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Ophthalmic Start-Up Chief Executive Officers' Perceptions of Development Hurdles

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Abstract
Purpose: To identify current challenges facing ophthalmic pharmaceutical start-ups in developing new products. ***Methods:*** Surveys were distributed to the chief executive officer (CEO) or president of ophthalmic start-ups. ***Results:*** The survey attracted 24 responses from 78 surveys distributed (31%). The CEOs stated that a lack of financial capital (n = 18, 75%), FDA regulations (n = 6, 25%), and failure to meet clinical endpoints (n = 6, 25%) were their greatest development hurdles. Risk aversion to medicines in early development (n = 18, 75%), mergers and acquisitions reducing corporate choice for licensing agreements (n = 7, 29%), the emergence of large pharmaceutical-based venture capital funding groups (n = 12, 50%), and the failure of many large pharmaceutical companies to develop their own medicines (n = 10, 42%) were noted as recent prominent trends affecting fundraising. ***Conclusion:*** The study suggests that development funding, regulatory burden, and meeting clinical endpoints are the greatest development challenges faced by ophthalmic start-up CEOs.

Introduction

Pharmaceutical drug development is a long, expensive, and risky endeavor. It typically takes 10–12 years for development, usually without a stable revenue stream, to obtain approval for a new systemic medicine at a cost as high as USD 2.5 billion [1–4]. The average cost of clinical trials across all therapeutic areas in the US was around USD 30–40 million before approval (Phase 1–3) and roughly an equivalent amount after approval (Phase 4) [5]. These costs increase by a few million every year. The US Department of Health and Human Services reported ophthalmology as having an overall average per-study cost of USD 50 million (Phase 1–3) [5].

Unfortunately, products developed to the point of human testing hold <12% chance of obtaining Food and Drug Administration (FDA) approval [1–4]. A recent study also found the likelihood of approval from Phase I is 17% in the field of ophthalmology [6].

In a recent survey of ophthalmic start-up chief executive officers (CEOs), we provided initial findings that financing and regulatory burdens most often represent the greatest obstacle for ophthalmic endeavors [7]. The purpose of this survey was to identify current challenges facing ophthalmic pharmaceutical start-ups in developing new products and to explore specifically challenges related to financing product development.

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Methods

We used an existing internal, proprietary database of small (less than 50 employees) ophthalmic pharmaceutical start-up companies currently in operation (60 US based and 18 non-US). The database was created from all small ophthalmic pharmaceutical companies found on web-based searches. The survey was sent to each CEO of companies in the database up to 3 times within a 6-week period between December 2015 and January 2016. Survey questions were developed internally by one of the authors (see Appendix), and the survey was linked through SurveyMonkey (https://www.surveymonkey.com/).

Results

There were 24 responses to the 78 survey invitations distributed (31%).

Current Development Obstacles

CEOs stated the most difficult part of their job was raising capital (n = 18, 75%), which was usually most problematic in the mid-range development period between actual start-up and venture capital (VC) funding (n = 17, 71%). The greatest source of funding was from VC firms (n = 6, 25%) and grants (n = 6, 25%), but a wide variety of financial sources were used, including friends and family, angel and individual investors, licensing deals, initial public offering (IPO), and product revenue. CEOs also mentioned that the time required to fundraise was a problem by distracting from other development tasks (n = 8, 33%).

CEOs thought that maintaining a wide network of contacts (n = 11, 50%) and an undefeatable spirit (n = 11, 50%) were most important for successful fundraising. Further, CEOs noted that the difficulty in raising funds, compared to a few years ago, had not improved (n = 15, 63%).

FDA regulations were viewed as the second greatest burden by CEOs (n = 6, 25%). Specifically, they mentioned the time and cost to meet regulatory requirements (n = 11, 46%) and the difficulty in obtaining access to agency personnel (n = 7, 29%) as key obstacles to development. CEOs also noted the problem of meeting relevant research endpoints to prove clinical value as a frequent development issue (n = 6, 25%).

Fundraising Trends

CEOs indicated that the most important recent trends in raising capital were the risk aversion to medicines in early development (n = 18, 75%) and the reduction in corporate choice when seeking a license agreement due to recent mergers and acquisitions (n = 7, 29%). However, CEOs also believed that the emergence of large pharmaceutical-based VC funding groups (n = 12, 50%) and the failure of many large pharmaceutical companies to develop their own medicines (n = 10, 42%) were recent important developments.

Discussion

Consistent with our prior survey, obtaining funding remains the greatest concern for start-up CEOs [7]. The problem of financing was evidenced further by the wide variety of funding sources used by start-ups.

The most difficult aspect of fundraising was reported as the time between the friends and family round and later rounds when capital venture funds become interested. This middle time is typically in the late preclinical or early clinical phases when initial funding is depleted but there is not yet enough clinical data to attract larger institutional investors. The "gap" time in fundraising may have been worsened in recent years by the greater risk aversion from large institutions noted in the survey. Additionally, the greater number of mergers and acquisitions and increased risk aversion to projects in early development, also cited in the survey, may have limited the licensing choices of start-ups.

