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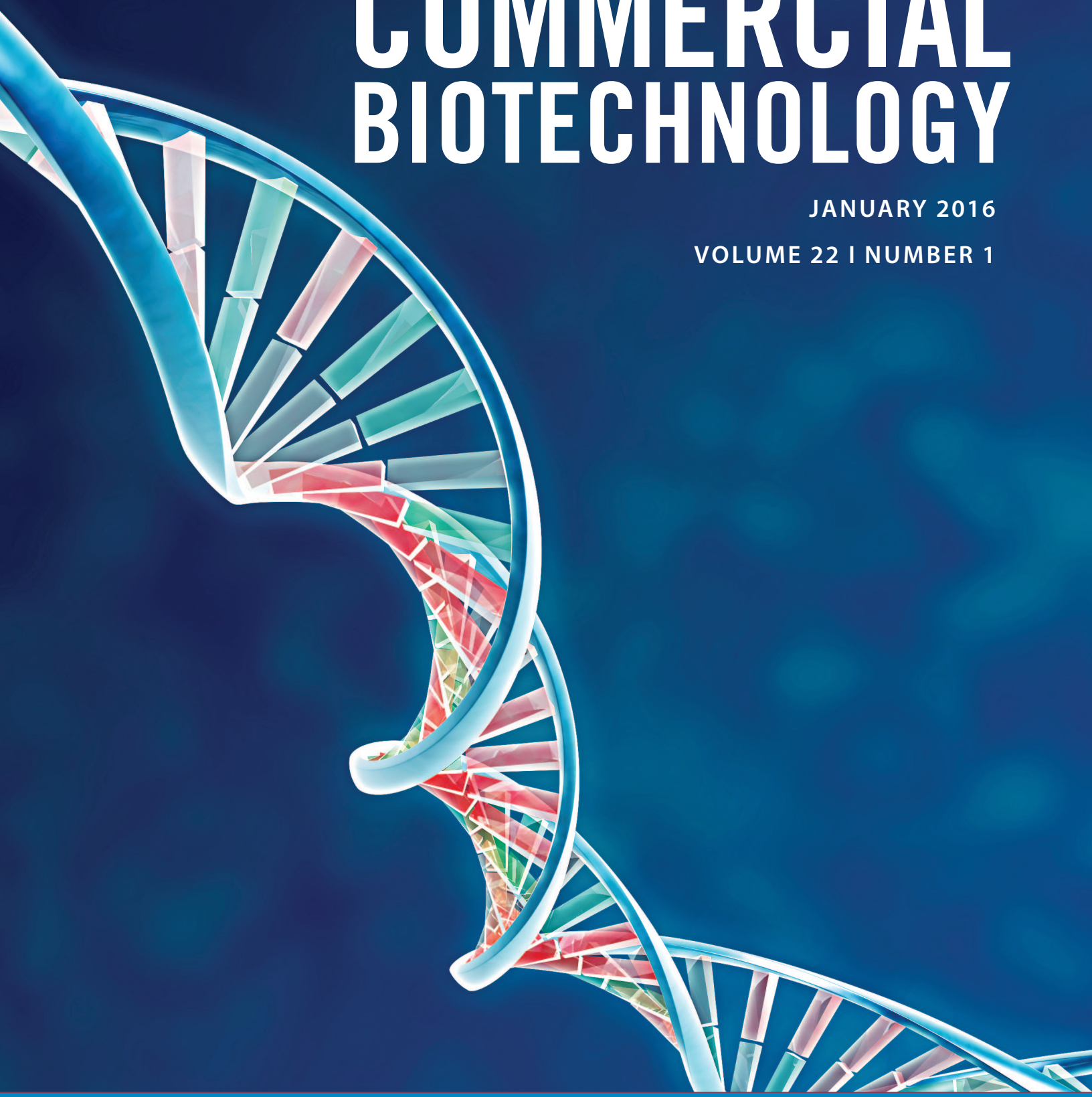

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Commentary

An Impediment to Personalized Medicine Commercialization is the Lack of Understanding of the Value of the Testing

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ABSTRACT

Over the past 20 years there have been tremendous advancements in technology in areas such as imaging, medicinal chemistry, data integration, the digitization of medical records, computing power and yet the medical delivery model is largely unchanged. The healthcare community now has a treasure chest of new tools that should permit it to be much more proactive, effective and thus produce improved outcomes at lower costs. Personalized medicine (PM), also called Precision Medicine by some, is the category in which all of these new tools can be grouped. While there are a myriad of reasons such as legacy infrastructure, lack of incentives, costs of adopting new technologies, one of the major reasons, is the lack of understanding of the value of such testing by payers. Moving to a value based pricing model for diagnostic testing will increase adoption rate of PM, raise reimbursement rates for PM testing and improve quality of care at a lower cost for patients. The end result of this will be tests that have a demonstrated benefit in PM business models and result in the acceleration of commercialization.

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Keywords: personalized medicine; molecular diagnostics; regulation; commercialization

The world population in the 20th Century has grown from 1.65 B to 6 B people and the costs of healthcare in 2010 are estimated to be more than $6.5 [1]Trillion dollars and growing at a rate of ~5% through 2018[2]. The need for a more effective medical model has never been more paramount. Over the past 20 years there have been tremendous technology advancements in areas such as imaging, medicinal chemistry, data integration, digitization of medical records, computing power and yet the medical delivery model has largely been unchanged. It is as if the system has continually added more tools to its quiver, but continues to "hunt" in the exact same manner. The healthcare community now has a treasure chest of new tools that should permit it to be much more proactive, effective and thus produce improved outcomes at lower costs.

Personalized medicine (PM), also called Precision Medicine by some, is the category in which all of these new tools can be grouped. PM is a medical model where healthcare is customized to the needs of the individual patient and leverages genomic and cellular tools to diagnose patients and then design the optimal therapeutic intervention. This PM healthcare paradigm, when implemented should serve to diagnose patients earlier, monitor disease progression and to get the right treatment to the right patient in the right amount and at the right time. This will help to bend the healthcare cost curve, improve patient outcomes and also improve access to care for more individuals.

With all the great benefits of PM and the grave challenges facing the global healthcare system why, we must ask, is PM not the new standard practice in today's

1 Source: World Health Organization Factsheet No 319.
2 Source: 2015 Global life sciences outlook Adapting in an era of transformation.

healthcare realm? While there are a myriad of reasons such as legacy infrastructure, lack of incentives, costs of adopting new technologies, one of the major reasons, is the *lack of understanding of the value of such testing by payers*. Addressing this one area will accelerate the adoption of PM.

Traditionally healthcare has existed on a reimbursement model of fee for service (FFS) that compensates based on the volume of procedures. This has led to an ever increasing rise in healthcare costs that is contrary to population growth rates over the same period and the long term decreasing population growth rate in the USA.

The FFS model created an incentive for companies to offer more medical services and for physicians to adopt as many procedures as medically justifiable, since their compensation was directly related to the volume of services rendered (see figure 2). The increase in costs is further exacerbated by the loopholes used to accelerate diagnostic test approval as well as no requirement for demonstrating medical utility. The laboratory developed test (LDT) market has turned into a "free-for-all" where commercial entities can bring tests to market, without anyone monitoring the validity of the testing.

Moving to a value based pricing model for diagnostic testing will have the following benefits:

(1) Increase adoption rate of PM
(2) Increase reimbursement rates for PM testing
(3) Increase the quality of care with an overall lower cost for patients

Payers want to know that the fees they spend on PM testing will help them to provide quantifiably better services to their customers. So the question becomes how the PM industry can move to a value based pricing system.

First the industry must move from self-regulation and a lack of transparency to a model where outcome data is presented for public evaluation. Transparency has never been an aspect of diagnostic testing because the market is characterized by a high level of competition and the difficulty of protecting intellectual property rights. Even with patents, there are a variety of manners to workaround IP and homebrew testing lets customers design their own tests. This environment has led vendors to value privacy as the manner to protect intellectual rights. This has the opposite effect of limiting the adoption of PM because payers and clinicians have had to make decisions on new technologies without having enough data to truly understand the value. Transparency should be a point of differentiation for the testing industry as many who cannot substantiate their claims with data will not be able to compete. Also, the external regulation of the clinical utility of assays will remove internal

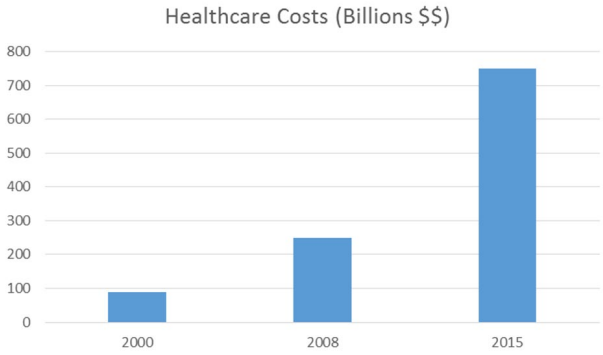

Figure 1: Rise in USA healthcare costs associated with diagnosis

bias and instill confidence in results by payers, clinicians and patients.

Second, the industry must provide more blinded prospective clinical studies. Value for PM tests ultimately has to be proven by demonstrating a clear improvement in disease management. This aspect of PM for diagnostic testing is notoriously difficult, due to the lack of adequate samples and access to clinical outcome data, usually owned by hospitals or drug firms. To achieve this end, testing vendors need to form partnerships with the owners of the outcome data and patient samples. It is beneficial to the entire PM industry to have these partnerships created. A logical means of accomplishing this is through consortia, where all members can jointly work for large scale studies with access to patient samples and outcome data. The end result of this will be tests that have a demonstrated benefit in PM business models and result in the acceleration of commercialization.

Lastly, vendors in the PM space need to present financial models that show the value of implementation of their tests. Payers currently compare new tests to similar methodologies and then establish a payment schedule based on an incremental percentage above the costs of running the tests. In a value based pricing model testing vendors need to demonstrate the costs savings of disease management with and without testing. This is the best manner to establish a value price for tests. This means that vendors need to demonstrate clinical validity data as opposed to traditional analytical validity data. The pharmaceutical and medical device industries have historically provided clinical utility through clinical trial data and for PM to realize its true potential testing vendors need to do the same. This will require vendors to hire personnel that can provide financial models to prove this value to payers and in a format that they are used to seeing.

Personalized medicine has a tremendous potential to improve disease management and lower healthcare costs. The challenge for commercialization is to change key aspects, which are limiting PM adoption, in order

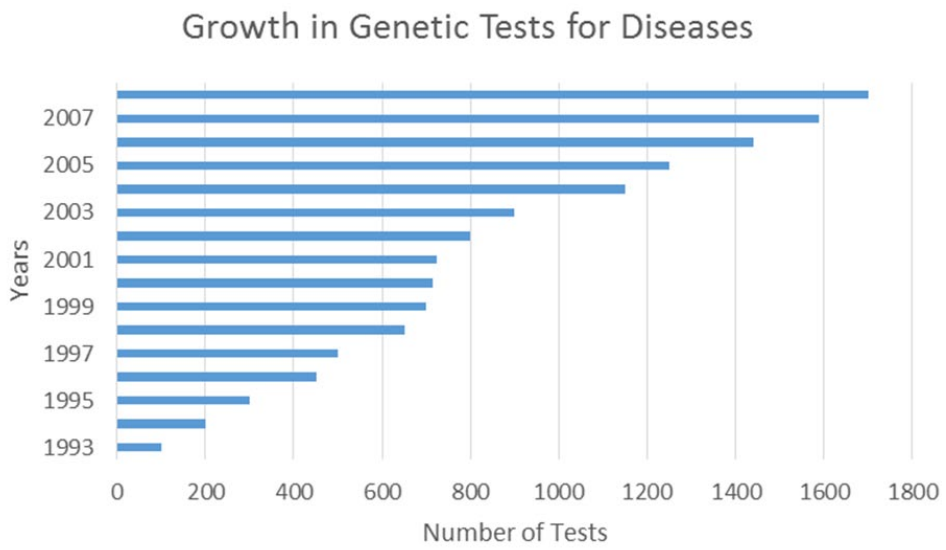

Figure 2: Growth of genetic testing, including both clinical and research testing.
Source: Hudson, K. et al. Oversight of US genetic testing laboratories. Nature Biotechnology **24,** *1084 (2006)..*

to realize the potential. The recommendations of this article are not easy to adopt as they represent a paradigm shift for the industry. However, with the increasing levels of scrutiny and relentless downward pricing pressure for the testing industry, a paradigm shift is what is required at this point, if for nothing else than to save the industry. Change is coming whether incumbents like it or not so it would be wise to get ahead f the curve and institute these changes now for the sake of the patient, healthcare costs and to bring about the reality of Personalized Medicine.

Article

Biopharmaceutical Startup's Need of Regulatory Intelligence

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ABSTRACT

Drug development and approval is a risky process. To assess the importance of the regulatory part, especially for startup's or not yet established companies, we performed a survey amongst European venture capital investors. We asked: how do regulatory issues in biopharmaceutical development impact young companies' progress and their financing? In addition to the survey an intensive literature research and analysis on drug failures and refusals was undertaken. Overall the expectations of responding venture capital investors were very congruent to those of regulators.

Regulatory issues are an important part of the risk/value evaluation and therefore investment decision. As conclusion, developing companies looking for first and follow on financing should prepare to have a regulatory strategy available and to implement regulatory know-how early in development.

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Keywords: drug development, regulatory, approval, venture capital, investor, startup

Drug development is a business with a high risk of failure. The limited predictability of drug effects in the highly complex human body is one reason. The other and better to control contributing factor is around "doing the things right" and "doing the right thing". Companies and their investors are facing and have to manage these risks.

Regulatory intelligence may build the bridge between the scientific excellence ("doing the things right") and the requirements to proceed successfully on the development path ("doing the right thing"). Failing this exercise could lead to setbacks for both the sponsor and their investors as the following example shows:

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Mid of November 2015, Clovis Oncology, a US based biopharmaceutical company focused on acquiring, developing and commercializing cancer drugs, experienced a harsh 72% plunge in the value of their shares, erasing nearly 3 billion US$ in its market cap in minutes. What happened?

The company announced that the US Food and Drug Administration (FDA) asked for more clinical data on lung-cancer treatment rociletinib. The problem for Clovis is that the agency would like to focus solely on confirmed responses. But the rolling New Drug Application (NDA) submission to the FDA (dated on July 1st 2015) contained interim results with immature data sets based on both unconfirmed and confirmed response rates. Nevertheless, mid of July the company was able to sell new stocks to the public worth more than 300 million US$. The interim data were also presented publicly and at medical meetings. This led to a 20 percent

increase of the share price in September and October 2015. Then Clovis submitted the 90 day efficacy update to the agency which revealed that the number of patients with an unconfirmed response who converted to a confirmed response was lower than expected. Shortly after the crash a US law firm filed a securities class action lawsuit on behalf of shareholders of Clovis Oncology. Since, a FDA briefing document for an upcoming advisory meeting questioned efficacy of rociletinib when compared to AstraZeneca's lung cancer drug Tagrisso (32% vs. 59% overall response rate), which was approved last year. In addition serious safety issues were raised associated with the drug will require a "black box" warning to patients.

What can be done to minimize the need for re-work and related drops in market capitalization?

- 1st: Analyze and learn from failures,
- 2nd: Listen to the investors

1ST: ANALYZE AND LEARN FROM FAILURES

There are some publications where the authors have analyzed – partly in considerable detail – the reasons for refusals of new drug applications (NDAs), either by the US Food and Drug Administration (FDA)[1,2] or the European Medicines Agency (EMA).[3-6]

The most comprehensive analysis was done by FDA employees Sacks et al.[1] (2014), who examined 302 CDER drug applications first submitted to the FDA for new molecular entities (NMEs) between 2000 and 2012. The objective was to identify the reasons why FDA marketing approval was delayed or denied. Wang et al.[2] (2013) only covered the period from 2007 to 2009 and reviewed 52 NDAs and Biologics License Applications (BLAs) evaluated by FDA advisory committees.

Regarding the European situation, there are three less detailed studies available: Tafuri et al.[3] (2012) focused on years 2003 to 2010 and looked at 86 refused or withdrawn drug applications, Regnstrom et al.[4] (2010) with a focus on years 2004 to 2007 evaluated 188 Market Authorisation Applications (MAAs) and Eichler et al.[5] (2010) focused only on 2009 and analyzed 48 MAAs for new active substances (NASs).

The most interesting results were as follows:

FDA REFUSALS

Out of the 302 FDA NDAs in the 13 years from 2000 onwards, Sacks et al.[1] identified 151 each (50%) as approved and not approved in 1st-cycle review. After re-submission, ultimately 222 (74%) NMEs got approval. Of the 222, 71 applications required one or more resubmissions before approval, with a median delay to approval of 435 days following the first unsuccessful submission[2]. This means that 80, or one quarter of the original applications have never reached a marketing authorization, i.e. six per year compared to 17 successful ones per year.

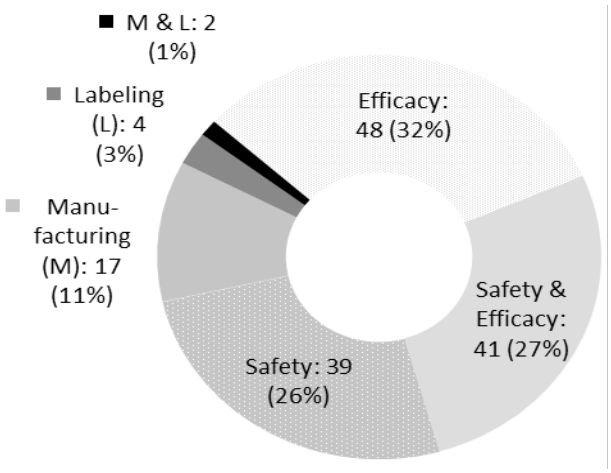

Figure 1: Reasons for FDA NDA refusals (n=151)

Figure 1 shows reasons for the 151 refusals. The highest portion (32%) was solely due to efficacy issues, followed by combined efficacy and safety matters (27%). Purely safety concerns contributed another major share (26%). All three topics total 85% and thus represented the major hurdles before final approval. What is interesting is the breakdown of efficacy issues. Sacks et al.[1] listed the following deficiencies in the demonstration of efficacy during 1st-cycle review:

- Population
  - Population not appropriate to reflect intended use
  - Size of population too small to demonstrate efficacy
- Intervention
  - Uncertainty / disagreement about appro-priate dose
  - Inability to define noninferiority margin
  - Confounding by concomitant medication
- Endpoint
  - Unsatisfactory endpoint
- Study conduct
  - Missing data
  - Data integrity

- Study outcome
  - Inconsistent results for multiple end points
  - Inconsistent results in different trials or at different study sites
  - Inadequate efficacy compared with standard of care

Safety issues were differentiated into:

- Studies not done or inadequate
  - QT prolongation studies
  - CYP enzyme studies
  - Carcinogenicity studies
  - Reproductive toxicology studies
  - Potential risks based on animal toxicology
  - Theoretical risks related to drug mechanism of action, structure, or class
- Potential risks to untested study populations
  - Population too small to characterize drug safety
  - Safety population inadequate for proposed dose / duration of therapy
  - Population inadequate to address safety in patients with renal / hepatic impairment
  - Dose selection

The authors demonstrated that of the unsuccessful first-time applications (151),

- 24 (16%) showed uncertainties about appropriate dose,
- 20 (13%) chose unsatisfactory (clinically meaningful) study end points,
- 20 (13%) reported inconsistent results when different end points were tested,
- 17 (11%) stated inconsistent results when different trials or sites were compared, and
- 20 (13%) revealed poor efficacy when compared with the standard of care.

Amongst the compounds which have never been approved these issues still were those with the highest share. Sacks et al.[1] concluded: "Several potentially preventable deficiencies, including failure to select optimal drug doses and suitable study end points, accounted for significant delays in the approval of new drugs."

EMA REFUSALS

The most comprehensive analysis on EMA withdrawn and refused applications stems from Tafuri et al.[3] (2012). They retrieved and evaluated European public assessment reports (EPARs) on withdrawals and refusals of all initial authorization applications published between 2003 and 2010. A total of 86 drug applications could be identified as a withdrawal (70 out of 86) or a refusal (16 out of 86). Major objections (156) were related to one or more of the three assessment criteria, i.e. efficacy (106/156, 68%), safety (27/156, 17%) and quality (23/156, 22%). Within the scope of major efficacy objections, five main categories were identified:

- Lack of clinical relevance (44/106, 42%)
- Methodological deficiencies (23/106, 22%)
- Pharmacokinetic (PK) issues, including bioequivalence (20/106, 19%)
- Lack of statistical significance (13/106, 12%)
- Major Good Clinical Practice (GCP) issues (5/106, 5%)

Nearly one quarter of the major objections were due to methodological deficiencies. This concern was also expressed by Eichler et al.[5] (2010) who investigated new drug approval success rate in Europe in 2009. The lead author, Senior Medical Officer at the EMA, articulated: "Was a negative outcome the result of a failed drug, or of a failed drug development plan? Retrospective analysis of this question involves subjective judgement, but inspection of assessment reports for negative MAAs support the possibility that, in many instances, the regulators' conclusion was not one of a clearly negative benefit–risk profile (a failed drug) but of inadequate demonstration of efficacy and/or safety (a failed development strategy or immature application). … We speculate that a substantial fraction of the NASs … might have fared better with a different development plan."

In this regard it is interesting to look if success / attrition rates are correlated to scientific advice status. Scientific advice is given by the EMA to make sure that companies perform appropriate tests and studies, so that no major objections regarding the design of the tests are likely to be raised during evaluation of the MAA.

In their analysis of MAAs from 2004 to 2007 Regnstrom et al.[4] (2010) proved that 59 of 188 MAA (31%) obtained scientific advice (SA) although obtaining SA per se was not associated with positive outcome. However, compliance mattered: of 59 MAA with SA, 39 (66%) were compliant; of these 38 (97%) got approval, whereas only 6 out of 20 (30%) non-compliant MAA got approval. In addition they found out that larger companies request SA more often than small or medium sized firms. The authors pointed out that "interaction between regulators and drug developers is important to avoid unnecessary use of resources during the most costly

phase of drug development. There is evidence that a good line of communication between sponsors and regulators throughout the drug developmental process may increase the chance of market access".

They finally concluded: "The strong association between company size and outcome suggests that resources and experience in drug development and obtaining regulatory approval are critical factors for a successful MAA. In addition, obtaining and complying with SA appears to be a predictor of outcome. Based on this analysis, companies, particularly smaller ones and those developing orphan drugs, are recommended to engage early and at major transition points in a dialogue with European regulators via the SA procedure."

Eichler et al.[5] added: "Drug research and development-to-market are different tasks that require different skill sets; excellence in the former does not necessarily predict success in the latter."

Instructive findings were also presented by individuals of the German regulatory agency Paul-Ehrlich-Institute (PEI). Schneider and Schäffner-Dallmann[6] (2008) investigated typical pitfalls in applications for marketing authorization of biotechnological products in Europe. They stated: "An interdisciplinary bridging of information from quality, non-clinical and clinical development should be used from early in the process, both for product development by applicants and for assessment by regulators. This, in combination with increased communication with regulators, a deliberated

PEI: Main critical findings in the CMC part of failed MAAs[6]

Below are some of the most critical findings in the review of chemistry, manufacturing and controls (CMC) data of unapproved marketing authorization applications (MAAs).

Development of the medicinal product. Incomplete information on:

- Characterization of the expression construct and genomic DNA.
- Data to show consistency of the manufacturing process.
- Development of the formulation of the drug product.
- Validation of the capacity of the manufacturing process to eliminate infectious agents.
- Data on auxiliary substances or equipment used in manufacture.
- Real-time stability data.

Quality control. Inadequate assay formats and incomplete assay validation.

Characterization. Incomplete information on:

- Characterization of the molecule.
- Definition of microheterogeneities and their biological properties, and/or their batch-to-batch consistency.
- Knowledge on the activity of different isoforms and their link to batches used in the clinical trial.
- Presence of aggregates or unacceptably high levels of impurities such as host-cell-derived proteins.

Comparability data for major changes. Comparability data for the manufacturing process, especially for late-stage changes, were inadequate.

Design of non-clinical studies. Designs of non-clinical studies to characterize quality attributes of the compound such as impurities, new or particular auxiliary material or excipients used in the manufacture or formulation of the product were inadequate. In addition, there was a lack of relevant measures distinguishing findings between quality-related or pharmacologically-related actions of the compound.

PEI: Main critical clinical findings in the clinical part of failed MAAs[6]

Below are some of the most critical findings in the review of the clinical part of unapproved marketing authorization applications (MAAs).

Proof of the product rationale. Many of the failed applications had insufficient demonstration of the hypothesized mechanism of action; an insufficient link to pathogenesis of the disease, for example, the expression of the target structure in patients; or an ill-defined dose regimen.

Magnitude of demonstrated clinical effect. Most lacked statistical significance or effects were not clinically relevant.

Methodological flaws of the pivotal study design.

- Lack of active comparator data to current standard treatment and unconvincing efficacy compared to placebo.
- Study population not related to target indication.

- Limitations in definition of the study population. For example, heterogeneous study population; lack of information on previous active treatments, including reasons for discontinuation (intolerance versus lack of efficacy); or lack of standardization of concomitant treatment.
- Selection of irrelevant end points and flaws in their determination. E.g., activity instead of benefit (such as tumor response instead of overall survival); study visit intervals that were too wide, which did not enable sufficient determination of treatment difference between the study groups; lack of blinded assessment, which could lead to potential evaluator bias; or lack of centralized assessment, which could lead to potential centre bias.
- Lack of prospective definitions of relevant subgroup analyses.

Approach to handling of safety findings.

- The safety database of many failed applications were insufficient in terms of size (limited exposure data); in duration (lack of long-term safety data); in quality (heterogeneous study population); or in terms of critical and integrated discussion of safety findings.
- Insufficient reflection on safety findings and algorithms for risk-mitigating measures in the Summary of Medicinal Product Characteristics (SmPC).
- Lack of risk-management strategies.
- Insufficient evaluation of immunogenicity. For example, insufficient sampling schedules, assay format and validation; non-systematic evaluation of findings; or lack of data in children if paediatric indication is also intended.

Bridging of non-clinical findings to parameters for inclusion in clinical studies. Many failed applications lacked identification of specific end points and parameters from non-clinical safety findings for further use in clinical studies, or lacked integration of relevant findings in the post-approval risk-management plan proposal.

approach of proactive identification and management of proven and possible risks, and devotion of sufficient time to the development programme, are key factors to success."

The two boxes on this page give insights into findings which the PEI identified to be critical either in the CMC part or the clinical part of failed EMA MAAs.

Other interesting insights from failure analysis came from Ringel et al.[7] (2013) who analyzed 842 molecules with a known development outcome, chipped in by 419 companies (years 2002 to 2011). Out of these 842 molecules, 205 achieved regulatory approval and 637 failed in Phase II trials or later. Each molecule was analyzed according to 18 attributes for correlation with success or failure. Their main findings were as follows:

- Attributes with no observed relationship:
  - Company size (R&D spend)
  - Location
  - Market size of indication
  - Indication therapeutic area
  - Target family
  - Molecular properties

- Attributes that do have a significant relationship with success:
  - Indicators of scientific acumen
    - Scientific track record (publications & citations, patents per R&D $ spent)
    - R&D facility in a science hub
    - 'Easy' (eg infection) versus 'hard' (eg neuroscience) therapeutic area
    - Precedented target
    - Human(ized) monoclonal antibody

  - Indicators of good judgment
    - R&D tenure (prior years)
    - Frequent mention of ROI
    - Frequent mention of 'decision-making'
    - Early termination of projects (strongest single correlator with success)

"Making the right decision on what to progress to late-stage clinical trials is paramount in driving productivity", the authors claimed and discussed ways to set up the right organization of a R&D team.

Another analysis of FDA approvals and late-stage clinical failures done by Czerepak and Ryser[8] (2008), covering years 2006 and 2007, concluded: "Our belief is that many clinical failures in biotech companies are the result of **underfunding**, which goes hand in hand with less than optimal clinical staffing and clinical programme design."

2ND: LISTEN TO THE BIOTECH INVESTORS

Funding is a key to successful developments and therefore prompted us to prepare and conduct a survey amongst European venture capital investors who were asked: How do regulatory issues in biopharmaceutical development impact young companies' development and their financing? The questionnaire differentiated between general questions and others focused on Due Diligence/ investment decision plus one specifically on data packages (see box Questions to VCs).

We were supported by the Swiss Biotech Association and contacted 30 investors, 20 of them replied (66%). As two parties were stated as not to be eligible, we were able to analyze the statements of 18 venture investors (see Table 1). Their main feedback was that regulatory due diligence is very important for investment decision (89% affirmed this). Although two third of the investors have internal regulatory know-how, they add expertise via relationships to external professionals.

Half of the investors would finance clinical trials only (i.e. project financing), except sometimes under certain restrictions such as downside protection through equity in mother company, license option or in general the overall opportunity.

REGULATORY ISSUES & INVESTMENT DECISION

Almost 75% of the VCs stated that regulatory issues come into play during Due Diligence. In addition, nearly 40% considered the topic already important during the first contact.

More than half of the financiers linked intellectual property (IP) and regulatory strategy. Linking means for example, coming to a negative investment decision due to regulatory limits despite strong IP. If linked, regulatory and IP strategy mostly would have the same priority, however, sometimes regulatory has even higher priority (see Figure 2).

In general, the investors put medium to high importance on the regulatory expertise of the company's board / advisory persons and of the company's team. However, the latter was often somewhat higher than the first. For decision making following critical information was expected (quotes from survey):

- Clear regulatory pathway or at least defined pathway to deal with
- Regulatory pathway: Plan on clinical trials (realistic design), costs & timelines
- Risk assessments, gaps, success probabilities
- Differentiation
- Science
- Link of target to disease, proof of principle/concept, depending on stage
- Clarity on primary and secondary endpoints, clinically meaningful efficacy, trial design, minimal required safety database
- Clear minutes from EMA and FDA are essential
- Regulators written feedback, minutes, expert opinion
- Contacts, meetings with regulatory agencies; examples/timelines of comparables

Questions to VCs regarding regulatory issues in biopharmaceutical development

- General questions:
  - Do you have any relations to external experts on regulatory processes?
  - Do you have internal regulatory know-how?
  - Would you finance clinical trials only?
- Questions relating to Due Diligence / Investment decision:
  - Does regulatory due diligence usually play a role for your investment decision?
  - If yes, when do regulatory questions come into play for your decision making?
  - What critical information are you expecting to receive for your decision making?
  - Do you link regulatory strategy and IP for decision?
  - Do you put importance on the regulatory expertise of the company's board / advisory persons and of the company's team?
- Special on data packages
  - Which data packages do you expect in which investment phase?

Table 1: Survey participating venture investors (listed alphabetically)

VC company	… and selected quotes on the importance of regulatory issues:
Abingworth, UK	• "One of a few key criteria" • "Very important" • "Fundamental part of value/risk" • "It deeply impacts the overall and specifically the financial planning" • Important is a "regulatory path in terms of clarity on clinical endpoints, achievability of clinical endpoints and size of safety database" • We expect "very clear layout to end of phase II" • "Clinical trials are usually a critical element of any financing round"
Advent Life Sciences, UK	
Aeris Capital, CH	
BioMed Partners, CH	
Boehringer Ingelheim Venture Fund, D	
Forbion Capital Partners, NL	
Gilde Healthcare, NL	
GIMV, NL	
HBM Healthcare Investments, CH	
Hightech-Gründerfonds, D	
Index Ventures, CH	
LSP, NL	
Lundbeck Venture Fund, DK	
Nextech, CH	
Novartis Venture Fund, CH	
Takeda Ventures, US	
Vesalius Biocapital, LUX	
Ysios Capital, E	

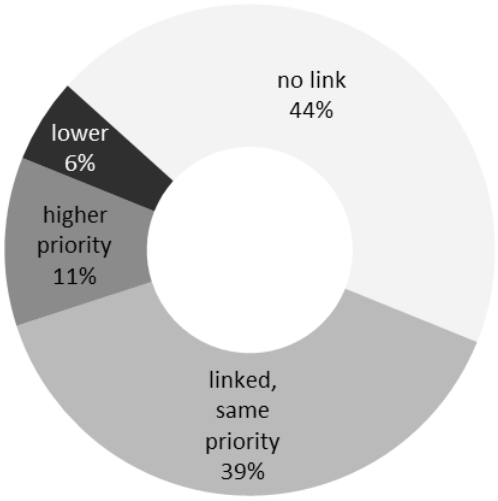

Figure 2: Linkage of IP and regulatory strategy

EXPECTED DATA PACKAGES FOR BIOPHARMACEUTICAL DEVELOPMENT

We asked the investors to correlate specific expectations for data packages with investment phases within biopharmaceutical development projects (see Table 2).

Regarding seed round investments, "drug target identification data" and "molecular description of lead compound" were highlighted most by the participants, followed by "animal data evidence of concept". For an early round financing companies should provide "validation of master cell bank", "production cell line generation" as well as "short term toxicity studies". Important were also "production and stability of DS and DP" and "phase I clinical data". Concerning later stage investments, the "validation of analytical

Table 2: Answers to question: Which data packages do you expect in which investment phase (n=14) (Highest three ranks marked with "!!!", "!!" and "!", zero expectations marked "-", i.e. here no correlation was indicated)

Development	Data package	Seed round	Early financing	Late financing
Early	Animal data evidence of concept	57% (!!)	43%	-
	Drug target identification data	79% (!!!)	14%	-
	Description of drug candidates	29%	50% (!)	7%
	Description of production process for drug candidates	14%	50% (!)	21% (!)
	Description of lead optimization process planned	50% (!)	36%	-
	Scientific advice initiation status	43%	43%	-
Until lead identification	Target product profile	50%	50%	-
	Molecular description of lead compound	79% (!!!)	14%	7%
	Description of production process	14%	50% (!)	21% (!)
	Validation of master cell bank	14%	64% (!!!)	7%
	Production cell line generation	21%	64% (!!!)	7%
	Analytical development for product testing	7%	50% (!)	29% (!!)
	Scientific advice update	36%	36%	14%
Identified lead until Phase II	Production and stability of DS and DP	14%	57% (!!)	21% (!)
	Short term toxicity studies	29%	64% (!!!)	7%
	Chronic toxicology studies	21&	36%	29% (!!)
	Validation of analytical methodologies for product characterization and release testing	14%	43%	36% (!!!)
	Phase I clinical data	21%	57% (!!)	14%

methodologies for product characterization and release testing" was expected the most, followed by "analytical development for product testing" and "chronic toxicology studies".

The higher the potential (due to the indication or the novelty of the drug/device), the more the investor has the tendency to accept higher risks, especially if there is a financing consortium already at the beginning and it is powerful enough to finance an answer".

LEARNINGS FROM THE SURVEY AND TAKE HOME MESSAGES

The survey results deliver some evidence on what investors think about regulatory issues to secure appropriate funding of biopharmaceutical drug development companies or projects. Most striking is that they demand companies to have a regulatory strategy or plan which is often expected during the first contact. Regulatory issues are an important part of the risk/value evaluation and therefore investment decision.

The survey discovered a string correlation between specific expectations on regulatory compliant data packages and investment decisions. However this topic remains a complex exercise. As a limitation to this

outcome, we also got the responses: "It is independent of series of investment" or "You can't just link the investment phase to the development phase of a drug or a medical device! I know, this is seductive and at a first look seems logical, but it's not the reality. There are many factors influencing what kind of 'open questions' you are willing to accept as an investor.

Experts who commonly work with regulatory authorities and drug development companies gathered a lot of insights and can give advice on how to build a regulatory strategy. Key take home messages are:

- Regulatory intelligence should be implementted at the R&D stage and not at late stage development.
- Regulatory strategy is mainly influenced by science. Consequently, science and regulatory affairs should be closely linked in drug research (regulatory sciences). Best, engage a regulatory scientist in your R&D team!
- Regulatory strategy represents a risk management and mitigation tool applied by investors and should be adequately reflected in the developing company.
- Scientific advice is a key step for the developer to evaluate development risk and for the investor to evaluate investment risk.

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Article

Marketing authorization of medical devices in China

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ABSTRACT

Medical device regulations across the globe have significant variations. The Chinese medical device market, like China's economy, is developing rapidly. This article reviews the medical device regulations in China and illustrates the major changes that have been recently implemented according to the new medical device regulations that came into force on the 1st June, 2014. Most regulatory research has focused on the US and EU medical device regulations with little written about the Chinese medical device regulations. The purpose of this article is to bridge the research gap and to introduce the Chinese medical devices regulatory environment to investors or companies who are engaged in the medical device market or doing business in China.

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Keywords: medical device, regulation, China, medical device market, regulatory frameworks

INTRODUCTION

Medical Devices — covers a very broad area, from simple but essential products (such as a wheelchair) to complex high-tech products (such as a pacemaker). Unlike ordinary products, medical devices utilise a large number of the latest achievements of modern science and technology and play a significant role in promoting human health. Due to the potential health risks, and the evaluation of the safety and effectiveness of medical devices, many countries have established medical device regulations for their supervision and management. Medical devices must be qualified by passing the safety and effectiveness procedures before they can be marketed in any particular country.

The US was the first country to legally define a 'medical device', and also was the first country to establish a medical devices management procedure.[1] As the second largest medical devices manufacturers and consumers in the world, the EU also has a rich history of medical devices regulation. The US and EU have established relatively mature medical device regulations, which have a key influence in the world. For instance, most of the guidance documents of the Global Harmonization Task Force (GHTF)[i] are based on the US and the EU medical device regulations. China established 'Regulations for the Supervision and Administration of Medical Devices' in 2000; these regulations aim to strengthen the supervision and administration of medical devices, ensuring their safety and protecting human health and life. The Chinese State Council released new Regulations for the Supervision and Administration of Medical Devices and these came into force on June 1st, 2014. The revisions are intended to create a more scientific and efficient regulatory regime for medical device supervision. There is little research into the Chinese medical device regulations because compared with the relatively mature US and EU regulations, Chinese regulations are evolving with the new regulations just released, hence there is a requirement for more research in this area. In this article, we describe the differences between the "Old Regulations" and the "New Regulations" to bridge the research gap. Generally speaking, the New Regulations moderate the supervision on low-risk devices and strengthens the oversight of high-risk devices. Thus, this article bridges the research gap and contributes to the Chinese medical device regulations area.

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i The organization GHTF (was born in 1992) has been permanently replaced by the International Medical Device Regulators Forum (IMDRF) in 2011.

MEDICAL DEVICE REGULATION IN CHINA

In the year of 1938, the US congress passed the Federal Food, Drug, and Cosmetic Act (the Act). The Act made provisions for medical devices. The US Food and Drug Administration (FDA) has the primary authority to oversee and manage medical devices, to make sure that the manufacturers produce safe and effective medical equipment.

Until the 1990s, in the area of medical devices, the EU enacted three directives to replace each member state's regulations. The directives harmonised the EU medical devices market, ensuring medical device safety and a high level of protection for human health and effective functioning of the "single market".

Relatively speaking, the Chinese medical device regulations were established late. In 2000, "Regulations for the Supervision and Administration of Medical Devices" were established, the regulations laid down the legal status of medical devices' supervision and management. This was a milestone in China's medical device regulation history. The "Regulations" gave the China Food and Drug Administration (CFDA) authority to oversee medical devices and ensure their safety and effectiveness, and protect human health and life.

China's definition for medical devices can be found in the Regulations for the Supervision and Administration of Medical Devices, 2000.[2] Medical devices are defined as:

Any instrument, apparatus, material, or other article whether used alone or in combination, including the software necessary for its proper application. It does not achieve its principal action in or on the human body by means of pharmacology, immunology or metabolism, but which may be assisted in its function by such means; the use of which is to achieve the following intended objectives:

1. Diagnosis, prevention, monitoring, treatment or alleviation of disease;
2. Diagnosis, monitoring, treatment, alleviation of or compensation for injuries or handicap conditions;
3. Investigation, replacement or modification for anatomy or a physiological process;
4. Control of conception.

Similar to the US medical devices regulation, the CFDA classify medical devices into three classes.[2] Class I devices are those for which safety and effectiveness can be ensured subject to routine administration (general controls) and do not need clinical trials; Class II devices need further controls (special controls) to ensure their safety and effectiveness. Class III devices are subject to strict controls because these kinds of devices may be implanted into the human body, or be for life support, they have the potential to put the patient's life at risk. For example: artificial heart valves or artificial kidney. The Chinese medical device registration system is different from the US system and EU system. In China, Class I devices are inspected and approved by the city's CFDA (city level). The province's CFDA (province level) are responsible for Class II devices' inspection and registration certificate. All the Class III devices are controlled by the State Council CFDA/central CFDA (national level).[3] Most Class I devices can be registered for production directly but must follow general controls. Class II and III devices' registration is not only subject to special and strict controls, but also requires clinical trial evaluation before they are put into production. Furthermore, when importing medical devices into the Chinese market for the first time, no matter what the class level is, the central CFDA will be responsible for the device's supervision and administration. The importer needs to provide details of the devices' intended use, quality standards, testing methods, product sample and other relevant documents for the central CFDA oversight.

The US FDA has established classifications for about 1,700 distinct types of medical devices and organized them into 16 medical specialty "panels" such as cardiovascular devices or ear and nose devices. These panels can be found in 21 CFR Part 862-892.[4,5] These actions ensure that all the devices on the US market have scientific and unique names. The Class I and Class II devices accounted for 90% of medical devices in the US market, from which 47% of medical devices fall under Class I and 43% fall under Class II. 10% of medical devices fall under Class III (see Table 1). In addition, about 95% of Class I devices and a small number of Class II devices (about 8%) are exempt from the premarket notification process.[6]

The Chinese medical device classification criteria are similar to the US's. The CFDA classify the devices into three classes, see Table 1. There are no more than 5,000 types of medical devices in the Chinese market, but there are more than 60,000 devices that have the registration certificate issued by the CFDA regulatory agencies.[7] The reason for this is that under the old standard, the naming of devices was inconsistent, this results in the same products having different names or the same names may be different products. In contrast, in the US, one device can only have one name and one product code; different products have different names and codes. The US FDA device classification system is a database system associated with an expert group providing technical support; the EU devices classification system is based on the 'Directives Rules'. The CFDA uses the devices 'classification rules'

Table 1: Percentage breakdown of medical devices classification levels

Country/Class	Class I devices	Class II devices	Class III devices
US	47%	43%	10%
China	36%	41%	23%

and 'classification catalogues' to implement the medical devices classification. For instance, when a device needs to be classified, the reviewers will first look for classification catalogues, if the product does not appear in the catalogues, the reviewers will classify the device according to the 'classification rules'. In addition, only about 8%–10% of medical devices are classified as high-risk devices in the US whereas more than 20% of devices are classified as high-risk devices in China, see Table 1. For instance, the computed tomography (CT) scanner was classified into Class II devices in the US,[8,9] while it is classified into Class III in China.[10] Too many products are classified as high-risk devices in China. This not only brings a heavy economic burden to the manufacturers, but also creates high cost and low efficiency for the government management. The US FDA pays more attention to review 10% high-risk Class III devices because they are usually the new products using new technology; In China, Class III devices accounted for 23% of the total devices, but, high-risk and innovative products do not exceed 5% of total applications for registration.[11]

The Chinese medical device registration system is a hierarchical system, see Figure 1. This system theoretically should have a short processing time and high efficiency but can be slow. The CFDA has local regulatory agencies, which includes 31 provincial, 433 municipal and 1,936 county-level agencies. Technical organizations include 16 state, 122 provincial, 373 municipal and 436 county-level organizations.[12] The regulatory agencies (except county-level), can issue medical device registration certificates.

Medical devices in China are covered by China National Standards (GB standards) and professional/industry standards (YY standards).[13] Medical devices must at least meet the requirements of the Chinese GB standards or professional standards, or meet other standards like ISO or equivalent if the devices want to sell in the Chinese market. Some medical devices still need the China Compulsory Certification (CCC) mark for product safety, such as medical diagnostic X-ray equipment, electrocardiograph, pacemaker, etc.[14]

China established the adverse events monitoring system and information networks, medical devices re-evaluation and medical device recalls but these systems are still under construction and need more legislative support.

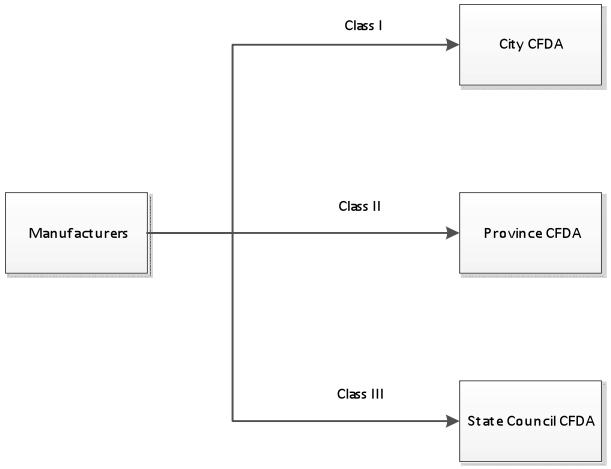

Figure 1: CFDA registration system

The mission of the CFDA is: public health protection and to ensure that all the marketed medical devices are safe and effective. The CFDA usually carries out random testing for medical devices' manufacturers and users. The CFDA has established the adverse events systems to collect all the information on medical devices surveillance, this encourages medical devices related people to report any medical devices relevant information, like quality issues and serious injuries or deaths of patients.[15]

THE NEW MEDICAL DEVICE REGULATION IN CHINA—MAJOR CHANGES

The Chinese State Council released the new Regulations for the Supervision and Administration of Medical Devices in 2014. Compared with the old regulations (48 articles), the new ones have 80 articles and many changes on device registration; clinical trials; adverse events; recalls, etc. The new regulations are consistent with the goal of the "National 12th five-Year Plan"[ii] to foster innovation and encourage domestic

ii Five-Year Plan (FYP) is a series of social and economic development initiatives, which renews every five years.

companies' research and development while enhancing the protection of public health.[16] The government overhauls the regulations in order to catch up with the fast development in the medical device industry and economy.

According to the New Regulations, the revised definition of medical devices are:[17]

Any instrument, apparatus, appliance, in-vitro diagnostic reagent and calibrator, material, or other articles alike, including the necessary software, directly or indirectly used on human body, which functions by means of physical ways, instead of by means of pharmacology, immunology or metabolism, or the participation of pharmacology, immunology or metabolism means only plays an assistive role; the use of medical devices is to achieve the following expected purposes:

1. Diagnosis, prevention, monitoring, treatment or alleviation of disease;
2. Diagnosis, monitoring, treatment, alleviation of or compensation for injuries or handicap conditions;
3. Investigation, replacement, modification or support of a physiological structure or process;
4. Supporting or maintaining of life;
5. Control of conception;
6. Providing information for treatment or diagnosis purpose by inspecting the samples from human body.

Classification of Medical Device

The New Regulations classify and administer medical devices based on their risk levels. Class I medical devices are those with a low-risk level, which through routine administration their safety and effectiveness can be ensured; Class II medical devices are those with a middle-risk level, for which strict control and administration is required to ensure their safety and effectiveness; Class III medical devices are those with a higher-risk level, for which special measures and strict control shall be taken to ensure their safety and effectiveness. Compared with the old regulations, the new regime introduces risk management into the regulations. Risk management not only in the device classification sections, but also in other parts. For example, "medical device registration should submit a risk analysis report of the product; medical device recalls and adverse events".

Medical Device Registration

According to the New Regulations, Class I devices will no longer require registration, but will change to record-filing. The applicant shall submit the required documents to a city level regulatory authority (same as the Old Regulations) for device record-filing procedure. The applicant shall submit the following material to the regulatory authority for Class I devices record-filing and Class II and Class III devices registration: (1) Risk analysis report of the product; (2) Technical requirements of the product; (3) Testing report of the product; (4) Clinical trial material; (5) Product instructions for use and sample label; (6) Quality management system documentations related to research and development (R&D) and manufacturing of the product; (7) Other documents which prove the safety and effectiveness of the product. Moreover, the applicant for the medical devices record-filing or registration shall be responsible for the authenticity of the submitted documents.[18] Like the Old Regulations registration procedure, Class II devices are administered by a provincial regulatory authority and Class III devices are administered by the central CFDA. Class I devices do not require clinical trials for the record-filing procedure, Class II and Class III devices require clinical trials for registration. However, clinical trials can be exempted in any of the following circumstances: the device is at least as safe and effective as a previously cleared (predicate) device (legally Chinese marketed device), which has similar intended use and no severe adverse events record; a medical device which proves to be safe and effective through non-clinical evaluation assessments; a medical device which proves to be safe and effective through the analysis and evaluation of the data obtained from clinical trials or clinical application of the substantially equivalent medical devices. In addition, the duration of the medical device registration certificate is five years (the Old Regulations suggest the registration certificate must be renewed every four years).

Medical Device Production

The New Regulations pay more attention to Good Manufacturing Practices (GMPs) for medical device production management. GMP is that part of quality assurance, which ensures that medical products are

The Five-Year Plan was shaped by the Communist Party of China, who plays a leading role in mapping strategies for China's economic development, setting growth targets and launching reforms. First FYP: 1953–1957, the rest can be done in the same manner. So 11th FYP is from 2006–2010 and 12th FYP is from 2011–2015.

consistently produced to the required product specification and controlled to the quality standards appropriate to their intended use. GMP is concerned with both production and quality control.[19]

CFDA requires that all the medical devices in the Chinese market should be accompanied with product specifications and labels. In addition, the New Regulations require Class II and Class III devices should also indicate the registration certificate number and register's affiliations with product specifications and labels. Moreover, if the medical device can be used by the consumer independently, the product specifications and labels should include special instructions for its safe use.

According to the New Regulations, if a medical device is within a manufacturing consignment, the consigner shall be responsible for the quality of medical devices. The consignee shall be a medical device manufacturer which meets the CFDA's requirements. In addition, the imbedded medical devices with a high-risk level shall not be manufactured in consignments.[20]

Distribution/Operation and Use of Medical Devices

The Old Regulations required companies who distribute/operate Class I medical devices to file records with the provincial CFDA. Companies distributing/operating Class II and Class III medical devices need to obtain the Medical Device Distributing Enterprise License, which is issued by the provincial CFDA. The New Regulations removes record-filing for Class I device distributors and requires Class II device distributors to file records with the provincial CFDA.

The New Regulations also place more obligations on medical device distributors and users. Such obligations cover all aspects of using medical devices including device supplier's certificates, quality certificates, records of purchase/sales, transportation and storage, operator technical training. Moreover, the medical device user shall inspect, verify and maintain the devices periodically to ensure the devices are in good condition, safe and effective.

Imported medical devices shall be accompanied with product specifications or user manuals and labels in Chinese, and specify the devices' place of origin and agent's affiliations. The medical device exporters shall ensure the exported devices comply with the requirements of the importing countries.

Medical Device Adverse Events and Recalls

The Old Regulations were silent about medical device adverse events and recalls. However, the central CFDA and the Chinese Ministry of Health (MOH) issued provisional Decree 425 for tracking adverse events[21] and provisional Decree 82 for managing medical device recalls[22] in 2011, respectively.

The New Regulations issued requirements on monitoring medical device adverse events and managing recalls. These requirements set clear responsibilities from device manufacturer personnel to distributors and patients/consumers. The central CFDA established the medical device adverse events monitoring system and information networks to: collect information, analyse, evaluate and control adverse events in a timely manner. Any medical device manufacturer, distributor and user has rights to report adverse events to this monitoring system and information networks, and the CFDA will also collect adverse events information proactively.

The New Regulations require the device manufacturer to stop production if the device does not meet the compulsory standards or contains other defects, furthermore, they must notify relevant distributors or users to stop distributing or using this kind of device and recall the devices which are already on the market. According to MOH Decree 82, there are three levels of recalls based on the severity of medical device defects.[22] Level I recalls means that if use of the medical device has caused, or may cause, serious health hazards that are of a permanent nature; Level II recalls means use of the medical device may cause health hazards that are of a temporary or permanent nature; Level III recalls mean use of the medical device may not be likely to cause harm but it is still defective.[14]

Supervision and Inspection

The New Regulations require that the CFDA enhance supervision and inspection of medical devices' registration, record-filing, production, distribution and use, sometimes using random checks. The provincial CFDA or central CFDA will issue medical device quality circulars based on the results of timely random checks.

The central CFDA has established a shared medical device supervision and inspection information network. The CFDA should legally and in a timely manner publish the medical devices' license, record-filing, random check results and illegal behaviour through

the information network. In addition, the CFDA also established the credit files for medical device registrants, record-filing applicants, manufacturers, distributors and users, and increased the frequency of inspection upon those who have a poor credibility record. Moreover, the CFDA publish their contact information for inquires, complaints and reports. Information disclosure is a major breakthrough for the Chinese medical device market participants' supervision and inspection.

Legal Liabilities

The New Regulations have increased sanctions and penalties for various violations. For example, administrative penalties up to 20 times (5 times in the Old Regulations) the value of the manufactured products may be imposed on medical devices produced without the proper permits. In some severe circumstances, relevant personnel and companies will be suspended from application for any medical device permits or licences for 5 years, and may be subject to criminal sanctions if such violation constitutes a criminal offense. Penalties or criminal offenses may be incurred for the following actions: permits (medical device registration certificate, production permit, distribution permit, advertisement approval certificate) are obtained by providing false information or by using other methods of cheating; relevant medical device permits or certificates are forged, altered, transferred, leased and lent; manufacture, distribute or use of devices which are not compliant with the compulsory standards or technical requirements; any clinical trials conducted in violation of the Regulations or medical device clinical trial institutes issuing false reports, etc.

DISCUSSION

The New Regulations are intended to establish a more efficient and scientific regulatory regime for supervision and administration of medical devices. Risk management has been introduced to the New Regulations such as device classification. In addition, the CFDA pays more attention to the Class III devices supervision and moderates the Class I devices oversight. The Old Regulations required that all the Class II and Class III devices need clinical trials, inspection and approval by the provincial CFDA and central CFDA, respectively.[3] The exemption from clinical trials for some special circumstances has been introduced in the New Regulations. Moreover, the registration certificate is replaced by record-filing for Class I devices application, which make the registration process more efficient.

As previously described, due to there not being a national unified product naming and coding system; too many devices are classified as high-risk devices when they should not be categorised at the high-risk level, resulting in an unnecessary waste of effort and low efficiency of medical device supervision in China. Nevertheless, the New Regulations have tried to establish a unique unified national medical device naming and coding system, to reduce the number of: "the same products having different names or the same names referring to different products" , and the central CFDA will analyse and evaluate medical device's risk, to adjust the "classification catalogue".[23]

In the US and EU, the legislation clearly prescribes that the device manufacturer or applicant will take the main responsibilities for device safety and all the consequences resulting from the device performance. However, the old legislation did not clearly define this situation, the CFDA bears some responsibility for the medical devices' use, failures, and even adverse events. The New Regulations clearly delineate every medical device related participant's responsibilities. For example, medical device manufacturers, distributors and users shall monitor adverse events. If any adverse events are identified, they shall report it to the medical device adverse event monitoring technique institutes.[24]

The post-market surveillance is an important guarantee to ensure that the devices continue to be safe and effective. The US and EU's medical devices regulatory legislation have strict requirements for the marketed devices. For example, the EU has the vigilance system for post-market surveillance, such as the European Databank on Medical Devices (EUDAMED)[iii]. The adverse events and recall of medical devices does not appear in the Old Regulations. The New Regulations combined the central CFDA Decree 425 and MOH Decree 82 requirements, they clearly describe the device participants' responsibilities and have established the medical device adverse events monitoring system and information networks to control adverse events and recalls; they have established

iii EUDAMED contains data on manufacturers, authorized representatives and devices; certificates issued, modified, supplemented, suspended, withdrawn or refused; clinical investigations, which use is obligatory since May 2011. The purpose of EUDAMED is to enhance market surveillance and transparency in the medical devices area by providing Competent Authorities with quick access to information as well as to contribute to a uniform application of the Directive.

a re-evaluation system for registered medical devices to regulate supervisory activities.

CONCLUSIONS

The changes made in the New Regulations demonstrate the Chinese government's efforts to upgrade and maintain an effective regulatory framework for the medical device market. The Chinese government has promulgated the New Regulations, which covers various perspectives of the regulatory regime of medical devices, such as device classification and registration, supervision of production and distribution, etc. Driven by the more powerful regulatory requirements under the New Regulations, the Chinese medical device market will become increasingly dynamic in the future.

Further in-depth research on this topic will be carried out in the future. Some regulations and policies still need modification and the recommendation is for more studies to understand the changing market environments, this should result in continuous improvement of policies.

DECLARATION OF CONFLICTING INTERESTS

The authors declare that there is no conflict of interest

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Article

VC-backed Biotechnology Firms: What is Entrepreneurs' Return?

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ABSTRACT

Valuation is a highly significant process used extensively not only by start-ups seeking Venture Capital (VC) funding but also by large, established companies that are in need to set a price for an acquisition or merger. Such process becomes increasingly complex in the biotechnology sector where the realization of the true value of a firm is largely correlated with the success or failure of lead drug candidates undergoing clinical trials. In this article, the author sets up a simple long-term financial model that aims at providing an easy tool for estimating entrepreneurs' return at exit.

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Keywords: valuation, discounted cash flow, comparable multiples, net present value

INTRODUCTION

Valuation is an important tool when it comes to realizing the true value of pharmaceutical products pipeline. The number of start-ups and highly specialized early-stage biotechnology firms has been booming; these firms aim at meeting not only the increased medical needs of the aging population but also need to find effective treatments of complex diseases in oncology and Central Nervous System (CNS) therapeutic areas. To achieve these targets, early-stage biotechnology firms seek to raise funds, mainly through: (1) VC financing and (2) securing a value-sharing deal with a large pharmaceutical company or (3) a combination of (1) and (2). In either case, it is necessary that these firms need to have a strong grasp of their capabilities and more importantly, how these capabilities are valued by investors.

This paper aims at providing two interconnected valuation-based models that can be utilized by early-stage VC-backed biotechnology firms and provide them with strong grounds when estimating entrepreneurs' returns at exit. The first model combines the traditional Discounted Cash Flow (DCF) method during the sales period with the Net Present Value (NPV) method during the R&D period for a one-product "average" company. In the DCF / NPV model, the effect of initial sales and compound annual growth rate (CAGR) is examined. The second model is a VC investment model that translates VC common term sheet requirements and examines how these terms affect entrepreneurs' returns. Firstly, the methodology and assumptions of both models are established and thereafter, the results are presented and discussed.

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COMPLEXITIES INVOLVED IN VALUING AN EARLY-STAGE BIOTECHNOLOGY FIRM

Valuation is a highly complex subject even for top industry-specific valuation advisory firms. That is, because valuation involves a wide range of uncertainties and specificities which can lead to making assumptions that can prove to be wrong even in the short-term. In particular, valuation analysts need to address various issues when it comes to valuing the product portfolio of an early-stage biotechnology, as presented in Table 1.

VALUATION MODEL 1 (DISCOUNTED CASH FLOW AND NET PRESENT VALUE)

Despite these hurdles in DCF this paper aims at illustrating a simple DCF model that can be utilized by a one-product early-stage biotechnology firm. The disadvantages of the DCF model can be managed by introducing a second model which will be explained at a later stage. The steps to construct the DCF model are presented below.

Table 1: Common valuation issues in valuing an early-stage biotechnology firm through DCF

R&D Period	Explanation
Beta and Discount Rate Calculation through the CAPM Model	Through the Capital Asset Pricing Model (CAPM) one can calculate beta by using comparable companies and the discount rate using the risk-free rate and the market risk premium. However, this methodology may raise flags to some investors as assuming beta and market risk premium to value a highly innovative firm can be flawed. In particular, comparable companies (in terms of size, product portfolio etc.) for such firms do not exist which makes the beta and market risk premium assumptions subjective.
R&D expenses	Drug discovery and drug development expenses cannot be estimated with confidence, since many obstacles may arise that cannot be predicted. For instance, cash burn rate might be higher than expected and the firm may need to raise more equity to further fund drug development.
Attrition rates	Attrition rates vary by therapeutic area. Based on previous literature and clinical studies, one may approximate the attrition rates by phase of development, though it might not be exactly accurate[1].
Post-Revenue Period	
Revenue	The R&D period may last up to 12-15 years and therefore, the accuracy of predicting sales in the post-R&D period is highly questionable.
Gross Profit Margins	Gross profit margins can be approximated based on similar marketed products. However, the market structure as well as regulatory environment might different in the future.
Operational Expenses	The main hurdle in estimating operational expenses is that one cannot know the size of the company in such time-frame. In principle, operational expenses correlate positively with sales.
Free Cash Flow Items	Capital Expenditure (CAPEX), Depreciation and Working Capital need all to be assumed as a percentage of revenue. That is, balance sheet projections are needed to estimate these items. Although this assumption can distort the free cash flow, a key determinant of DCF valuation, predicting these balance sheet items in 20 years time is also impossible.

Step 1: R&D costs by phase

The R&D costs by phase usually fall within the ranges presented in Table 2[1]. The average cost has been calculated by taking the average of the minimum and the maximum cost reported.

Table 2: R&D costs by phase

R&D Period	Cost	Average Cost
Lead Optimization	$ 2 – 3 mn.	$ 2.5 mn.
Pre-Clinical Phase	$ 2 – 3 mn.	$ 2.5 mn.
Phase I	$ 1 – 5 mn.	$ 3 mn.
Phase II	$ 3 – 11 mn.	$ 7 mn.
Phase III	$ 10 – 60 mn.	$ 35 mn.
Approval	$ 2 – 4 mn.	$ 3 mn.

Step 2: Discount Rate by Stage of Development

The discount rate can be estimated by using the Capital Asset Pricing Model (CAPM) presented below:

$$r=r_f+\beta\times(r_m-r_f)$$

Where r_f is the risk-free rate, (r_m-r_f) is the market risk premium and β is the beta coefficient. The risk-free rate reflects the risk-free rate of an investment for which the usual measure is the 10-year U.S. government bond yield (~2%). The market risk premium is the difference between the average market return and the risk-free rate assumed to be 6.7% as pointed by Morningstar[2]. Finally, beta coefficient relates to the relative volatility or systematic risk between the return on an asset (company's shares) and that of the market. Beta coefficient varies by stage

Table 3: Discount rate by phase – R&D period

Stage of Development	Risk-free Rate	Market Risk Premium	Beta	Discount Rate	Success Rate[5]
Research and Pre-clinical Stage	~2%	6.7%	2.73	20.3%	100%
Phase I	~2%	6.7%	2.32	17.6%	27%
Phase II	~2%	6.7%	1.92	14.8%	60%
Phase III	~2%	6.7%	1.51	12.1%	33%
Approval	~2%	6.7%	1.10	9.4%	91%

Table 4: Model 1 assumptions – Market period

Variable	Value
Initial Sales ($ mn.)	17.1
Time Period (years)	10*
Compound Annual Growth Rate (CAGR)	30.0%
EBIT Margin as % of Sales	22.92%
Capital Expenses as % of Sales	4.5%
Change in Working Capital as % of Sales	2.5%
Effective Tax Rate on EBIT	20.1%
Discount Rate	8.25%

of development because the project becomes less risky as the drug candidate reaches the market. The starting beta for a venture has been estimated to be 2.73[3]. It is assumed that at the time of approval, beta will be equal to the average beta of listed biotechnology companies equal to 1.1[4]. The betas of the intermediate stages have been linearly extrapolated. The success rate by phase was obtained by DiMasi et. al. (2010)[5] and refers to large molecules.

Step 3: Free Cash Flow Estimation – Market Period

The model will focus on the effect of initial sales on the value of the project and hence of the company (as it is assumed that the company has only one product in the market). Therefore, a random value has been assigned for the revenue of the company at year 1. The values for Earnings before Income and Taxes (EBIT) margin, discount rate and effective tax rate have been obtained by Damodaran[6,7,8] while the capital expenditure, change in working capital (as percentage of revenue) have been calculated by the author (average for companies with sales between $10 and $100 mn. excluding any outliers[9]). To estimate the average compound annual growth rate, all drug products of the EvaluatePharma database were filtered using the following criteria:

i. Top 50 products based on 2013 sales
ii. > 20 mn. in initial sales
iii. FDA approval post-1999
iv. Peak sales have been reached prior to 2016
v. Sales keep decreasing after peak sales and do not bounce up (s-curve)

This resulted in average peak sales year being year 10 of sales and a mean CAGR of 30% (excluding any outliers). Table 4 summarizes the model 1 assumptions.

VALUATION MODEL 1 – RESULTS

The results obtained using the EXCEL model inputs described in table 4 are presented in Table 5. The DCF Value of the one-product company before any R&D expenses are deducted is estimated at $ 198 mn.

Similarly, the assumptions presented in table 3 and table 4 have been applied to the R&D period. It can be seen that the effect of the time-value of money and discount rates has a significant impact on the NPV value of the project bringing the DCF value of $ 198 mn. down to an NPV of $ 0 mn. at the research / pre-clinical stage. It should be noted that the initial revenue has been assumed deliberately to be equal to $ 17.1 mn. so that NPV = 0.

A sensitivity analysis has been performed in order to observe how initial sales and compound annual growth rate (CAGR) affect the DCF value (the main unknown variables at market entry). The results of this analysis are presented in table 8. The results show that in order for a project to be worthy undertaking it (NPV > 0), the product must either have at least $ 50 mn. in sales with CAGR of 15% or $ 10 mn. in sales with CAGR equal or greater than 40%.

Table 5: Model 1 results – Market period

DCF Valuation	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	Perpetuity
Year	1	2	3	4	5	6	7	8	9	10	
Sales	17.1	22.2	28.8	37.5	48.8	63.4	82.4	107.1	139.2	181.0	
Total CAGR	30.0%										
EBIT % of sales	22.9%	22.9%	22.9%	22.9%	22.9%	22.9%	22.9%	22.9%	22.9%	22.9%	
EBIT	3.9	5.1	6.6	8.6	11.2	14.5	18.9	24.6	31.9	41.5	
Tax rate	20.0%										
CAPEX % of Sales	4.51%										
CAPEX	0.8	1.0	1.3	1.7	2.2	2.9	3.7	4.8	6.3	8.2	
Working Capital % of Sales	2.50%										
Working Capital	0.4	0.6	0.7	0.9	1.2	1.6	2.1	2.7	3.5	4.5	
Free Cash Flow	1.9	2.5	3.3	4.2	5.5	7.2	9.3	12.1	15.7	20.5	
WACC	8.25%										
Discount Factor	0.92	0.85	0.79	0.73	0.67	0.62	0.57	0.53	0.49	0.45	
DCF	1.8	2.1	2.6	3.1	3.7	4.5	5.3	6.4	7.7	9.3	
Sum of DCF	46										
GDP Growth											2%
Terminal Value											334
Discounted Terminal Value	151										
Total DCF Value	198										

Table 6: Model 1 results – R&D period

NPV	Research & Preclinical	Phase I	Phase II	Phase III	FDA Review	DCF Value (Market Entry)
Year	1	4	6	8	10	11
R&D Costs by Phase	-5	-3	-7	-35	-3	0
Discount Rate by Phase	20.29%	17.54%	14.86%	12.12%	9.37%	8.25%
Probability of Success	100.0%	84.0%	53.0%	74.0%	96.0%	100%
E(NPV) by Phase	0.0	8.7	19.2	65.3	170.5	198

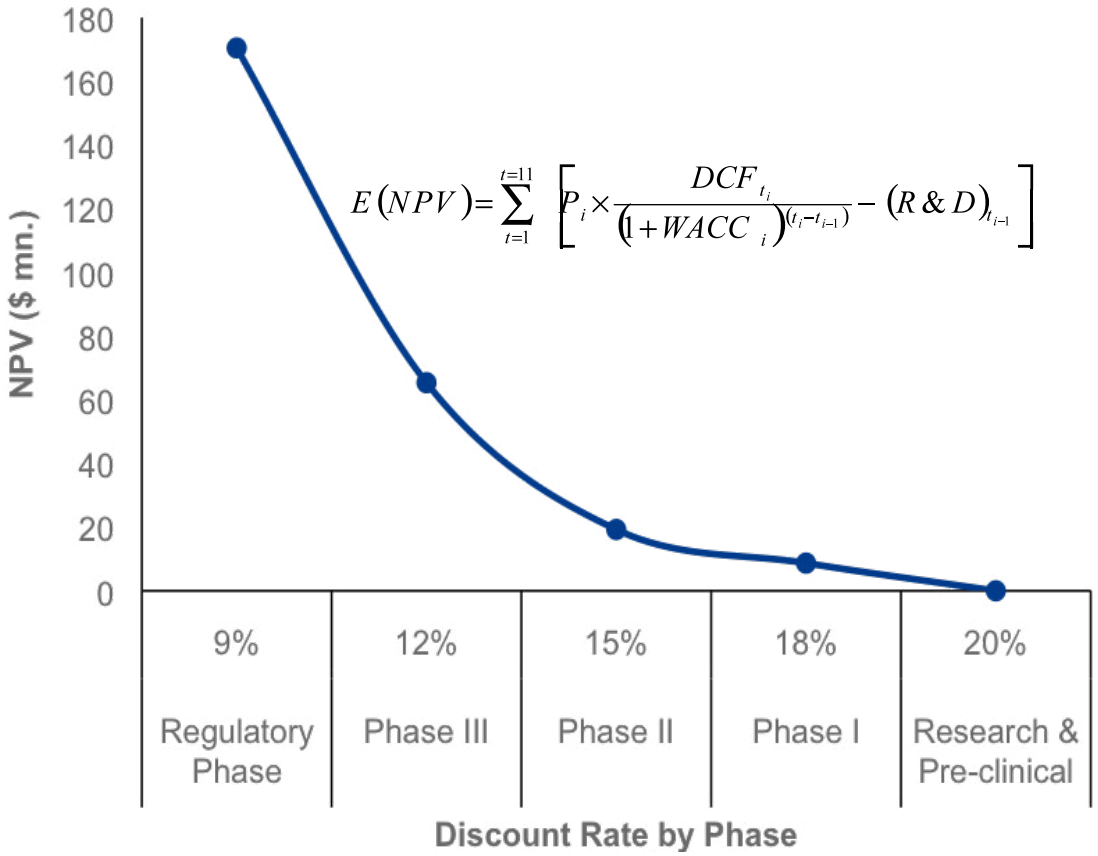

Table 7: Model 1 results – Sensitivity analysis on DCF value

		Initial Sales								
		10	15	20	25	30	35	40	45	50
CAGR	15%	43	65	87	108	130	152	173	195	216
	20%	60	91	121	151	181	211	242	272	302
	25%	84	126	168	210	252	294	336	378	420
	30%	116	174	232	289	347	405	463	521	579
	35%	159	238	317	396	376	555	634	714	793
	40%	216	323	431	539	647	754	862	970	1,078

VALUATION MODEL 2 (VC INVESTMENT MODEL)

A VC investment model should incorporate two main features: the (i) Return and (ii) Control desired by VC investors. Return is important because when VCs invest in an early-stage biotechnology company, they actually invest in one of the riskiest industries of the world and they want control to participate in the decision-making. This happens primarily because control provides investors with the ability to monitor financial decision-making which may affect future returns on their investment. In particular, VCs want:

- Ownership: Percentage of stock owned by VCs based on their initial investment.
- Dividend Provision: Participation in issued dividends (can be flat or cumulative)
- Exit Strategy: trade sale (through a merger or acquisition) or initial public offering (IPO)
- Liquidation Preferences: Return multiple (i.e. x times their initial investment)
- Convertible preferred stock: At an early stage, investors usually require start-ups to issue preferred stock and they are allowed to convert it to common stock at exit. In case of bankruptcy, preferred stockholders are paid first among equity holders. Therefore, convertible preferred stock can be viewed as a "shield" ensuring a partial recovery of funds in case an investment fails.
- Participation: If the company is sold at a value higher than its post-money valuation (or if the equity raised through an IPO) then investors can "participate" in that premium as well.

Table 8: Model 2 inputs – VC investment model

Assumptions by Series of Investment	A (Pre-clinical/ Phase I)	B (Phase II)	C (Phase III)
Investment ($ mn.)	5	10	55
Ownership Required	20%	35%	40%
Conversion ratio (preferred to common stock ratio)	1	1	1
Liquidation preferences (investment return multiple)	x 4.5	x 3.5	x 2.0
Participation at Exit (total: 90%)	40%	30%	20%

Table 9: Model 2 results – Ownership estimation

Results by Series of Investment	A	B	C
Post-money Valuation ($ mn.)	25.0	28.6	137.5
Pre-money Valuation ($ mn.)	20.0	18.6	82.5
Total number of shares (mn.)	12.5	19.2	32.1
- Outstanding Shares (mn.)	10.0	12.5	19.2
- Shares to be issued (mn.)	2.5	6.7	12.8
Required Investment Return at exit ($ mn.)	22.5	35.0	110.0
VC Total Required Investment Return at exit ($ mn.)	167.5		
Ownership Structure (Post-Series C)	8%	21%	40%

Table 10: Model 2 results – VC investment model

M&A Exit Scenario	
M&A Multiple at Exit	x 2.82
M&A value ($ mn.)	197.6
VC Total Required Return with Participation ($ mn.)	194.6
Entrepreneurs' Return ($ mn.)	3.0

Table 11: Model 2 results – Sensitivity analysis on entrepreneur's return

		Total Required investment return at exit (excl. participation)			
		140	155	170	185
Total Participation	80%	11.5	8.5	5.5	2.5
	85%	8.6	6.4	4.1	1.9
	90%	5.8	4.3	2.8	1.3
	95%	2.9	2.1	1.4	0.6

- Protective Covenants: usually a non-competition covenant is applied – an employee is not allowed to work for a competitor for a specified period of time.
- Board of Directors (BoD) Control: In order for VCs to have actual control on importance decisions made in the company they will certainly ask for board sits.
- Rights of First Refusal: Rights of first refusal allows VCs to prevent dilution of ownership in case additional series of investments take place. Full rights of first refusal means that the shares owned by series A investors will not be diluted at all when series B investment occurs. Instead, series A investors will maintain the same ownership regardless of the investments made in future series of investments.
- Stock Repurchase Agreement: Restriction on stock repurchases from existing shareholders (mainly founders) to avoid concentration of shares in a single or very few shareholders.

The VC valuation method incorporates most of investors' requirements presented above and is illustrated using the case below:

ABC Biotech is a biotechnology company that with its own funds and Angel investors has succeeded in bringing a drug from research to phase I and seeks VC funding for testing the drug in clinical trials. On average a promising early-stage biotech company needs approximately $ 70 mn. (time-value of money ignored) in total throughout the R&D period. An indicative structure of a series of investments is proposed as follows:

VALUATION MODEL 2 – RESULTS

The number of outstanding shares prior to series A investment is assumed at the arbitrary value of 10 mn., which does not affect the post-money valuation of the firm. Based on the shares issued and the required ownership, investors together own 69% of the company while the founders have maintained 39% of the shares.

The M&A exit multiple is defined as the deal value at which a company is acquired divided by the total investments that company received prior to acquisition. Using EvaluatePharma, all VC-backed companies were screened using the following criteria: (i) all series of investments have been disclosed, (ii) all of the companies have exited only through M&A, (iii) total VC investment (all series) (iv) outliers have been excluded (only investments with M&A multiples between 2 and 15 have been included). The screening resulted in a sample of 63 companies of which the mean M&A exit multiple is x 6.04. In this scenario however, the DCF value has been estimated at $ 198 mn., representing an M&A exit multiple of x 2.82. This is still a large return on investment that is realized mainly by the investors as they apply their liquidation preference and participation rights. These terms lead to a small return for entrepreneurs of $ 3.0 mn. (1.5% of total M&A value). In this particular scenario the break-even point – the minimum M&A exit multiple so that entrepreneurs have positive returns – is x 2.39.

Entrepreneurs' returns are highly affected by the total required investment return at exit as well as participation rate. In particular, Entrepreneurs' returns can be positive up to a 95% participation only if total required investment return does not exceed $ 185 mn (Table 11).

CONCLUSION

There exist some limitations in this study. The model inputs were assumed based on "average" data that is publicly available. Although, these parameters may widely vary in practice, the model was designed to give a flavor of what entrepreneurs can expect in return from going forward with VC funding based on their firms' revenue potential, initial sales and VC requirements.

In addition, the R&D expenses by phase were assumed to be at the mid-point between the minimum and the maximum value as referenced by Bogdan and Villiger[1]. This process can be improved if actual R&D expenditure by phase of early stage biotechnology firms can be obtained. However, there are no publicly available sources that provide such data. Attrition rates obtained from DiMasi et. al.[5] refer to clinical candidates of the top 50 pharmaceutical companies, and therefore these rates might not be fully representative of early-stage biotechnology firms, which are more efficient in allocating resources and identifying potentially successful drug candidates. However, there is a gap in literature regarding success rates of early-stage biotechnology firms.

In summary, the current study aims at providing a simple model for biotechnology entrepreneurs that are starting or looking forward to raise funding from VCs. The main conclusion to be drawn from the analysis performed is that entrepreneurs should be aware of VC term sheet requirements, how these terms are translated into numbers, and, bottom line, how do these affect entrepreneurs' potential returns at exit. In practice, if participation rights are too high and the M&A exit multiple is not high enough, then entrepreneurs might end up getting no return.

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Article

Encouraging Innovation in Preventive Health Technology: A Spotlight on Women's Health

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ABSTRACT

Encouraging technology innovation, specifically preventive health technology, can use the intellectual property regime to the public health's benefit. Patents today are currently concentrated in reactive care technology. However some preventive technologies, particularly the IUD, are gaining popularity. The Affordable Care Act and other government policies present an opportunity for more preventive care techologies to flourish.

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INTRODUCTION

The popularity of the intrauterine device (IUD) has exploded in the last five years and it is estimated that more than 10 percent of American women who use birth control now choose IUDs.[1] From 2008 to 2012, Planned Parenthood saw a seventy-five percent increase in IUD use among its patients.[2] Bayer, the drug company that produces the newer model Mirena, says it saw a thirty-three percent rise in worldwide sales between 2010 and 2013.[3] Other available models include the non-hormonal ParaGard, Skyla, a smaller version of Mirena, and most recently the extremely affordable Liletta.[4] However in Europe, women have three times as many models from which to choose,[5] increasing market competition and making prices more affordable for consumers. This begs the question, how can those of us working in public health encourage innovation in the development of more preventive health technology in the United States such as long-acting reversible contraception?

First patented in the 1960s, the IUD gained a bad reputation after sub-par models started to become associated with infertility and even death in the 1970s. An estimated 2.5 million women used the Dalkon Shield, an IUD shaped like a ten-armed stingray, during 1970–1974.[6] A class-action lawsuit against A.H. Robins, the company that owned the Dalkon Shield, alleged the product was responsible for the deaths of eighteen women and the infertility of thousands during that four-year period.[7] The Centers for Disease Control and Prevention (CDC) found a five-fold increased risk for pelvic inflammatory disease for women using the Dalkon Shield compared to other IUDs and recommended their removal.[8] In 1984 Robins itself recommended the discontinuation of its product to physicians, and in 1989 a legal settlement created a $2.5 billion trust fund to compensate victims.[9] The press surrounding this lawsuit scarred the IUD's reputation in the U.S., and Searle subsequently removed its IUD products from the American Market, leaving a gaping hole in the domestic development of IUD technology until very recently.[10]

This paper explores the idea of encouraging technology innovation, specifically preventive health technology, in order to use intellectual property regimes to the public health's benefit. It will begin by discussing the current focus of patents on reactive health technology. Next, this paper will analyze opportunities and pitfalls for preventive health technology as a result of the Affordable Care Act (ACA). Additionally it will highlight the prize system as a possible mechanism for government intervention and conclude with policy recommendations.

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PATENT FOCUS ON REACTIVE HEALTH TECHNOLOGY

The patent system is designed to promote innovation and simultaneously create a mechanism for ensuring that the products of innovation are accessible to society.[11] The exclusive right conferred by a patent is one of the incentives for developers of new technologies to make the necessary heavy investments into long-term clinical research.[12] If used optimally, patents allow inventors to provide technological innovations to improve health conditions, and the needs of the general public.[13] However, the system is currently heavily devoted to down-stream medications and devices, products that are useful only after the onset of disease. Biologics, for example, are a huge topic of interest in the technology field right now, under the assumption that biologics are uniquely important for innovation because they will "unlock treatments for the world's most challenging and prevalent diseases."[14]

The ACA contains the Biologics Price Competition and Innovation Act (BPCIA). Under the BPCIA, applicants can file a biologics license application, commonly known as a biosimilars application, creating an abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with an FDA-licensed reference product.[15] Additionally, the biologics industry has been heavily involved in President Obama's Trans-Pacific Partnership (TPP), an international free trade deal. In support of the TPP, Jay Taylor, vice president of the Pharmaceutical Research and Manufacturers of America, said that innovation is "especially important in the area of biologic medicines, which could hold the key to unlocking treatments for disease that have thwarted researchers for years."[16] However, such a bold statement is not consistent with the current states of world health. With non-communicable chronic diseases are on the rise, effective preventive health technology will not easily fit into a biologic product. According to Figure 1, the principle determinants of health, in order of importance, are behavioral patterns, genetic predisposition, social circumstances, shortfalls in medical care, and environmental exposure. Given this data, the majority of healthcare expenditure should not be on medical treatments, but on health promotion and other strategies that aim to prevent the need for medical care.[17]

Technology on its own is not a substitute for a strong culture of commitment to the practice of preventive health wellness, however it can supplement such culture and provide support for individuals wishing to take more responsibility for their self-care and lifestyle choices.[18]

The increased scope for personalized information provision in a wellness context that health technology brings with it is important in getting wellness and lifestyle messages across to the public.[19] Encouragement can be provided remotely to people via technological means, from informational text messaging services, to electronic medical records, activity monitors[20], telemedicine, and more.[21]

Instead of prioritizing biologics and small molecule drugs, which can cost hundreds of thousands of dollars a year for patients with illnesses like rheumatoid arthritis, hepatitis B, and cancer,[22] U.S. health policy should reflect a commitment to innovation in preventive health technology; consequently our patent system should reflect this priority in order to maximize public health. It has been argued that the incentives provided by the patent system are not sufficient to ensure the development of new products in certain areas, for example in the area of orphan drugs.[23] This also may be the case for preventive care and wellness technology, necessitating disruption in order to see change. Disruptive innovation theory, first articulated by Harvard Business School professor Clayton M. Christensen, explains how innovations that decrease cost and increase accessibility transform entire industries.[24] These new innovations are initially inferior to established products, but improve until they "disrupt" and eventually topple existing competitors.[25] The IUD appears to be in the process of disrupting the need for abortion drugs, pregnancy medications, and the birth control pill. By analyzing how the IUD has been able to gain market strides, one can determine policy implications for the preventive health technology industry at large in disrupting reactive health technology moving forward.

AFFORDABLE CARE ACT

The individual mandate of the ACA requires every person to carry health insurance.[26] This is creating an influx of previously uninsured patients, overwhelming the current primary care system and creating the need for new disruptive care technologies in the market.[27] The ACA also requires health plans to provide, at a minimum, a package that includes access to certain types of care and services, specifically preventive health care, including contraception coverage.[28] It is therefore not surprising that more and more women with health insurance are utilizing the IUD, a previously prohibitively expensive medical device. However, the Clayton Christensen Institute argues "this essential health benefits provision discourages disruptive innovation by essentially establishing a floor on the low end of the market, making it even more difficult for disruptive entrants to gain market share."[29] It remains to be seen whether IUD technology

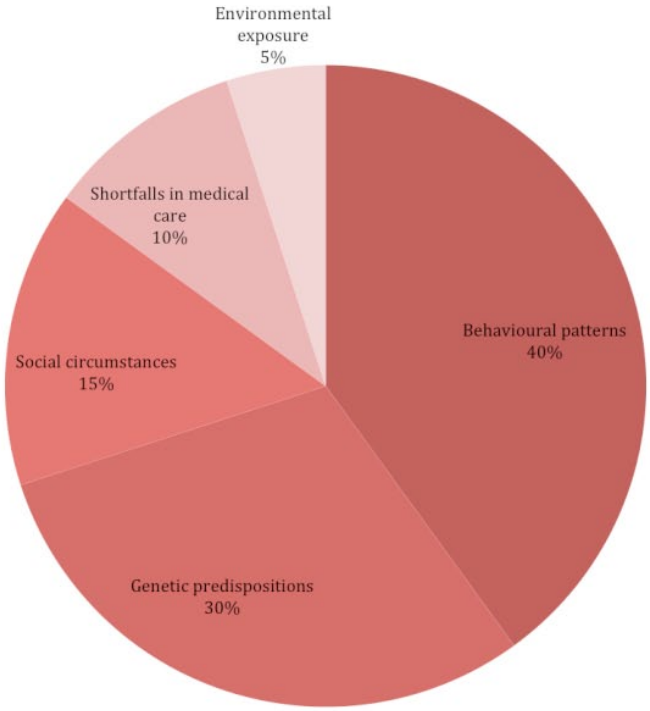

Figure 1: The determinants of health
Source: McGinnis, M.J., Williams-Russo, P., Knickman, J.R. (2002). The Case for More Active Policy Attention to Health Promotion. Health Affairs 2002; 21(78)-93.

will continue to disrupt the existing market, or if this initial surge will fade away.

Another opportunity for biotechnology after the ACA is investment in vaccines, biological products designed to produce immunity to a disease by stimulating the production of antibodies.[30] The human papillomavirus vaccine has proven efficacy in preventing cervical cancer; a study in *Lancet Oncology* "showed that Cervarix was 100 percent effective protecting young women who were not previously infected with HPV from HPV-caused cervical cancer, and offered substantial protection against cancer even for women already exposed to HPV."[31] The University of Rochester was awarded a patent in 2011 for the creation of virus-like particles that mimic HPV 16, which causes the majority of all HPV-related cancers.[32] Soon after, the Advisory Committee on Immunization Practices (ACIP) recommended routine HPV vaccination for women and men ages 11 through 26.[33] Under the ACA's preventive care coverage, individuals will have access to all vaccines recommended by ACIP without co-payments or other cost-sharing requirements.[34] Under this regime, innovators like the University of Rochester benefit financially through patent protection, and patients benefit by gaining no-cost access to preventive health technology.

Lesser-known and less explicit portions of the ACA also seek to encourage focus on prevention.[35] For instance, the ACA "provisions that support the development of Wellness Programs yield another exciting possibility for innovation. These provisions require health plans to offer wellness-focused components targeting preventive and self-directed care. Few argue against the notion that health care costs would drop substantially if we could prevent more chronic diseases and acute illnesses."[36] However, one key hindrance to disruption success is the "job-to-be-done" concept. Products and services that do not meet clearly identifiable jobs-to-be-done tend not to succeed in the marketplace.[37] Most people do not perceive of staying healthy as a "job-to-be-done" until they are already acutely sick, needing reactive care not preventive care.[38] Google Health was a brilliant effort to create a convenient personal health record. The venture failed, however, likely because the vast majority of people do not currently identify "manage my personal health data" as a job.[39] It is also worth noting that increased national focus on preventing unwanted pregnancy and taking responsibility for sexual activity may have resonated with many women as creating a "job-to-be-done" around family planning. Wellness programs hold the promise of encouraging

disruption in health care delivery by helping patients take more ownership of their health, for example utilizing preventive health technology.[40] Innovative companies that create products and/or services that patients can connect with as a "job-to-be-done" will be poised for "explosive growth that could disrupt much of the existing system."[41]

One of the more controversial provisions of the ACA is the medical device tax, which will impose a 2.3% excise tax on domestic sales of all medical devices, except those predominantly sold at retail for use by individuals.[42] The medical device industry has complained that this provision will generate tax dollars at the expense of jobs and innovation.[43] However, this argument is difficult to prove. It is true that a company's revenue funds its investments in research and development, but there is no direct evidence that a tax would affect these investments.[44] It is also true that since the tax is based on a fixed percentage of sales, it will fall most heavily on small and startup companies, which are huge players in the development of innovative technology.[45] On the other hand it is also possible that the device tax could help spur technological innovation. "Large medical device companies have sometimes been criticized for relying on small changes to existing product lines to drive revenue, but such changes may not be able to command so much of a pricing premium as health care dollars become increasingly limited. If a small tax made the industry more effective, enhanced competition could push more investment toward innovations that provide major advances in patient care."[46]

Some of the provisions of the ACA may open doors for disruptive innovation, and some provisions may create barriers to innovation; the responsibility nonetheless rests upon the technology sector—existing players and new innovators alike—to seize the disruption opportunities and create products and services that make health care more affordable and accessible.[47]

GOVERNMENT INTERVENTION

Given the barriers to intervention, present both in health legislation and the patent system in general, it would behoove policymakers to examine alternative or complementary mechanisms for stimulating innovation. Joseph Stiglitz, a Nobel Prize-winning economist, has proposed a prize system: a medical prize fund would reward those innovators who develop treatments or preventions for costly diseases affecting hundreds of millions of people.[48] "Of course, the patent system is itself a prize system, albeit a peculiar one: the prize is temporary monopoly power, implying high prices and restricted access to the benefits that can be derived from the new knowledge."[49] The prize fund would not replace patents, but would be part of the mechanisms for encouraging and supporting research. The prize fund is intended to stimulate areas in which technology needs are well known but not sufficiently developed, perfect for the area of preventive health.[50]

Congress attempted to promote a medical prize fund through H.R. 417, the Medical Innovation Prize Act of 2005.[51] The bill, authored by Representative Bernard Sanders (I-VT), would have directly rewarded developers of medicines, on the basis of the incremental therapeutic benefit to consumers, instead of relying on the patent system and the resulting high drug prices to fund research and development.[52] The intent was to provide more equitable access to health care, and manage overall research and development incentives through a separate mechanism that can be increased or decreased depending on society's needs.[53]

The proposed bill was never passed into law, likely because of the remaining questions surrounding implementation of a prize system. How would one determine whether a technology deserves a prize?[54] How will disputes about awards be adjudicated?[55] The rise of Bernie Sanders on the 2016 presidential circuit may provide an opportunity for Congress to reconvene the possibility of incorporating a prize system into health care.

CONCLUSION

Despite extreme polarization in this country about "Obamacare," nearly everyone can agree that preventive health care in the United States needs to become more affordable and accessible without compromising quality.[56] For that to happen it is crucial for innovators and policymakers to understand and seize the disruption opportunities presented by the changing health demographics of national and global populations.[57] "Harnessing new preventive health technologies to help people live healthier lives is the next great opportunity of our generation," said Young Sohn, president and chief strategy officer of Samsung Electronics.[58] Technological progress such as wearable computing, health sensors, cloud-based analytics, vaccines, and contraception promise to help people take control of their own health and to improve the quality of life for millions of people, if we successfully harness the intellectual property system to take advantage of such technology.[59]

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Legal & Regulatory Update

Recent Developments in Compulsory Licensing of Pharmaceutical Patents in India

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ABSTRACT

On March 9, 2012, under Section 84(1) of the Indian Patents Act, Controller General of Patents granted country's first and only compulsory licence to Natco Pharma to sell Bayer AG's patented oncology drug Nexavar (Sorafenib Tosylate). Since then, India has not issued any other compulsory licence even though two more such applications have been received. India has also implemented a special compulsory licence regime under Section 92A(1), for the manufacture and export of patented pharmaceutical products to any country having insufficient or no manufacturing capacity to address public health needs. In view of the recent developments, and given the economic consequences of compulsory licensing, it has become important for multinational pharmaceutical companies procuring patents and doing business in India to understand the country's compulsory licensing laws and reevaluate their business strategies, while domestic companies pursue alternate options to access patented lifesaving medicines within the legal system.

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INTRODUCTION

In January 1995, when WTO came into existence, the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement introduced minimum standards for protecting and enforcing intellectual property rights based on the existing multilateral treaties administered by the WIPO, including new monitoring and dispute settlement provisions. At the same time, TRIPS (Article 30 and 31) also provided a reasonable fetter on the rights of the patentee, thereby allowing member countries to enact provisions, *inter alia*, for granting compulsory licence (CL) to prevent the abuse of patent right.[1,2] Provision for granting compulsory licence exists in the patent laws of developed (Canada, France, UK, USA, Italy, Germany and Australia) as well as developing (Zimbabwe, Ghana, Brazil, Ecuador, Malaysia, Thailand, Mozambique, Zambia, and India) countries.[3]

A compulsory licence is a statutorily created licence that allows certain parties to use or manufacture a product encompassed by the claims of a patent without the permission of the patent owner (patentee) in exchange for a specified royalty. Compulsory licensing is enabled under four sections of the Indian Patents Act. These are Section 84 (general CLs to be issued by the Controller on application), Section 91(issue of CL by the Controller for a related patent on application), Section 92 (issue of CL by the Controller based upon a notification by the Central Government of circumstances of national emergency or in circumstances of extreme urgency or in case of public non-commercial use) and Section 92A (issue of CL by the Controller on application for manufacture and export of patented pharmaceutical product to any country having insufficient or no manufacturing capacity in the pharmaceutical sector for the product to address public health problems).[4,5]

The Indian Patents Act, 1970 and its Amendment, 2005 contains two very broad compulsory licensing provisions under Sections 84[6] and 92[7].

SECTION 84(1)

Under Section 84(1), the Controller of Patents can issue a compulsory licence three years after the issuance of a patent on any of the following grounds:

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a. The reasonable requirements of the public with respect to the patented invention have not been satisfied, or
b. The patented invention is not available to the public at a reasonably affordable price, or
c. The patented invention is not worked in the territory of India.

Bayer AG v Natco Pharma Ltd.

The Controller General of Patents Designs and Trademarks of India granted country's first and only compulsory licence to Natco Pharma Ltd., an Indian generic drug manufacturer to sell Bayer's patented chemotherapy drug Nexavar (Sorafenib Tosylate, i.e. Carboxy Diphenyl Substituted Ureas) that extends the patient's life by half a year but does not cure the underlying condition. The compulsory licence was issued under Section 84 of the Indian Patents Act on the grounds that the drug was not meeting the reasonable requirements of the public; the drug was not available to the public at a reasonable price and the drug was not being sufficiently "worked" in India as required by the law.

On March 3, 2008, Bayer's patent IN215758 was granted in India and Bayer received regulatory approval for importing and marketing the drug in India. The Indian Patent Office (IPO) found that despite the huge demand, Bayer did not import the drug in 2008 and only a small quantity was imported in 2009 and 2010 and the drug was available to a small percentage of eligible patients (about 2 percent), which did not meet the requirements of the public. Secondly, Bayer cited the cost of drug at a huge price of Rs 280,000 per month (approximately US$ 5,600), which was not "reasonably affordable" to the general cancer patient in India. On the other hand, Natco proposed to sell the drug within India at a price of not more than Rs 8,800 (approximately US$ 176) for a pack of 120 tablets required for one month's treatment and also committed to donate free supplies of the medicines to 600 needy patients every year. Finally, Bayer's patent was not being "worked" in India as Nexavar was not being manufactured in India. Importation from manufacturing facilities outside India did not satisfy the mandatory requirement of working the patent in India. Bayer also refused the request from Natco for a voluntary licence to marketing the drug only in the territory of India. The compulsory licence was issued with 7% royalty to be paid to Bayer.[8]

Bristol Myers Squibs Company v BDR Pharmaceuticals International Pvt. Ltd.

On October 30, 2013, the Controller of Patents of India rejected BDR Pharmaceutical's (BDR) compulsory licence application to sell a generic version of Bristol Myers Squibs's (BMS) blood cancer drug, Sprycel (Dasatinib) for Chronic Myeloid Leukemia (CML) on procedural grounds that sufficient efforts had not been made by BDR to seek a voluntary licence from BMS. The order states that BDR proposed to make the drug available at Rs 8,100 per month per patient (approximately US$ 162), whereas BMS sold the drug at Rs 1,65,680 per month per patient (approximately US$ 3314).[9]

Under Section 84(6)(iv) of Indian Patents Act, any applicant before applying for a compulsory licence must first attempt to procure a voluntary licence from the patentee on reasonable terms and conditions and if such efforts have not been successful within a "reasonable period" not ordinarily exceeding six months, the applicant is free to file a compulsory licence application. In this case, BDR initially requested for a voluntary licence to BMS for manufacturing Dasatinib. In response, BMS raised a series of questions challenging BDR's basic regulatory standards and Good Manufacturing Practices requirements, quality assurance due diligence, commercial supply teams, safety and environmental profile, and risk of local corruption. BDR considered this reply as 'clearly indication of rejection of the application for voluntary licence' and did not make any efforts to retaliate in its defense and exercised the option of filing of compulsory licence. Therefore, the IPO rejected BDR's application on the grounds of lack of *prima facie* case considering insufficient efforts to obtain a voluntary licence for the drug.

AstraZeneca AB v Lee Pharma Ltd.

On August 18, 2015, the Controller of Patents Office in India rejected the Lee Pharma's compulsory licence application for AstraZeneca's Saxagliptin, sold under the brand name Onglyza and Kombiglyze, and prescribed for Type-II Diabetes Mellitus on all the three grounds of Section 84(1): (a) that the substitutes to the drug are readily available in the market; (b) the claim that requirements of public with respect to the patented invention are not being satisfied has not been proven; and (c) the applicant has failed to *prima facie* demonstrate that the patented invention is not worked in the territory of India.[10]

Lee Pharma has stated in its application that (a) there are around 60 million diabetes type II patients in India,

and that 'even if' only 1 million were to be prescribed Saxagliptin, there is more than 99% shortage of the drug in Indian market; (b) the cost for importing one tablet in India is only Rs 0.80 per tablet and the same is being sold by AstraZeneca at market price of Rs 41-45 per tablet (approximately US$ 24-27 per month per patient), whereas the applicant's proposed selling price at Rs 30 per tablet (approximately US$ 18 per month per patient); and (c) the drug is not manufactured in India even after 8 years of grant of the Indian patent by BMS, rather is being imported to India by BMS or AstraZeneca and marketed by AstraZeneca.

However, there were several possible points of contention to Lee Pharma's claims as it seemed to be predicated on a number of factors: First, Saxagliptin is one of at least four (Sitagliptin, Vildagliptin and Linagliptin being the others) available Dipeptidyl Peptidase-4 (DPP-4) inhibitors used to treat Type II Diabetes which are also available in India. Second, the applicant's cost and availability claims were obscured given that patients can already obtain an Indian-manufactured generic version of a similar drug for slightly less than the applicant's proposed selling price, and third, the Controller of Patents stated that to manufacture in India is not a necessary precondition in all cases to establish working in India.

SECTION 92

Under Section 92 of the Indian Patents Act, compulsory licences can be granted on notification by Central Government:

1. In a case of a national emergency (including a public health crisis), extreme urgency or in the event of public non-commercial use; (Section 92(1)); or
2. For export (Section 92A(1)).

In January 2013, Department of Industrial Policy and Promotion (DIPP) under Ministry of Health & Family Welfare set up a Committee for invoking CL provisions on three commonly used anti-cancer drugs in India: Trastuzumab (or Herceptin, used for breast cancer), Lxempra (or Lxabepilone, used for chemotherapy) and Sprycel (or Dasatinib, used for leukemia) under Compulsory Licensing provisions of Section 92(1) of the Patents Act, 1970.

Herceptin, owned by Genentech, (a subsidiary of Roche) was originally priced at Rs 1,10,000 per dose and a breast cancer patient ordinarily requires between 18-20 doses per year that ranges between Rs 22,00,000 to Rs 25,00,000 (approximately US$ 44,000 to US$ 50,000). The price was subsequently reduced marginally to Rs 75,000 per dose i.e. Rs 15,00,000 per year (approximately US$ 30,000), when civil society groups had petitioned the government to adopt policies to reduce the price of drug. Similarly, the patents for the remaining two drugs, Lxempra and Sprycel, both owned by Bristol Myers Squibbs (BMS) has cited the costs at Rs 80,000 and Rs 15,000 per dose (approximately US$ 1,600 and US$ 300), respectively.

SECTION 92A(1)

Section 92A(1)[11] of the Indian law states that a compulsory licence shall be available for manufacture and export of patented pharmaceutical products to any country having insufficient or no manufacturing capacity in the pharmaceutical sector that need them to address public health problems on the condition that the importing country should have issued a compulsory licence or, by notification or otherwise, allowed the importation of these products from India. Whereas, Section 92A(2) states that the compulsory licence is to be granted solely for manufacture and export of the concerned pharmaceutical product, as per the terms and conditions specified by the Controller of Patents, and which must be published. However, no special rules have been put into place to implement Section 92A and this may be viewed as ensuring transparency and appropriate safeguards against implementing the flexibilities under TRIPS.

PRE-EMPTING STRATEGIES TO COMPULSORY LICENSING

Exclusive Voluntary Product Licensing Deals

Multinational companies (MNCs) may sign exclusive voluntary product licence deals with domestic firms. Unlike under compulsory licensing, the MNCs may have the freedom to set the terms at which domestic firms may sell generic versions of their drugs, and this would not only help drug makers to expand the market but also avoid compulsory licensing action. Some of the examples of such deals include: (a) between India's Strides Arcolab Ltd. and the United States-based Gilead Sciences Inc. for a group of HIV/AIDS drugs; (b) Pune-based Emcure Pharmaceuticals Ltd. and Swiss drug manufacturer F. Hoffman La Roche Ltd. for patented cancer drugs; (c) United States-based Merck and India's MSD Pharmaceuticals Pvt. Ltd. and Sun Pharmaceuticals Industries Ltd for patented diabetes drugs; and(d) Swiss drug manufacturer Novartis and Mumbai-based Lupin for a chronic obstructive pulmonary disease drug.[12]

Tiered Drug Pricing Structure in Separate Markets

Pre-empting the move to issue compulsory licences, MNCs may follow a differential pricing system for a drug in developed and developing countries. With assured market separation, the MNCs may offer prices comparable to the prices that a local generic firms would charge, which eliminates the need for compulsory licensing. Therefore, the multinationals will have to explore ways and means of engaging with the government, public bodies and civil society at large to ensure that reasonable profit is not perceived as profiteering.[13] The foreign drug makers may offer these medicines at different tiers of prices for government supply, patient access programmes, hospitals in rural areas and non-profit organizations.

For example, the European Commission Council Regulation (EU, 2002, 2003) intended to create a voluntary global tiered pricing system for key pharmaceuticals for the prevention, diagnosis and treatment of HIV/AIDS, TB and malaria and related diseases for developed countries, developing countries and least developed countries and to prevent product diversion to other markets by ensuring effective safeguards.[14]

CONCLUSION

For many years, pharmaceutical patents and their impact on prices have been a major international debate over insufficient access to lifesaving patented medicines in developing countries. The source of conflict has largely revolved around the implementation of an intellectual property system in the developing world, and the TRIPS mandated international patent laws.

In India, the grant of compulsory licences has been riddled with technical and legal roadblocks. The Natco-Bayer ruling led to extensive debate within the international and domestic pharmaceutical industry and met with a great deal of disapproval from the multinational enterprises regarding the compatibility of the decision with TRIPS. However, India maintained that it had not violated any multilateral trade agreement by granting the compulsory licence and was well within the requirements of international and national legislation, as the Doha Declaration clearly states that member countries are free to determine the grounds on which such licences can be granted. Affordability and availability of life saving patented medicines is a key issue in India considering high disease burden, poor coverage of public insurance and poor per capita income. Therefore, it is believed that, the resultant competition from compulsory licences in the pharmaceutical industry in India would help discipline the market and regulate the prices.

Although, no more compulsory licences have been granted so far, the Indian government has decided to grant innovator drug companies a hearing, whenever an Indian company petitions for the government to grant a compulsory licence on a patented drug. Now, probably, it is time for the multinational companies to change their policies, and adopt to differential pricing and business environment in India, while the Indian companies need to evaluate alternate options for improving and facilitating affordable access to life saving patented medicines within the Indian legal system.

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Article

Intellectual Property Protection for Biologics: Why the Trans-Pacific Partnership (TPP) Trade Agreement Fails to Deliver[i]

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ABSTRACT

Biopharmaceutical research and development is overwhelmingly focused in the U.S. because here it is incentivized and encouraged through a robust intellectual property rights protection environment. Across the board, the United States provides the most comprehensive, effective intellectual property rights protections for biopharmaceuticals. As a result, the industry locates here, researches here and thrives here. With an acknowledgement of the importance of intellectual property rights as well as the wider benefits of biopharmaceutical research and development, it's tremendously disappointing that the recently negotiated Trans-Pacific Partnership (TPP) Trade Agreement fails to deliver sufficient IP protection for biologics. This article explores the importance of a rigorous intellectual property environment for the biopharmaceutical industry through an examination of the importance of data exclusivity provisions. Such protection is critical as the number, complexity and cost of clinical trials increases. Technology inevitably evolves faster than the legal architecture that surrounds it. As technology evolves, making the development of new biologic vaccines and therapies possible, society's commitment to incentivize innovation and protect it must be enshrined in the intellectual property protections of agreements such as the TPP.

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For many patients the new medicines in the development pipeline offer the hope of a treatment or cure. To date there are approximately 7,000 medicines globally in development for a wide variety of diseases. Of these, more than 5,000 are in development in the United States, pointing to the dominance of the United States biopharmaceutical industry (PhRMA, 2015). The numbers are revealing, if not shocking. Biopharmaceutical research and development is overwhelmingly focused in the U.S. because here it is incentivized and encouraged through a robust intellectual property rights protection environment. Across the board, the United States provides the most comprehensive intellectual property rights for biopharmaceuticals. As a result, the industry locates here, researches here and thrives here. It is difficult to argue that the strength and success of the U.S.

i This piece is an extension of an earlier contribution to IPWatchDog. Lybecker, Kristina. "IP Protection for Biologics in the TPP: Trading Away Future Treatments and Cures," IPWatchDog, 26 October 2015. The shorter original article may be found at: http://www.ipwatchdog.com/2015/10/26/ip-protection-for-biologics-in-the-tpp-trading-away-future-treatments-and-cures/id=62692/.

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biopharmaceutical industry is uncorrelated with the IP protection available here.

With an acknowledgement of the importance of intellectual property rights as well as the wider benefits of biopharmaceutical research and development, it's tremendously disappointing that the recently negotiated Trans-Pacific Partnership (TPP) Trade Agreement fails to deliver sufficient IP protection for biologics. The final sticking points, leading up to the final draft, largely focused on the provisions for data exclusivity for biologic medicines. Ultimately, the ratification of the TPP agreement may hinge on precisely this issue. Although Senator Orin G. Hatch (Utah) allied himself with President Obama to help conclude the trade negotiations among the 12 Pacific Rim nations, he has made it clear that the TPP falls short in its protection for biologic medicines, going so far as to call for a renegotiation of the agreement (Calmes, 2015).

To start, it is critical to understand why this is an issue and what the debate consists of. Due to the great expense of bringing a new medicine to market, the intellectual property rights protection granted to innovators is disproportionally important for the biopharmaceutical industry to ensure that the researcher appropriates the returns to R&D.[ii] Protection is essential in these industries due to the extremely high costs of R&D that accompany many new drugs, as well as the competitive nature of the industry.[iii] That is, given the ease of replicating chemical and pharmaceutical innovations, intellectual property protection is vital for the economic profitability of these firms. Current estimates place the preapproval cost of developing a biologic at close to $1.2 billion and the time needed to recover these costs is between 12.9 and 16.2 years (DiMasi & Grabowski, 2007; Grabowski, Long & Mortimer, 2011). Acknowledging that these numbers are highly controversial, drug development is undeniably expensive and the process requires a significant investment of time, scientific talent, and money.

Intellectual property rights protection incentivizes these investments, facilitating biopharmaceutical research and development. Biologic medicines are fundamentally different from traditional "small molecule" therapies, presenting a host of new challenges in the design and enforcement of the intellectual property (IP) architecture that will protect them.[iv] Protecting the intellectual property of biologics is complex, difficult, and essential to the future of medicine. The nuances of producing biologics greatly complicate the logistics of protecting their intellectual property, making patents alone inadequate for safeguarding their IP. In the context of the TPP, the crux of the debate over IP protection for biologics focuses on the provisions of data exclusivity protection. For the innovator, the period of data exclusivity provides a window of time, following marketing approval, during which competing firms are prohibited from using the innovative firm's safety and efficacy data, from proprietary preclinical and clinical trial results, to secure marketing authorization for a biosimilar (generic) version of the drug. Proprietary data is generated from day one when the compound first shows medicinal promise – a process that is lengthy, time-consuming, and expensive. The firm's investment in clinical trials and the collection of this data is thus protected for a fixed period,

ii Building on the 1987 "Yale Survey" (Levin, Klevorick, Nelson and Winter 1987), Cohen et al. reexamine the effectiveness of various means of appropriating intellectual property. Echoing the earlier findings, the 1994 "Carnegie-Mellon" survey finds that there are tremendous differences in the effectiveness of various appropriability mechanisms, both among industries as well as within them. Overall, while patents are again seen as "unambiguously the least effective of the appropriability mechanisms," the drug industry regards them as strictly more effective than alternative mechanisms (Cohen, Nelson and Walsh 1996, p.14). This is confirmed by the industry's high propensity to patent both product innovations (overall highest propensity at 99%) and process innovations (fourth highest propensity at 43%) (Cohen, Nelson, and Walsh 1996, pp.21-22). Dozens of other studies report that the protection of intellectual property is disproportionally more important to the chemical and pharmaceutical industries. These originated with: Levin, Klevorick, Nelson and Winter (1987), Taylor and Silberston (1973), Scherer (1997), Mansfield (1986), Mansfield, Schwartz and Wagner (1981), and Tocker (1988). These studies are echoed by arguments from within the pharmaceutical industry: Mossinghoff (1998), Peretz (1983), Mossinghoff (1987), Santoro (1995), Smith (1990a, 1990b), and Mossinghoff and Bombelles (1996).

iii The competitive nature of the industry has increased with the aggressive introduction of generics upon patent expiry. In a recent study of 18 patented brand-name drugs, Grabowski and Vernon (1990) found that generics gained close to half of the market share within two years of entry.

iv Historically, pharmaceuticals have been small, chemically manufactured molecules and these molecules still comprise more than ninety percent of drugs currently available. "Small molecule" therapies are synthesized by chemical reactions between different organic and/or inorganic compounds. In comparison, biologics or large molecules are therapeutic proteins and are most often derived from living cells. Biologics are produced from micro-organisms or animals by utilizing the metabolic processes of the organisms themselves.

Table 1: Trends in clinical trial protocol complexity[vi,vii]

	2000-2003	2008-2011	Percentage change
Total Procedures per Trial Protocol (media) (e.g., bloodwork, routine exams, x-rays, etc.)	105.9	166.6	57%
Total Investigative Site Work Burden (median units)	28.9	47.5	64%
Total Eligibility Criteria	31	46	58%
Clinical Trial Treatment Period (median days)	140	175	25%
Number of Case Report Form Pages per Protocol (median)	55	171	227%

regardless of the length of time necessary to bring the drug to market.

While patents and data exclusivity protection are complementary in incentivizing innovation, they function in different ways and serve distinct purposes. Patents protect innovations that meet the standards of patentability and are novel, nonobvious, and useful. In the context of biologics and the biopharmaceutical industry, patents protect both breakthrough discoveries as well as incremental improvements. Due to the length of the drug-development and patent-approval processes, effective patent terms rarely correspond to FDA approval. Accordingly, in some cases innovative therapies may experience patent expiry shortly after arriving on the market. In contrast to patents, data exclusivity protects the tremendous investments of time, talent, and financial resources required to establish a new therapy as safe and effective, protection that may extend beyond patent expiry. Data exclusivity is not an extension of patent rights, and it does not preclude a third party from introducing a generic version of the innovator's therapy during the data exclusivity period, provided that the innovator's data is not used to secure marketing approval. This is accomplished by requiring biosimilar firms applying for regulatory approval of the same or a similar product to independently generate the comprehensive preclinical and clinical trial data rather than rely on or use the innovator's data to establish safety and efficacy of their competing product. Given the nontrivial cost of generating and collecting this data, the competing firm may instead wait a set period of time after which they are able to utilize the innovator's prior approval in an abbreviated regulatory approval, eliminating the need for independently generated data. Fundamentally, data exclusivity protection incentivizes biopharmaceutical firms to invest the necessary time and financial resources in establishing the safety and efficacy of their product and prevents competitors from free riding on these efforts for a limited period of time.

While data exclusivity protection provisions are included in the Trans-Pacific Partnership Trade Agreement, the length of this period of protection was a major source of disagreement during the negotiations and remains at the heart of Senator Hatch's criticism of the final text. That is, how long are biosimilar firms required to wait before they are allowed to take the regulatory shortcut and use the innovator's data to secure regulatory approval. Internationally the period of time varies significantly across countries, including across TPP signatories. In Europe, for marketing authorization applications made after November 2005, the period of data exclusivity has been harmonized at eight years from the date of first authorization. Australia, Singapore and South Korea provide five years of data exclusivity. Under U.S. law, the innovator's data is granted 12 years of exclusivity. This period was vigorously debated and analyzed before being established. And yet, even this timeframe fails to provide the minimum (12.9 years) number of years needed to recover the development costs.[v,vi,vii] Under the proposed TPP Agreement, innovators would only be granted five years of protection. Critics claim that this is a victory for the pharmaceutical industry, noting that Peru, Vietnam, Malaysia and Mexico who currently provide no data exclusivity for biologic medicines, will have

v As mentioned earlier, according to recent studies, the preapproval cost of developing a biologic is close to $1.2 billion and the time needed to recover these costs is between 12.9 and 16.2 years.

vi The complexity of the clinical trials results from a variety of factors including a shift in focus from acute to chronic illness, collection of increasingly intricate data elements, closer attention to each element of trial design, and concern about potential requests from regulatory agencies (Getz, Campo and Kaitin, 2011).

vii Source: PhRMA. "Biopharmaceuticals in Perspective," Spring 2013. Available at: http://www.slideshare.net/PhRMA/phrma-chart-pack-april-2013?related=1.

to wait at least five years before allowing biosimilars onto the market. Notably these are not innovator countries, yet they fully enjoy the benefits of costly pharmaceutical innovation. Removing the incentives to innovate cannot be considered a victory by any stretch of the imagination.

Given that data exclusivity provisions are at the heart of securing Congressional support for the Trans-Pacific Partnership, it is essential to understand why this protection is of utmost importance to the biopharmaceutical industry. First, it is worth noting that the complexity of clinical trials and the approval process has increased considerably, as shown in Table 1 above.

As clinical trials increase in length and complexity for FDA approval, the medicine's effective patent life is shortened. Biopharmaceutical firms seeking approval by the U.S. Food and Drug Administration (FDA) will have examined 5,000 to 10,000 experimental compounds over a ten to fifteen year period, and ultimately typically only one will gain approval. Moreover, a mere three out of every ten pharmaceuticals developed will recover the financing required for their development, leaving those few blockbuster products to cover the expenses of numerous failures.[viii] All the while, the uniqueness of the innovation is threatened by the ease of their replication. Innovative biologic firms are significantly disadvantaged if biosimilar firms do not have to bear the research and development costs and are still able to bring a biosimilar (generic version) to market, compete and sell the drugs.

This is further compounded by the significant and increasing cost of clinical trials, which are overwhelmingly borne by biopharmaceutical firms. Clinical trials now account for the largest portion of drug development costs. According to Adams and Brantner (2010), in 2010, the average costs of Phase I, II and II clinical trials were estimated to be $24 million, $86 million, and $61 million, respectively. More recently, a 2012 study calculates that on average 90 percent or more of a drug's development costs are incurred in Phase III trials (Roy, 2012). In 2013 the biopharmaceutical industry sponsored 6,199 clinical trials of medicines in the United States, involving a total of 1.1 million participants (Battelle, 2015). Table 2, below, describes the breakdown of these trials, while Figure 1 provides the estimated average per-patient clinical trial costs, by phase.

The lion's share of the expense of lengthy clinical trials is borne by the biopharmaceutical industry. According to a recent study by researchers at Johns Hopkins Bloomberg School of Public Health, the biopharmaceutical drug and medical device industry now funds six times more clinical trials than the federal government (Desmon, 2015). The study reports on both industry-sponsored trials and National Institutes of Health (NIH) funded trials between 2006 and 2014.[ix] The researchers find that the number of newly registered industry-sponsored trials grew by 43 percent in the intervening eight years, from 4,585 in 2006 to 6,550 in 2014, while the number of newly registered NIH-funded trials decreased 24 percent over the same period, from 1,376 in 2006 to 1,048 in 2014. The trend emerged as the budget for the National Institutes of Health suffered a 14 percent decrease since 2006 (Cohn, 2015).

Table 2: Estimated number of industry-sponsored clinical trials and trial participants by phase, 2013

Phase	Number of Active Clinical Trials	Estimated Total U.S. Enrollment
Phase 0	35	3,222
Phase I	1,392	119,536
Phase II	2,562	215,740
Phase III	1,680	644,684
Phase IV	530	165,158
Total	6,199	1,148,340

Source: Battelle, 2015.

The numbers are indicative of an important trend. As described by Dr. Reshma Jagsi, the deputy chair of the Department of Radiation Oncology at the University of Michigan, the study confirms "a quiet but critical shift in the funding of clinical trial – the evidence upon which we base changes in medical practice" (Cohn, 2015). As such, it is critical that clinical trials deliver the information that best informs public health decisions. Not surprisingly, clinical trials funded by the biopharmaceutical industry frequently differ from those funded by government entities such as the NIH. Dr. Stephan Ehrhardt, the leader of the Johns Hopkins study, points out that while an industry-funded trial of a blood pressure drug might test that drug in comparison to a placebo, an NIH-funded study would investigate the drugs performance against other drugs or diet and exercise. In like manner, an industry-funded trial of a drug for tumors might analyze the drug's ability to shrink a tumor, not its ability to

viii Grabowski, Vernon, and DiMasi, PharmacoEcon 2002.

ix The authors searched ClinicalTrials.gov for trials identified as an "interventional study" and then identified the funder type for trials registered between 2006 and 2014. Registration on ClinicalTrials.gov is required for both industry-funded and NIH trials if the researchers intend to publish the results. The study notes that ClinicalTrials.gov is the largest online registry in the world.

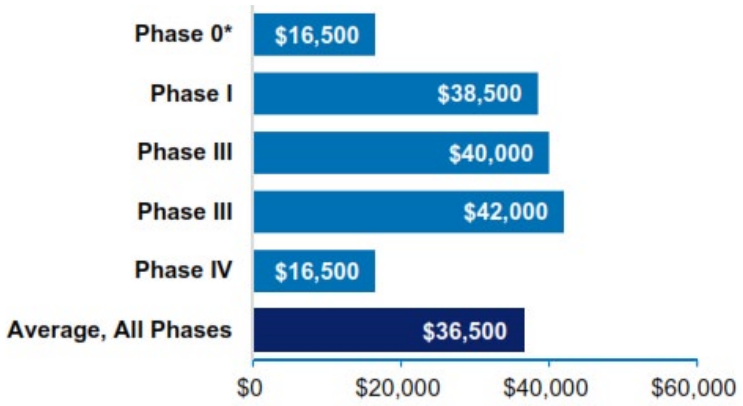

Figure 1: Estimated Average Per-Patient Clinical Trial Costs, by Phase, 2013
Source: Battelle, 2015.

extend a patient's life or enhance the quality of that life (Cohn, 2015).

The Johns Hopkins study highlights the significant role of the biopharmaceutical industry in funding clinical trials. Assuring innovators a return on their investments in drug development, including costly clinical trials, is essential to incentivizing this research and to the discovery of future treatments and cures. This points to the critical importance of data exclusivity protection, in the TPP Agreement and future trade agreements.

The design of intellectual property rights protection shapes innovation. As such, the data exclusivity provisions in the TPP and all intellectual property policies that have the potential to stifle innovation should be viewed with skepticism and adopted with caution. In the context of healthcare and drug development, a recent study by Budish, Roin, and Williams (2015) provides important evidence on how IP policy decisions influence the direction of research and ultimately the biopharmaceutical medicines that are developed. The study shows that biopharmaceutical firms underinvest in long-term research on treatments for early-stage cancers due to the increased time and expense required to engage in such research, specifically lengthy clinical trials. Drugs for the treatment of late-stage cancers are less expensive to develop, in part because late-stage drugs extend patients' lives for a shorter period of time such that clinical trials are concluded more quickly. Accordingly, drugs for late-stage cancers require less time to research, develop, test and bring to market than those that treat earlier stage cancers, providing the innovator with a longer effective patent life. In essence, less research and development investment is directed toward drugs that treat patient groups requiring lengthy clinical trials, those with longer commercialization lags.

Budish, Roin and Williams proxy the commercialization lag with a greater five-year survival rate which equates to a shorter effective patent life. Their results indicate that, for a given diagnosis, a ten percent increase in the five-year survival rate is correlated with an 8.7 percent reduction in R&D investment. The study includes over 200 subcategories of cancers, spanning a number of different stages of development. Utilizing data on clinical trials that use mortality vs. those that use "surrogate endpoints" (biomarkers[x]) to establish effectiveness, in addition to a host of complementary evidence, the study suggests that the distortions in R&D investments, resulting from variations in effective patent lives, generates an underinvestment in long-term cancer research. Accordingly, existing R&D investments fall short, delivering fewer potential life-years saved as they might if research and development on early-stage cancers and cancer prevention were incentivized with longer effective patent lives. If society wants innovation on treatments and cures for all diseases – even those that are the most challenging to treat, we must ensure that this research is incentivized and that firms are able to capture the benefit of their successes.

x That is, surrogate endpoints are outcome measures that reflect important milestones, though they are not of direct practical importance. For example: measures of cholesterol may be used in clinical trials where cholesterol reduction is used as a proxy (surrogate endpoint) for reduced mortality; blood pressure is frequently used as an outcome in clinical trials since it is a risk factor for stroke and heart attacks. Physiological or biochemical markers are frequently used as surrogate endpoints since they are quickly and easily measured and are assumed to predict important clinical outcomes. (www.medicine.ox.ac.uk/bandolier/booth/glossary/surrog.html).

Simply put, the benefits of breakthrough biopharmaceutical innovation should be available to all, but the innovator should be rewarded as well. Under the TPP Agreement, the incentive to invest in the risky, expensive, time-consuming drug development process is reduced. Shortened periods of data exclusivity protection will undoubtedly hasten biosimilar competition and save money for the non-innovating nations, but it may cost us all a future of breakthrough therapies and cures.

Technology inevitably evolves faster than the legal architecture that surrounds it. The provision of data exclusivity protections is a prudent legal step to catch up to the science that brings us biologic medicines. Biologic medicines are critical to the healthcare advances of the future, and data exclusivity is vital to innovative biologics. The period of data exclusivity provides innovators with an incentive to invest in generating and collecting the testing data necessary to prove a drug's safety and efficacy. Data exclusivity grants innovators a measure of certainty that they will enjoy a fixed amount of time during which they maintain proprietary control of the test data that resulted in the approval of their drug before requiring that data be made available to biosimilar imitators. As technology evolves, making the development of new biologic vaccines and therapies possible, society's commitment to incentivize innovation and protect it must be enshrined in the intellectual property protections of agreements such as the TPP.

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Article

Using a Rasch Model to Rank Big Pharmaceutical Firms by Financial Performance

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ABSTRACT

We explore a Rasch approach to ranking the top 15 firms in the pharmaceutical industry by their overall financial performance. Using an initial set of ratios spanning multiple dimensions of firm financial performance, we select the ratios that are compatible with the requirements of the Rasch model for this industry during 2002–2013. We then identify the firms that most frequently ranked among the top five performers. Three firms stand out as consistently disclosing the required data and showing up at the top of the performance spectrum. Our approach offers a new perspective on the valuation of managers and their firms.

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Keywords: biopharmaceutical, ranking, Rasch model, financial peformance

INTRODUCTION

Financial ratios in the biopharmaceutical industry have long been analyzed as measures of firms' financial condition to predict corporate failure and stock returns (e.g., Goodman, 2009, Lewellen, 2004). However, a recent study by Jiang and Lee (2012) suggests that the predictive power of financial ratios cannot be understood unless financial ratios are decomposed into their cyclical and stochastic trend components. Instead of contributing to the analysis of financial ratios as forecasting tools, we focus on their use as firm financial performance metrics. We select financial ratios that cover the main dimensions of firm performance, in order to better understand the varied challenges managers face when steering their firms towards success in all major financial performance components.

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To analyze the overall financial performance of the top 15 firms in the pharmaceutical industry, we apply the Rasch approach explored for individual industries by Schellhorn and Sharma (2013). We select a comprehensive set of financial ratios in order to better understand the main performance dimensions that determine whether managers are able to lead their firms to success in this sample of big pharmaceutical firms. The financial ratios selected for this study span eight dimensions: liquidity, profitability, financial leverage, resource utilization, growth, return on investment, market valuation, and enterprise value. Our application of the Rasch model reveals no particular financial ratio difficulty hierarchy but a distinct ranking of firms' composite financial performance. Based on the results of Bertrand and Schoar (2003), we attribute the firm performance rankings, at least in part, to differences in the abilities of managers to lead their firms to success across the spectrum of relevant firm financial performance metrics.

In the human sciences, a dichotomous Rasch model is typically employed to predict the probability of a person's success on a test that consists of several questions or items. The probability of a correct response increases

with higher measures of person ability and with lower measures of item difficulty. In other words, a person is more likely to do well on any one test item, if the person has answered many of the test items correctly. A correct response is also more likely, if the test item is comparatively easy, i.e. most people, who have taken the test, have answered the item correctly.

We assume that firms being evaluated by a number of financial ratios covering various performance dimensions are comparable to people trying to successfully take a test consisting of several questions. Managers' ability to guide their firms to financial success, then, corresponds to person ability, and the difficulty of getting a favorable reading on a financial metric corresponds to the difficulty of finding the correct answer to a test question.

We apply the Rasch model to 24 financial ratios for the 15 biggest pharmaceutical firms for the years 2002 – 2013. Of the 24 ratios, we identify 18 ratios that are consistent with the requirements of the Rasch model and suitable for ranking composite firm financial performance for this sample during these years. Our results identify the firms that most consistently disclose relevant financial information and achieve top overall financial performance. We do not find a reliable metric difficulty ranking for this sample of firms.

In the next section, we briefly describe the Rasch model. Section 3 discusses our data and model application. Section 4 summarizes our results for the rankings of financial ratios and firms. Section 5 outlines the limitations of this approach and future research.

THE RASCH MODEL

We apply the dichotomous Rasch model developed by Georg Rasch in 1960,[i] the simplest in the family of Rasch models, to the ranking of firms by managerial ability as reflected in the firm's financial performance along several dimensions. Consistent with the assumptions made for measurements in the physical sciences, the Rasch models have been applied primarily in the human sciences for the calibration of tests and measurements of student ability. The dichotomous Rasch model used in this paper, defines the conditional probability P_{ni} of a correct answer with score x=1 (as opposed to x=0) by person n to a test item i as a function of the difference between the estimated ability of the person (B_n) and the estimated difficulty of the item (D_i):

$$P_{ni}(x_{ni}=1/B_n,D_i) = \frac{e^{(B_n - D_i)}}{1+e^{(B_n - D_i)}} \qquad (1)$$

The calculation of probabilities involves an iterative procedure, which estimates person ability and item difficulty on a logit scale with the average logit set to equal zero.[ii] The model implies that, when person ability is exactly matched by item difficulty (B_n-D_i=0), the person has a 50% chance of correctly answering the item. When item difficulty exceeds person ability, the probability of success is less than 50%, while it exceeds 50% when person ability is greater than item difficulty.

The application of the dichotomous Rasch model to ranking firms by the ability of their managers to lead them to success in multiple areas of financial performance simultaneously, is straightforward in that managers (and the firms they run) are comparable to students, whose performance and abilities are being tested. Various firm financial performance measures, then, correspond to the items on a test of student ability, and the difficulty of getting a favorable reading on a financial ratio corresponds to the difficulty of a particular test item.

The Rasch model requires a certain relationship among the data: The probability of managerial (and firm) success is a logistic function of the difference between managerial ability and financial ratio difficulty. The data for a set of financial ratios of firms in a particular industry at a particular time either fit this model, or they don't. Measures of fit provide information about how well any given data set meets the requirements of the Rasch model.

DATA AND MODEL APPLICATION

We chose 24 market and accounting ratios to represent a broad spectrum of firm financial performance for the top 15 firms by revenue in the pharmaceutical industry with NAICS code 325412. Our data from Compustat span the years 2002 – 2013. For all years, we eliminate firms that have a fiscal year end that is different from December 31st, and we eliminate firms with missing data or data that result in ratios that do not make sense. The number of firms reporting a complete set of financial information varies from year to year. In order to avoid losing information, for each year, we include all the firms for which data are available.

To measure managers' ability to lead their firms to broad-based financial success, we begin by looking at 24 ratios covering the following major dimensions of firm financial performance: liquidity, profitability, financial leverage, resource utilization, growth, return on investment, market valuation, and enterprise value. We use the current ratio (CR), the quick ratio (QR), and sales divided by receivables (SR) to measure the

i See Rasch (1960).

ii See Appendix A in Bond and Fox (2007) for an in-depth discussion of the technical aspects of the Rasch model.

firm's liquidity. Gross margin (GM), operating margin defined as EBITDA divided by sales (OM), net margin (NM) and EBITDA divided by assets (EA) measure profitability. The times-interest-earned ratio (TIE), the equity ratio (ER) and the assets-to-debt ratio (AD) measure financial leverage and the firm's exposure to financial risk. R&D divided by sales (RDS), sales divided by assets (SA) and sales divided by employee (SEM) measure resource utilization. Sales growth (SG) and the growth of earnings-per-share diluted excluding extraordinary items (EG) measure growth. The return-on-equity (ROE) and the return-on-assets (ROA) measure the return on a dollar invested in the firm's equity and assets, respectively. An alternative measure for return on investment, retained earnings divided by equity (REE), is also included. The price-to-sales ratio (PS), the price-to-earnings ratio (PE) and the price-to-book ratio (PB) measure investors' view of the value of the firm's sales, earnings and equity. Enterprise value divided by sales (EPVS), enterprise value growth (EPVG) and enterprise value divided by EBITDA (EPVE) are the enterprise value metrics.

Application of the dichotomous Rasch model requires translation of the firms' readings on these financial ratios into dichotomous values (1, 0). The value of one represents a correct response, i.e., success, while a value of zero denotes an incorrect response, i.e., failure. For the set of financial ratios used in this analysis, readings above the industry average are considered favorable (ratio value is set to 1), while readings below the industry average are categorized as unfavorable (ratio value is set to 0). This interpretation of a firm's financial ratios is admittedly simplistic. It is possible, in some instances, that very high values for individual ratios indicate problems with managerial performance rather than success. The reading is positive when, in fact, it should have been negative. This problem is similar to a student choosing a correct test question answer not deliberately, but by sheer luck, which would likely result in fit statistics outside the acceptable range for the student rankings. Similar to an educational setting, to the extent Rasch results for firm rankings are used for actual decision-making purposes, extreme fit statistics would have to be investigated more closely on a case-by-case basis.[iii]

Our analysis consists of two steps: In the first step, the firm rankings are ignored as the focus is solely on the standardized chi-square fit statistics (infit t and outfit t values) to help determine whether each financial ratio meaningfully contributes to the assessment of managers' ability to lead their firms to success across the financial performance spectrum. Infit t values and outfit t values in the range of +2.0 and -2.0 indicate that a given financial metric is compatible with the requirements of the Rasch model and suitable for ranking performance for the sample firms. While both infit and outfit statistics measure how well the data fit the Rasch model, the infit statistic gives relatively less weight to outliers and, therefore, tends to receive more attention than the outfit statistic. We use the infit t statistic to select the financial ratios to be included in the second step. If a ratio has an infit t statistic outside the acceptable range in any year during our sample period, that ratio is excluded from the second step of the analysis, regardless of whether or not the outfit t statistic is in the acceptable range.

In the second step, the selected ratios for this sample help determine the ranking of firm composite financial performance and, simultaneously, the ranking of financial ratio difficulty. The results of both steps are discussed in the next section.[iv]

RESULTS

The results for the first step of our analysis are reported in Table 1. The number of the top 15 pharmaceutical firms with data that conform to our requirements during 2002-2013 ranges from 9-15. The number of firms in our sample with all the required data is lowest for the years 2009, 2012 and 2013.

The Rasch Ratio Reliability Index for ratio difficulty is zero for most years with a high of 0.29 in 2002. This Reliability Index measures the repeatability of the difficulty rankings for these financial ratios, if these same ratios were measured for a similar sample of firms. Given the low reliability readings for our set of 24 metrics, we conclude that there is no meaningful financial metric difficulty hierarchy. However, we identify 18 ratios that conform to the requirements of the Rasch model in each of the 12 years.

In the second step of our analysis, we simultaneously investigate the ranking of firm financial performance and the hierarchy of financial metric difficulty for the 18 ratios that were found to conform to the requirements of the Rash model. Again, we fail to find a meaningful difficulty ranking for these financial metrics when measured for the top 15 pharmaceuticals, see Table 2. The Rasch Ratio Reliability Index is zero in most years with

iii It is also important to emphasize that the transformation of raw scores into logits for both composite firm performance (i.e., managerial ability) and ratio difficulty provides an ordinal rather than a cardinal measurement.

iv The Rasch analysis software for both steps of our analysis was provided on a CD that accompanied Bond and Fox (2007). The control and data file setup we use is associated with the discussion in chapter four of this book.

Table 1: Fit statistics outside the acceptable range for 24 financial ratios. Top 15 pharmaceutical firms infit t / outfit t greater than 2.0 or less than -2.0 (2002–2013)

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Liquidity												
CR	*	2.4	*	*	*	*	*	*	*	*	*	*
	*	2.1	*	*	*	*	*	*	*	*	*	*
QR	*	2.4	*	*	*	*	*	*	*	*	*	*
	*	2.1	*	*	*	*	*	*	*	*	*	*
SR	*	*	*	*	*	*	*	*	*	*	*	*
	*	*	*	*	*	*	*	*	*	*	*	*
Profitability												
GM	*	*	*	*	*	*	*	2.2	*	*	*	*
	*	*	*	*	*	*	*	2.2	*	*	*	*
OM	*	*	*	*	*	*	*	*	*	*	*	*
	*	*	*	*	*	*	*	*	*	*	*	*
NM	*	*	*	*	*	*	*	*	*	*	*	*
	*	*	*	*	*	*	*	*	*	*	*	*
EA	*	*	*	*	*	*	*	*	*	*	*	*
	*	*	*	*	*	*	*	*	*	*	*	*
Financial Leverage												
TIE	*	*	*	*	*	*	*	*	*	*	*	*
	*	*	*	*	*	*	*	*	*	*	*	*
ER	*	*	*	*	*	*	*	*	*	*	*	*
	*	*	*	*	*	*	*	*	*	*	2.1	*
AD	*	*	*	*	*	*	*	*	*	*	*	*
	*	*	*	*	*	*	*	*	*	*	*	*

Resource Utilization												
RDS	*	*	*	*	*	*	*	*	*	*	*	*
	2.1	*	*	*	*	*	*	*	*	*	*	*
SA	*	*	*	*	*	*	*	*	*	*	*	*
	*	*	*	*	*	*	*	*	*	*	*	*
SEM	*	*	*	*	*	*	*	*	*	*	*	*
	*	*	*	*	*	*	*	*	*	*	*	*
Growth												
SG	*	*	*	*	*	*	*	*	*	*	*	*
	*	*	*	*	*	*	*	*	*	*	2.4	*
EG	*	*	*	*	*	*	*	*	*	*	*	*
	*	*	*	*	*	*	*	*	*	*	*	*
Return on Investment												
ROE	*	*	*	*	*	*	*	*	*	*	*	*
	*	*	*	*	*	*	*	*	*	*	*	*
ROA	*	*	*	*	*	*	*	*	*	*	*	*
	*	*	*	*	*	*	*	*	*	*	*	*
REE	*	*	2.1	*	*	*	*	*	*	*	*	*
	*	*	2.3	*	*	*	*	*	*	*	*	*
Market Valuation												
PS	*	*	*	*	*	*	*	*	*	*	*	*
	*	*	*	*	*	*	*	*	*	*	*	*
PE	*	*	*	*	*	*	*	*	*	*	*	2.5
	*	*	*	*	*	*	*	*	*	*	*	2.7
PB	*	*	*	*	*	*	*	*	*	*	*	*
	*	*	*	*	*	*	*	*	*	*	*	*

Table 1: Continued

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Enterprise Value												
EPVS	*	*	*	*	*	*	*	*	*	*	*	*
	*	*	*	*	*	*	*	*	*	*	*	*
EPVG	*	*	*	*	*	*	*	*	*	*	*	*
	*	*	*	*	*	*	*	*	*	*	*	*
EPVE	*	*	*	*	*	*	*	*	*	2.1	*	*
	*	*	*	*	*	*	*	*	*	2.3	*	*
Rasch Ratio Reliability Index	0.29	0.25	0.00	0.00	0.02	0.26	0.00	0.00	0.00	0.00	0.00	0.00
No. of Firms	13	13	12	15	13	13	11	9	10	10	9	9

*Notes: Infit t and outfit t statistics measure whether the sample data meet the requirements of the Rasch model. * denotes infit t or outfit t values in the acceptable range, i.e., less than or equal to 2.0 or greater than or equal to -2.0. CR is the current ratio, QR is the quick ratio, SR is the sales-to-receivables ratio, GM is gross margin, OM is operating margin (EBITDA divided by sales), NM is net margin, EA is EBITDA divided by assets, TIE is the times-interest-earned ratio, ER is the equity ratio, AD is the assets-to-debt ratio, RDS is R&D divided by sales, SA is sales divided by assets, SEM is sales divided by employee, SG is sales growth, EG is growth of earnings-per-share diluted excl. extraordinary items, ROE is the return on equity, ROA is the return on assets, REE is retained earnings divided by equity, PS is the price-to-sales ratio, PE is the price-to-earnings ratio, and PB is the price-to-book ratio. EPVS is enterprise value divided by sales, EPVG is enterprise value growth, and EPVE is enterprise value divided by EBITDA. The ratio reliability index is reported on a 0 to 1 scale with 1 being maximum reliability for ranking metrics by how difficult it is to get a favorable reading.*

a high of 0.18 in 2007. Thus, we do not recognize any difference in financial metric difficulty for this particular set of firms and metrics.

Table 3 reports summary statistics for the analysis of the financial ratio difficulty hierarchy. The mean ratio difficulty measures are set to zero for non-extreme ratio readings by the model by default. Mean infit t and mean outfit t values for the non-extreme readings confirm that the available data largely conform to the requirements of the Rasch model.

We document the firm financial performance rankings in Table 4. Managers' ability to lead their firms to success across the firm financial performance spectrum appears to be concentrated in only three firms among the top 15 pharmaceutical firms: Bayer AG, Johnson and Johnson and Amgen, Inc. Each of these firms appears in the group of Top Five financial performers for 10 years during 2002–2013. Only three other firms are in the group of the Top Five for five or more years in this sample period: Roche Holding AG, GlaxoSmithKline PLC, and Lilly (Eli) & CO.

Both Rasch Real Firm Reliability and Cronbach-Alpha Reliability Indices are reported for every year in the sample period. The reliability indices indicate the replicability of firm rankings, if a given sample of firms were evaluated along another similar set of financial ratios. The reliability indices are reported on a 0 to 1 scale with 1 being maximum reliability. Both the Rasch Real Firm Reliability Index and the Cronbach-Alpha Reliability Index are based on raw scores rather than logit measures and, therefore, provide relatively conservative estimates of replicability.[v] Both reliability indices are relatively high ranging from 0.71 to 0.80 for the Rasch Real Firm Reliability Index and from 0.80 to 0.89 for the Cronbach-Alpha Reliability Index.

Table 5 reports summary statistics for the firm financial performance rankings. Mean performance measures near zero indicate that the ratio difficulties are well matched with the ability of the firms' managers to achieve success across the spectrum of performance metrics. Positive mean values indicate that managers, on average, find it relatively easy to achieve positive ratio readings. Negative mean values suggest that managers, on average, are struggling. In the case of the top 15 pharmaceutical firms, it appears that the managers of the firms that reported the required financial information found it particularly easy to achieve success in the years 2008-2011, during and right after the financial crisis. A possible explanation is that a very negative performance by a few firms during those years pulled down the averages so that it was relatively easy for the others to excel. Mean infit t and outfit t values for the non-extreme readings confirm that the data largely fit the requirements of the Rasch model. Big absolute differences between the Rasch Real Firm Reliability Index and the Cronbach-Alpha Reliability Index, as for 2011, most likely result from differences in the assumptions implied in the calculation of each index, and the way the index calculations treat extreme ratio readings for that year.

In summary, the Rasch rankings for the top 15 pharmaceutical firms for 2002-2013 reveal apparent differences, across firms and over time, in managers' ability to guide their firms to top overall financial performance.

5. LIMITATIONS AND FUTURE RESEARCH

The limitations and caveats emphasized in Schellhorn and Sharma (2013) also apply to this study. In order for the results to make sense, the relationships among the data have to fit the requirements of the Rasch model. While the data in this study exhibit reasonable fit, other industries and other time periods will yield different fit results.

It is important to remember that most financial ratios and other metrics are continuous. When these continuous variables are translated into binary measures for use in the dichotomous Rasch model, some of the information provided by the underlying variables is necessarily lost. In addition, it is not always clear which threshold distinguishes success or a "correct" outcome (ratio value is set to equal one) from failure, i.e. an "incorrect" outcome (ratio value is set to equal zero). Using the metric average for a given industry as the defining threshold is one possible solution to this problem, but alternatives may be worth considering. As mentioned in Section 3 above, extreme values may be misinterpreted as success when, in reality, they represent failures. The resulting fit statistics for individual metrics and firms are likely outside the acceptable range and would require more in-depth investigation on a case-by-case basis.

Application of the dichotomous Rasch model provides a new, comprehensive way of ranking firm performance and financial ratio difficulty. Yet, more sophisticated types of Rasch models may prove to be even better suited for this purpose, because they are likely better able to account for the effects of changing economic conditions on firm and metric rankings. Future research might explore the use of these more sophisticated models and the analysis of additional

v See http://www.winsteps.com/winman/index.htm?reliability.htm and http://www.rasch.org/rmt/rmt113l.htm for a discussion of the various reliability indices.

Table 2: Financial ratios (9 of 18) for which positive results were most difficult to attain. Top 15 pharmaceutical firms (2002–2013)

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Liquidity												
SR	X	X	X	X		X	X	X	X			
Profitability												
OM		X									X	X
NM					X			X		X	X	X
EA			X	X	X						X	
Financial Leverage												
TIE	X	X	X	X	X	X	X		X	X	X	X
ER	X											
AD	X	X	X		X	X	X	X	X	X	X	X
Resource Utilization												
RDS		X		X	X	X	X			X		
SA		X	X	X								
SEM	X					X						
Growth												
SG	X			X			X	X	X			
EG			X		X					X		
Return of investment												
ROE	X	X	X		X		X	X	X	X	X	X
ROA					X			X	X	X	X	

Market Valuation												
PS	X	X	X	X		X	X		X	X	X	X
PB			X	X		X	X	X	X	X	X	X
Enterprise Value												
EPVS	X	X		X		X	X	X				X
EPVG					X	X		X	X			X
Rasch Ratio Reliability Index	0.16	0.00	0.00	0.00	0.00	0.18	0.00	0.00	0.00	0.00	0.00	0.00
No. of Firms	13	13	12	15	13	13	11	9	10	10	9	9

Notes: SR is the sales-to-receivables ratio, OM is operating margin (EBITDA divided by sales), NM is net margin, EA is EBITDA divided by assets, TIE is the times-interest-earned ratio, ER is the equity ratio, AD is the assets-to-debt ratio, RDS is R&D divided by sales, SA is sales divided by assets, SEM is sales divided by employee, SG is sales growth, EG is growth of earnings-per-share diluted excl. extraordinary items, ROE is the return on equity, ROA is the return on assets, PS is the price-to-sales ratio, and PB is the price-to-book ratio. EPVS is enterprise value divided by sales, and EPVG is enterprise value growth. The ratio reliability index is reported on a 0 to 1 scale with 1 being maximum reliability for ranking metrics by how difficult it is to get a favorable reading.

Table 3: Summary statistics for financial ratio difficulty hierarchy. Top 15 pharmaceutical firms (2002–2013)

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Mean Ratio Difficulty	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Mean Std. Error	0.71	0.69	0.74	0.60	0.67	0.70	0.75	0.81	0.80	0.83	0.80	0.82
Mean Infit t	-0.1	0.0	0.1	0.0	0.0	-0.1	0.0	0.1	0.0	0.0	0.0	0.1
Mean Outfit t	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.0	-0.1	0.1	0.0
Rasch Ratio Reliability Index	0.16	0.00	0.00	0.00	0.00	0.18	0.00	0.00	0.00	0.00	0.00	0.00
No. of Firms	13	13	12	15	13	13	11	9	10	10	9	9

Notes: Mean ratio difficulty measures for non-extreme ratio readings are set to zero by the model by default. Infit t and outfit t statistics measure whether the sample data meet the requirements of the Rasch model for the non-extreme ratios. The ratio reliability index is reported on a 0 to 1 scale with 1 being maximum reliability for ranking metrics by how difficult it is to get a favorable reading.

Table 4: Among top 5 overall financial performers in more than one year. Top 15 pharmaceutical firms (2002–2013)

Firm Name	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	No. of Years in Top Five
Bayer AG	X	X	X	X	X	X	X	X	X	X			10
Johnson & Johnson	X	X	X	X	X	X	X		X		X	X	10
Amgen Inc.			X	X	X	X	X	X	X	X	X	X	10
Roche Holding AG						X	X	X	X	X	X	X	7
GlaxoSmithKline PLC	X	X	X	X	X						X		6
Lilly (Eli) & CO	X	X								X	X	X	5
Astrazeneca PLC		X		X	X								3
Pfizer Inc.	X		X									X	3
Bristol-Myers Squibb Co.								X	X	X			3
Merck & Co.							X	X					2
Rasch Real Firm Reliability Index	0.80	0.79	0.79	0.74	0.76	0.77	0.74	0.71	0.75	0.76	0.76	0.78	
Cronbach-Alpha Reliability Index	0.86	0.87	0.89	0.81	0.81	0.86	0.83	0.80	0.86	0.89	0.82	0.85	
No. of Firms	13	13	12	15	13	13	11	9	10	10	9	9	

Notes: The reliability indices are reported on a 0 to 1 scale with 1 being maximum reliability. Both the Rasch Real Reliability Index and the Cronbach-Alpha Reliability Index are based on raw scores rather than logit measures. A low reliability index may be due to a small performance range in the sample. Big absolute differences between the Indices likely result from differences in the treatment of extreme scores.

Table 5: Summary statistics for firm financial performance analysis. Top 15 pharmaceutical firms (2002–2013)

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Mean Performance	-0.19	0.14	0.45	0.42	0.42	0.49	0.84	0.92	0.77	0.83	0.38	0.32
Mean Std. Error	0.69	0.68	0.80	0.69	0.72	0.75	0.77	0.80	0.80	0.82	0.69	0.70
Mean Infit t	-0.1	0.0	0.1	0.0	-0.1	-0.1	0.0	0.0	0.0	0.1	0.0	0.1
Mean Outfit t	0.2	0.1	0.1	0.0	0.1	-0.1	0.1	0.0	0.2	0.3	-0.1	0.0
Rasch Real Firm Reliability Index	0.80	0.79	0.79	0.74	0.76	0.77	0.74	0.71	0.75	0.76	0.76	0.78
Cronbach-Alpha Reliability Index	0.86	0.87	0.89	0.81	0.81	0.86	0.83	0.80	0.86	0.89	0.82	0.85
Index Difference	0.06	0.08	0.10	0.07	0.05	0.09	0.09	0.09	0.11	0.13	0.06	0.07

Notes: Infit t and outfit t statistics measure whether the sample data meet the requirements of the Rasch model for the non-extreme firms. The reliability indices are reported on a 0 to 1 scale with 1 being maximum reliability. Both the Rasch Real Reliability Index and the Cronbach-Alpha Reliability Index are based on raw scores rather than logit measures. Big absolute differences between the Indices likely result from differences in the treatment of extreme scores.

and alternative performance categories. For instance, the evaluation of managerial ability might be extended beyond financial performance to include performance in the areas of risk management, supply chain management, corporate social responsibility and sustainability.

SUMMARY AND CONCLUSION

This study explores the use of a simple Rasch model for simultaneous rankings of financial ratio difficulty and broad-based firm financial performance for the top 15 firms in the pharmaceutical industry. Our results for the years 2002-2013 suggest that financial data may be compatible with the requirements of the dichotomous Rasch model though financial metric difficulty rankings were not robust.

Managers' ability to lead their firms to consistent and comprehensive success across a range of financial performance metrics appears to be relatively concentrated at the top among big pharma. Highly-ranked firms that have frequently demonstrated success across the main financial performance dimensions may be viewed as having better managers and greater "financial stamina" than the lower-ranked firms. This is particularly important for the largest pharmaceutical firms because the industry is buffeted by patent expirations, regulatory uncertainty and adverse economic conditions.

While a Rasch approach requires additional exploration and research, we conclude that the use of Rasch models for the evaluation of financial performance by big pharmaceutical firms is a valuable complement to existing methods. Beyond that, it may be possible and desirable to extend the Rasch assessment of firm performance to include non-financial, as well as financial, performance dimensions. Examples of non-financial areas of pharmaceutical firm performance that may benefit from a Rasch analysis include (but are not limited to) health outcomes, supply chain management, corporate social responsibility and sustainability.

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Conference Report

Moving from preclinical research to development

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As described by Johnson & Johnson Innovation, LLC, its focus is on "accelerating early-stage innovation worldwide and forming collaborations between entrepreneurs and Johnson & Johnson's global healthcare businesses" and "JLABS, part of Johnson & Johnson Innovation, LLC, is a network of life science incubators providing emerging companies many of the advantages of being in a big company, without the capital investment."

Johnson & Johnson Innovation, JLABS held 2 key events at the company's location in San Diego, CA. These are described as below.

Sandra Snook, Ph.D. (Senior Director, Preclinical Development & Safety) made a presentation entitled, "ABCs of the FDA – How to… Set a Preclinical Roadmap" (November 10, 2015). Dr. Snook has 23 years of experience in supporting the preclinical development of small molecules spanning therapeutic areas including infectious, metabolic and cardiovascular diseases, immunology, neuroscience and oncology. Her leadership of staff includes toxicology and drug metabolism and pharmacokinetics (DMPK) project support and also laboratory animal medicine, investigative toxicology and molecular pathology. Dr. Snook and her team have strong experience supporting novel compound development from lead optimization through global registration, and this includes management of the preclinical part of external alliances and partnerships. Some select highlights of Dr. Snook's presentation are discussed below.

Designing the best chemical/biologic molecule and ascertaining that it may be a new molecular entity (NME) that is ready for development involves some steps on the preclinical level. These include DMPK and safety studies, and the discovery team can comprise medicinal chemist(s), DMPK scientist(s), pharmacologist(s), and toxicologist(s) that work with each other. Upon dosing, part of a drug may be excreted, part may be metabolized and a fraction may become bioavailable. Thus to assess these, the drug metabolism and PK studies can involve various aspects such as *in vitro* assays (solubility, permeability and metabolism) and *in vivo* studies (intravenous (IV) or oral PK).

Metabolism/clearance studies assess a drug candidate's stability in microsomes/hepatocytes; and human cytochromes P450 (CYP) isoform involvement, inhibition, induction and reactive intermediate formation. The tissue distribution studies take into consideration plasma protein binding as only free drug can interact with target(s). