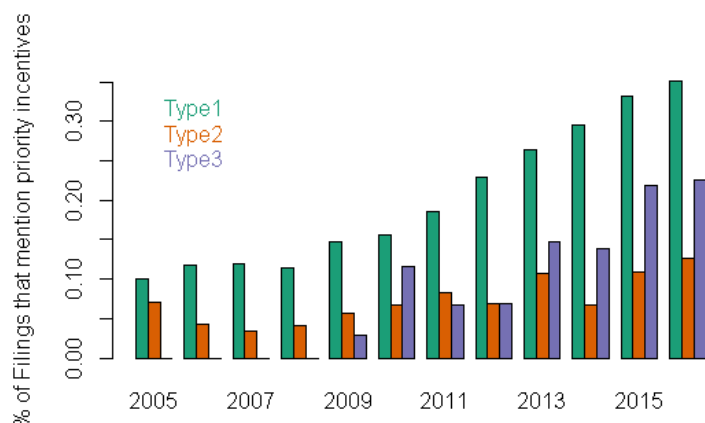
Factors section of the 10-K. While the number of 10-Ks primarily mentioning Type 3 diseases each year has not increased much during this time period, we observe large increases for 10-Ks primarily mentioning Type 1 and Type 2 diseases.

Using this restricted sample we first performed an automated search on incentives mentioned by different firms using the following keywords, under four broad classifications:

Push incentives: "tax incentive", "tax credit", "tax break", "tax reduction", "development fund", "innovation fund", "public research fund", "small business grant", "research grant", "research subsidy"
Priority incentives: "fee reduction", "fee waiver", "orphan", "rare pediatric", "humanitarian us", "neglected disease", "neglected tropical", "priority review", "priority voucher", "prv", "protocol assist",
Pull incentives: "prize", "purchase commitment", "market commitment", "patent buy", "attractive market", "market exclusiv", "volume guarantee", "royalt", "licensing right", "license right", "buy down", "buydown", "buy back", "buyback",
Organizational incentives: "product development partner", "parent comp", "contract research organization", "cro", "spin off", "spinoff"

As seen in Figure D3 the number of 10-K filings mentioning Priority incentives have increased in recent years. In relative terms, this change has been most dramatic in text surrounding Type 3 disease mentions, but in absolute terms this increase has happened in companies engaged in R&D for both Type 1 and Type 3 diseases. Over 20% of filings that mention Type 3 diseases contain some mention of Priority incentives, as do roughly 35% of the filings mentioning Type 1 diseases. Moreover, since filings that more frequently mention Type 3 diseases are on average much shorter (less text) than those that more frequently mention Type 1 diseases, as a proportion of the text Priority incentives make up a much greater portion for Type 3 disease-related text than any other type. In other words, the mean frequency of Priority incentive words in the text is much higher for Type 3 research firms than any other type.

Figure D3. 10-K filings mentioning Priority incentives within Item 1a Risk Factors text 2005-2016



Combined with the observation that the number of companies mentioning Type 3 diseases has not increased from year-to-year, these findings suggest that although Priority incentive words are appearing in 10-Ks of companies that mention Type 3 diseases, this has not been associated with an increase in the number of companies entering Type 3 disease markets.

Finally, structural topic modeling was conducted using the stm package in R. For the full sample of risk and business text from 3,287 10-K filings, the files were downloaded and processed to remove any HTML code. The text was isolated using separate code to identify regular expressions

signifying the beginning and end of the relevant sections. During this procedure, the text was also processed to remove any non-alphanumeric characters. Prior to machine-based topic modeling, the risk and business sections from each 10-K filing were combined to form a single block of text consisting of both sections. Documents with less than 8000 alphanumeric characters were removed from the corpus, to filter out smaller reporting companies that are not required to report these sections, but often include the sections to conform with the layout without providing substantive content.¹⁵

In the stm package, like other topic models, the estimation represents a probability that a term will be associated with a particular topic and a proportion of each document belonging to each topic. The model estimate is then: (1) a matrix of topic-term probabilities, and (2) a matrix of document-topic proportions. Details of the estimation procedure within the stm() function are reported in Roberts et al. (2016 and 2017).

Beyond a document corpus, topic models require the researcher to set the number of topics in the corpus. Previous research has indicated that for large numbers of documents (more than ten thousand), 50-100 topics tends to be stable (Roberts et al., 2016), while 40-60 topics are reasonable initial values for a medium sized corpus (Roberts et al., 2017). We chose an initial number of 45 for each of these models.¹⁶

We estimate a separate model for each of four corpora:

- (1) All documents as described above (n=3,287)
- (2) Only documents that mention Type 2/3 diseases at least as frequently as Type 1 (non-Type 1 >= Type 1) (n=297¹⁷)
- (3) Only documents that mention both Type 2/3 and Type 1 diseases, but mention Type 2/3 diseases less frequently than Type 1 diseases (non-Type 1 < Type 1) (n=1326)
- (4) Only documents that mention Type 1 diseases exclusively (Type 1 only) (n=1664).

Table D1 summarizes the 45 topics emerging from topic modeling based on the full sample (n=3,287 10-Ks). After removing a small set of “junk” topics (relating to document formatting, for example) we retained 41 topics which were then assigned a descriptive name (e.g., “legal”) and were further manually coded based on the degree to which different types of diseases, or different scientific, economic, or policy factors, appeared prominently in the topics based on the highest-probability terms within that topic (top 5 terms shown).

This process allows us to visualize the relative prevalence of different topics in company 10-Ks with different levels of attention to Type 2 and 3 diseases. Figures D4a and D4b compare results on the prevalence of different topics for the sample of 10-Ks which only mention Type 1 diseases (Figure D4a) and for the sample of 10-Ks which

¹⁵ Because our focus was on global health spending, we also removed from the corpus any document that did not contain a character string corresponding to any diseases or conditions (based on WHO disease lists) within the risk and business sections.

¹⁶ It is possible that the topics themselves are sensitive to the number of topics that have been defined.

¹⁷ Note that this sample N is very small for a topic model, hence our results should be seen as exploratory.

mention Type 2 and 3 diseases at least as frequently as Type 1 diseases (Figure 4b) over time.¹⁸ For example, predictably we see that Type 1 only 10-Ks consistently focus more on non-communicable disease terms (NCDs) while Type 2 or 3 10-Ks are more likely to contain infectious disease topics.

In terms of potential barriers to private sector investment, we see a preponderance of topics surrounding clinical trials in Type 2 and 3 10-Ks, while for Type 1 10-Ks clinical trial topics are relatively rare, and financial topics emerge much more prominently and increase over time. Such differences may reflect differences in the regulatory pathways faced by firms researching Type 2 and 3 diseases. As noted in the manual review in this report, while procedures for regulatory approval of Type 1 diseases have been clearly established, procedures for obtaining approval of treatments for less-studied diseases are less clear, perhaps requiring that Type 2 or 3 firms allocate more space in their 10-K filings to documenting these processes. Financial and legal topics are increasing over time for both samples of 10-Ks, but among firms focused on Type 1 diseases we also see increases financial incentives such as tax rebates. But among Type 2 and 3 firms financial and legal concerns (including several topics combining legal terms and developing country geographies) are steady or increasing, while tax break topics decrease over time.

¹⁸ We focus on this sample rather than the sample of 10-Ks with any mention of Type 2 or 3 diseases to focus on the sample of 10-Ks more likely to discuss actual R&D for Type 2 or 3 diseases and less likely to include singular mentions of a Type 2 or 3 disease in a non-R&D context.

Topic	Top 5 Terms (Highest Probability)	Description	Infectious	NCD	nutrition, respiratory, gastrointestinal	women's / men's health	brain or mental	blood or auto immune	Includes "orphan"	financial / legal	Includes "tax", "rebate", "reimburse", or "medicare/medicaid"	Includes "trial"	Geography
1	-	junk									Tax		
2	candid, trial, payor, fal, orphan	mixed (legal + others)							Yes	Legal/Financial	Tax, Rebate	Yes	
3	channel, cell, ion, oxygen, sickl	vascular red blood cells		Yes				Yes		Legal/Financial	Tax		
4	shall, loan, lender, borrow, tax	legal/financial terms											
5	israel, trial, capsul, isra, professor	geography (Israel + Africa)		Yes								Yes	Israel, Africa, Nigeria, Malawi
6	-	junk			Yes					Legal		Yes	
7	sharehold, tax, ordinari, ireland, irish	financial								Financial	Tax	Yes	Ireland, Canada, Italy
8	inhibitor, relap, lymphoma, refractori, leukemia	cancer		Yes					Yes			Yes	
9	cancer, trial, tumor, cell, chemotherapi	cancer		Yes					Yes			Yes	
10	cell, stem, trial, transplant, cultur	stem cell		Yes								Yes	
11	trial, alpha, interferon, orphan, protein	mixed (health)	Yes	Yes					Yes			Yes	
12	patch, women, hormon, fertil, trial	women's health				Yes						Yes	
13	trial, liver, placebo, candid, dialysi	liver and kidney		Yes					Yes			Yes	
14	china, chine, currenc, prc, provinci	geography (China)								Financial		Yes	China
15	trial, alzheimer, sleep, placebo, receptor	mental health		Yes			Yes					Yes	
16	heart, trial, cardiovascular, muscl, candid	cardiovascular health		Yes								Yes	
17	obe, trial, placebo, diabet, sexual	obesity		Yes								Yes	
18	tax, abbott, inventori, intang, amort	legal/financial terms								Financial	Tax, Rebate		
19	antibodi, candid, trial, cell, inflammatori	arthritis/autoimmune		Yes				Yes				Yes	
20	vaccin, immun, antigen, candid, immunotherapi	vaccine	Yes									Yes	
21	-	junk											
22	trial, infect, sci, app, candid	antibiotic/injection						Yes				Yes	
23	trial, acid, placebo, bowel, diarrhea	gastrointestinal health			Yes							Yes	
24	trial, candid, migraine, inhal, pain	respiratory health			Yes							Yes	
25	devic, polym, diagnost, implant, johnson	medical implants/devices											
26	penni, broker, dealer, sharehold, quotat	financial, marijuana					Yes			Financial			Nevada
27	trial, candid, inhibitor, infect, viral	viral disease	Yes									Yes	
28	dietari, nutrit, brand, stress, vitamin	dietary supplements			Yes		Yes						
29	skin, topic, dermatolog, psoriasis, acn	dermatology		Yes								Yes	
30	brand, wholes, retail, segment, cold	cold/allergy	Yes		Yes					Financial	Rebate		
31	infect, antibiot, trial, resist, bacteria	antibiotic resistance			Yes							Yes	
32	-	junk											
33	diagnost, gene, companion, imag, genet	mixed (health)											
34	prostat, trial, cancer, testosterone, men	men's health		Yes		Yes						Yes	
35	isi, gene, protein, strand, liver	cancer		Yes									
36	pain, trial, placebo, inject, analg	pain relief										Yes	
37	prc, china, chine, enterpri, capsul	geography (China) + finance								Financial	Tax		China
38	tabl, content, trial, payor, candid	legal/financial terms								Legal/Financial		Yes	
39	trial, protein, orphan, mutat, candid	mixed (health)		Yes	Yes				Yes			Yes	
40	radiat, lung, diagnost, kit, oxid	poison gases; lung cancer?		Yes	Yes								
41	orphan, rebat, fal, payer, plasma	mixed						Yes	Yes	Financial	Tax, Rebate	Yes	
42	veterinari, pet, dog, usda, cat	veterinary health											
43	trial, inject, ocular, wet, dri	eye health		Yes								Yes	
44	diabet, insulin, gluco, trial, candid	diabetes		Yes								Yes	
45	tablet, king, pain, deterr, quota	pain relief											

Figure D4a. Topics over time, Type 1 Only 10-Ks (n=1664)

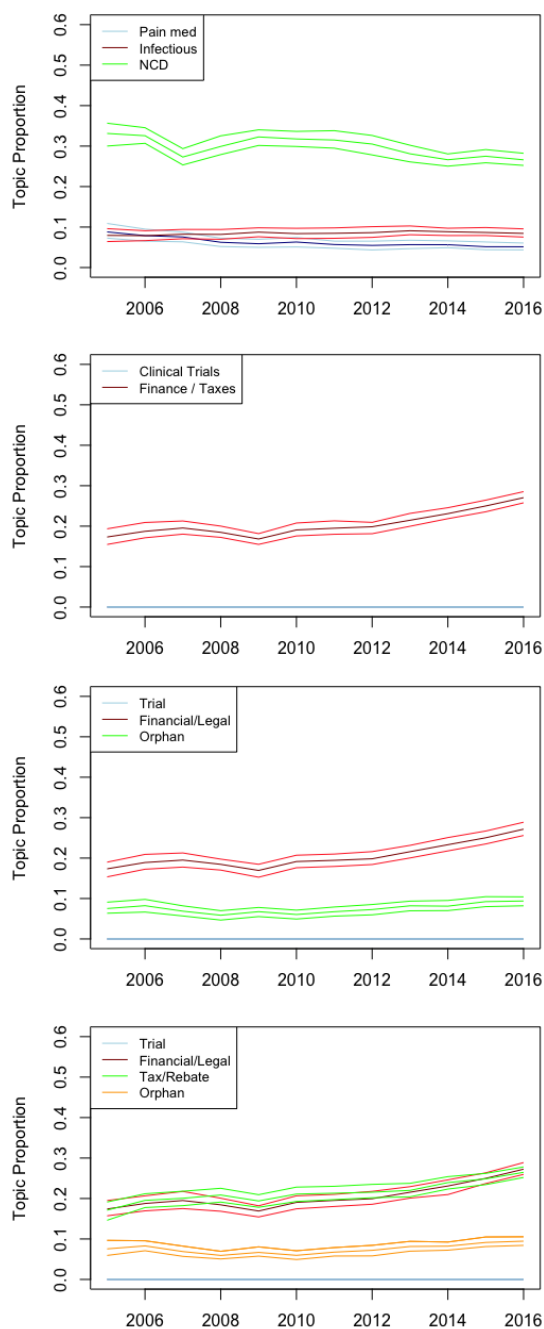
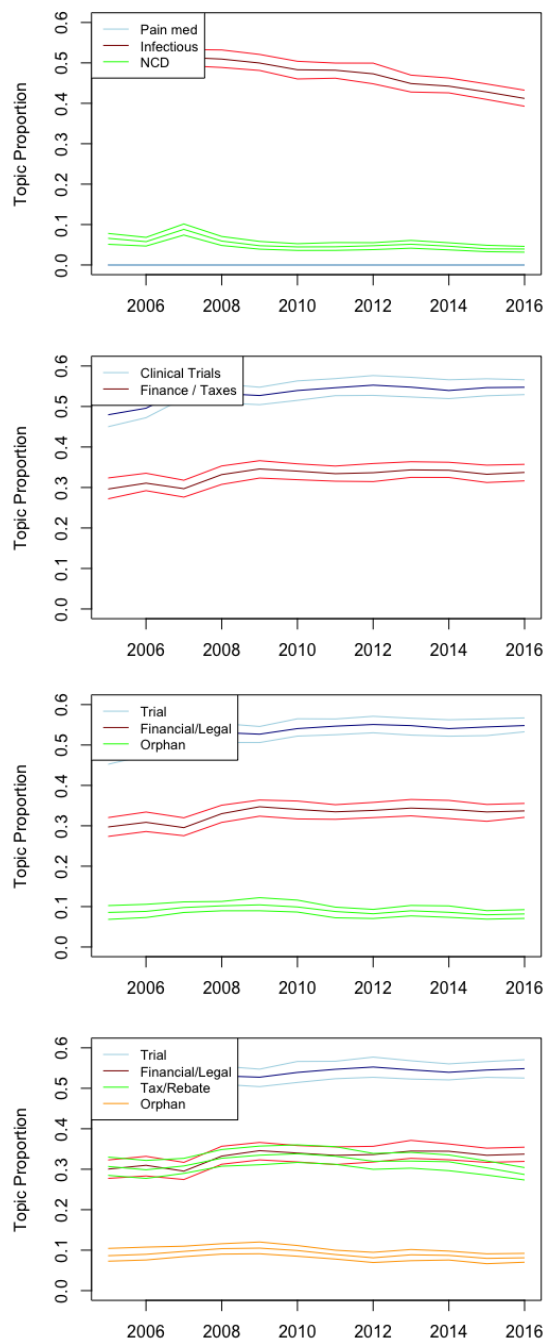


Figure D4b. Topics over time, Type 2 or 3 10-Ks (n=296)



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Appendix E. Summary of Disease-Level Findings

We recorded information for each specific disease mentioned in the 10-Ks in our sample following the same company-level review framework, with disease-specific mentions also coded positive, negative, mixed, or neutral. To be included in the disease-specific coding, the company had to mention an aspect of one hypothesis or policy incentive that pertained to that specific disease. For example, they may report the scientific certainty of progressing a hepatitis B drug candidate through all phases of research to a marketable product. Our disease-specific coding sample includes 247 Type 1 diseases, 109 Type 2 diseases, and 36 Type 3 diseases.

The tables below summarize the proportion of diseases specifically mentioned across the 10-Ks that companies specifically reference in discussion particular aspects of the five hypotheses in our review framework. In most cases, company discussions of these hypotheses is not at the disease-level, so the proportion of diseases with any mentions is low.

Table E1. Proportion of diseases mentioned specifically mentioned in company discussions of scientific uncertainty, by type of disease

Disease Type	Positive	Negative	Mixed	Neutral	No Mention
	Probability of Success				
Type 1 diseases	0.14	0.04	0.05	0.02	0.74
Type 2 diseases	0.07	0.01	0.0	0.01	0.91
Type 3 diseases	0.14	0.03	0.0	0.03	0.81
	Complexity of Research				
Type 1 diseases	0.01	0.0	0.0	0.01	0.98
Type 2 diseases	0.0	0.0	0.0	0.0	1.0
Type 3 diseases	0.0	0.0	0.0	0.0	1.0
	Access to Existing Research				
Type 1 diseases	0.06	0.0	0.0	0.06	0.87
Type 2 diseases	0.06	0.0	0.0	0.03	0.91
Type 3 diseases	0.03	0.0	0.0	0.0	0.97
	Evidence of Efficacy				
Type 1 diseases	0.19	0.02	0.06	0.04	0.68
Type 2 diseases	0.15	0.02	0.0	0.02	0.82
Type 3 diseases	0.06	0.03	0.03	0.0	0.89

Table E2. Proportion of diseases specifically mentioned in company discussions of policy and regulatory uncertainty, by type of disease

Disease Type	Positive	Negative	Mixed	Neutral	No Mention
	Policy or Regulatory Uncertainty				
Type 1 diseases	0.02	0.04	0.04	0.03	0.86
Type 2 diseases	0.02	0.02	0.01	0.0	0.95
Type 3 diseases	0.03	0.0	0.0	0.0	0.97
	Weak or Uncertain IP Rights				
Type 1 diseases	0.0	0.01	0.02	0.02	0.95
Type 2 diseases	0.0	0.01	0.0	0.0	0.99
Type 3 diseases	0.0	0.0	0.0	0.0	1.0
	Health Systems and Governance				
Type 1 diseases	0.0	0.01	0.01	0.04	0.95
Type 2 diseases	0.0	0.0	0.0	0.03	0.97
Type 3 diseases	0.0	0.0	0.0	0.06	0.94

Table E3. Proportion of diseases specifically mentioned in company discussions of market uncertainty, by type of disease

Disease Type	Positive	Negative	Mixed	Neutral	No Mention
	Competition				
Type 1 diseases	0.16	0.12	0.07	0.15	0.50
Type 2 diseases	0.08	0.04	0.06	0.12	0.70
Type 3 diseases	0.14	0.0	0.0	0.03	0.83
	Market Size (# of Potential Customers)				
Type 1 diseases	0.09	0.0	0.01	0.45	0.45
Type 2 diseases	0.12	0.01	0.02	0.20	0.65
Type 3 diseases	0.08	0.0	0.0	0.28	0.64
	Estimated Market Revenue				
Type 1 diseases	0.03	0.0	0.0	0.10	0.87
Type 2 diseases	0.06	0.06	0.01	0.04	0.83
Type 3 diseases	0.05	0.0	0.0	0.03	0.92
	National Insurance Scheme				
Type 1 diseases	.004	0.03	0.01	0.006	0.95
Type 2 diseases	0.0	0.01	0.0	0.0	0.99
Type 3 diseases	0.0	0.0	0.0	0.0	1.0

Table E4. Proportion of diseases specifically mentioned in company discussions of fixed costs or manufacturing costs, by type of disease

Disease Type	Positive	Negative	Mixed	Neutral	No Mention
	Discusses effect of capital, fixed or sunk cost on R&D investment				
Type 1 diseases	0.03	0	0.004	0.01	0.956
Type 2 diseases	0.01	0	0	0	0.99
Type 3 diseases	0	0	0.03	0	0.97
	Investments in Own Manufacturing Infrastructure				
Type 1 diseases	0.035	0.01	0.01	0.035	0.91
Type 2 diseases	0	0.01	0	0.06	0.93
Type 3 diseases	0	0	0	0.08	0.92

Table E5. Proportion of diseases specifically mentioned in company discussions of imperfect markets, by type of disease

Disease Type	Positive	Negative	Mixed	Neutral	No Mention
	Patents				
Type 1 diseases	0.0	0.0	0.0	0.02	0.98
Type 2 diseases	0.0	0.0	0.01	0.05	0.94
Type 3 diseases	0.0	0.0	0.03	0.0	0.97
	Other Intellectual property				
Type 1 diseases	0.0	0.0	0.01	0.04	0.95
Type 2 diseases	0.0	1.0	0.01	0.09	0.90
Type 3 diseases	0.0	0.0	0.03	0.03	0.94
	Licensing agreements				
Type 1 diseases	0.056	0.004	0.024	0.174	0.741
Type 2 diseases	0.12	0.01	0.02	0.17	0.68
Type 3 diseases	0.03	0.0	0.03	0.08	0.86

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