Consistent with the above findings, CEOs thought the most important characteristics they needed for start-up was an undefeatable spirit to market their product, as well as a wide network of contacts. Unfortunately, despite the slowly improving economy from the depths of the Great Recession, most CEOs thought that fundraising had not become easier.

The business model of start-ups generally is difficult, as evidenced by their high failure rate [8, 9]. However, typically, the model is even worse in pharmaceuticals because early products can rarely be developed to provide a revenue stream, and often 7–10 years are required before income can be realized to stabilize the company financially [10].

Further, consistent with our prior survey, CEOs noted regulatory demands, mixed with difficulty accessing agency personnel, as difficult aspects of running a start-up. These findings may contrast, however, with the FDA's ophthalmic division's reputation of generally being helpful to start-ups in their product development (author observation, W.C.S.). The FDA's vital charge to assure the safety and efficacy of new products must be considered along with the CEOs' concerns. Nonetheless, issues surrounding the difficulty and expense of regulations appear to be a real concern for CEOs. An area of future research may be to assess the cost-effectiveness of agency regulations.

CEOs also were burdened by the effort needed to meet clinical endpoints to prove efficacy. This may have both a scientific and a regulatory basis. Obviously, the start-up needs to develop a product which is clinically effective. Further, endpoints and measures for the intended clinical indication must be approved by the agency.

In contrast, CEOs may be assisted by the recent difficulty of large pharmaceutical companies to develop their own products internally and their pivot to start-ups to acquire novel new medicines. Further, some large pharmaceutical companies have developed their own in-house funding units, functioning much like VCs, which provide additional funding choices to the start-up [11].

The start-up community within ophthalmology is a vital resource in providing sight-saving medicines. Start-up personnel often toil long years in Spartan environments, frequently without pay, to develop new medications. The ophthalmic community should be aware of their efforts and find new ways to support their work in bringing new medicines to market.

The study suggests that development funding, regulatory burden, and meeting clinical endpoints are the most pressing issues for start-up CEOs within ophthalmology. However, because of the incomplete participation of contacted CEOs in the survey more research is needed to confirm these results and to further describe the needs of ophthalmic pharmaceutical start-ups.

Disclosure Statement

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Appendix

Survey

The goal of this survey is to explore the current issues facing start-ups and the challenges of bringing new pharmaceuticals to market. The results are intended to be used for an ARVO symposium in 2016 and for publication in a scientific journal. Please do not identify yourself in any way on this survey.

Background questions

1. Therapeutic area of lead product:
- ○ AMD – wet
- ○ AMD – dry
- ○ Glaucoma
- ○ Dry eye
- ○ Anti-infective
- ○ Other (please specify)

2. Current status of lead product under development:
- ○ API discovery/characterization
- ○ Pre-clinical non-GMP research
- ○ GLP toxicology and/or IND preparation
- ○ Clinical POC/ Phase I/II research
- ○ Clinical Phase III research
- ○ Exit (e.g. product license/sale, IPO, company sale)
- ○ Other (please specify)

3. How long have you been CEO?
- ○ <1 year
- ○ 1–5 years
- ○ 6–10 years
- ○ >10 years

4. How many employees does the company have apart from the CEO?
- ○ 0
- ○ 1–5
- ○ 6–20
- ○ 21–50
- ○ 51–100
- ○ >100

5. How many years has the start-up been in business?
- ○ <1 year
- ○ 2–5 years
- ○ 6–10 years
- ○ 11–20 years
- ○ >20 years

6. Location of headquarters:
- ○ Northeast US
- ○ Southeast US
- ○ Midwest US
- ○ Southwest US
- ○ Mountain West US
- ○ Coastal West US
- ○ Western Europe
- ○ Other (please specify)

7. What is your current primary source of funding?
- ○ Friends and family
- ○ Grants
- ○ Angel investors or groups
- ○ One to several high net worth investors or institutions
- ○ Venture capital firm(s)
- ○ Big pharma through a license deal
- ○ Other (please specify)

Questions

For each question please choose the three most important answers.

8. What most threatens your company?
- ☐ Lack of financial capital
- ☐ Lack of quality employees/contractors
- ☐ The burden of the government regulatory system
- ☐ Lack of comparable vision between the company's principals and equity partners
- ☐ Uncooperative or unhelpful board of directors
- ☐ Lack of scientific model/measure/endpoints to prove product's clinical value
- ☐ Difficulty of obtaining proof of product's clinical value
- ☐ Manufacturing issues
- ☐ None
- ☐ Other (please specify)

9. What is most difficult about raising funds?
- ☐ Finding initial funding from friends and family
- ☐ Obtaining funds in the mid-stage development period before big pharma or private equity is interested
- ☐ High rejection rate among private investors, angel groups and venture capitalists
- ☐ The time to write, and rejection rate of, grants
- ☐ Lack of sufficient funding sources
- ☐ Time required to raise funds which distracts from product development
- ☐ Nothing
- ☐ Other (please specify)

10. What are your greatest difficulties in dealing with the regulatory agency?
- ☐ Time and expense of the regulatory burden to show safety and efficacy
- ☐ Unclear guidance and regulations
- ☐ Lack of clear guidance for our product class
- ☐ Inconsistent adherence of the agency to their own instructions
- ☐ Access to agency personnel
- ☐ None
- ☐ Other (please specify)

11. What is most difficult about working with equity partners/investors?
- ☐ The lack of understanding of ophthalmology
- ☐ The lack of understanding of science
- ☐ Unreasonable demands on the management process
- ☐ Unreasonable financial demands
- ☐ Extent of control over the board
- ☐ Decision making over development and licensing
- ☐ Conflict of interest
- ☐ None
- ☐ Other (please specify)

12. What is most vital to financing a pharmaceutical start-up?
- ☐ Solid friends and family round of funding
- ☐ Always seek investments at all funding rounds simultaneously
- ☐ Consider alternative funding sources (e.g., grants, foundations)
- ☐ Develop a wide network of contacts
- ☐ Maintain an undefeatable positive attitude and belief in your product
- ☐ Know your product
- ☐ Other (please specify)

13. What is most important to establishing a successful pharmaceutical start-up?
- ☐ Virtual company structure/affordable office location and staff to limit costs
- ☐ Knowledgeable personnel who can work as a team
- ☐ Solid financial base
- ☐ Cost and time efficient clinical indication and regulatory pathway
- ☐ Solid market research
- ☐ Good scientific and clinical story for your product
- ☐ Other (please specify)

14. Is raising funds easier or more difficult than 5 years ago (choose one best answer)?
- ☐ Much easier
- ☐ Somewhat easier
- ☐ No change
- ☐ Somewhat harder
- ☐ Much harder
- ☐ Do not know
- ☐ Other (please specify)

15. What are corporate trends most influencing fundraising?
- ☐ Risk aversion from major pharma and VCs withdrawing to later stage funding
- ☐ Risk aversion of small investors and/or angel groups
- ☐ Political and economic environments unsupportive to entrepreneurial initiatives
- ☐ Large number start-ups competing for funds
- ☐ Mergers and acquisitions reducing corporate choice for start-ups for licensing
- ☐ More supportive investment community in recent years
- ☐ Reduced R and D spending in big pharma increasing licensing opportunities for start-ups
- ☐ Other (please specify)

16. What new structures do you perceive as most helpful to support development?

- ☐ Project financing (private equity purchases IP and hires start-up to develop it)
- ☐ Corporate based capital venture departments
- ☐ Acquisition by earn out (small upfront payments with subsequent milestones)
- ☐ Revenue interest financing (trading future royalties for cash infusion)
- ☐ None
- ☐ Other (please specify)

17. What changes in the industry are most impacting development?

- ☐ Mergers and acquisitions reducing R and D resources
- ☐ Big pharma failure to develop new products with subsequent reduced R and D spending enhancing the need for start-ups and new IP
- ☐ Global threats of political instability and poor economy
- ☐ Globalization due to more competitive tax structure and personnel costs over seas
- ☐ Profitability threats to big pharma due to patent expirations and reduced pipelines
- ☐ Increased use of outsourcing. (e.g., clinical and manufacturing CROs)
- ☐ Eye care market continuing to expand driving development
- ☐ None
- ☐ Other (please specify)

References

1 PhRMA: Biopharmaceutical Research and Development: The Process behind New Medicines. 2015. http://www.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf.

2 Baines W: Failure Rates in Drug Discovery and Development: Will We Ever Get Any Better? Drug Discovery World. 2004. www.ddw-online.com/media/32/2454/04.fal.failure-rates-in-drug-discovery-and-development:-will-we-ever-get-any-better.

3 Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J: Clinical development success rates for investigational drugs. Nat Biotechnol 2014;32:40–51.

4 Smietana K, Siatkowski M, Møller M: Trends in clinical success rates. Nat Rev Drug Discov 2016;15:379–380.

5 US Department of Health and Human Services: Examination of Clinical Trial Costs and Barriers for Drug Development. 2014. https://aspe.hhs.gov/report/examination-clinical-trial-costs-and-barriers-drug-development.

6 Biotechnology Innovation Organization: Clinical Development Success Rates 2006–2015. 2016. https://www.bio.org/sites/default/files/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf.

7 Stewart WC, Stewart JA, Kruft B, Nelson LA: Challenges facing ophthalmic start-up companies in developing new devices or medicines. Acta Ophthalmol 2013;91:e81–e83.

8 Ledford H: Biotechnology: the start-up engine. Nature 2013;501:476–478.

9 Statistic Brain: Startup Business Failure Rate by Industry. 2016. http://www.statisticbrain.com/start-up-failure-by-industry/.

10 Skok D: Five Reasons Startups Fail. *for*Entrepreneurs. 2010. http://www.forentrepreneurs.com/why-start-ups-fail/.

11 McKinsey & Company: New Frontiers in Pharma R&D Investment. 2010. http://www.mckinsey.com/insights/health_systems_and_services/new_frontiers_in_pharma_r_and_38d_investment.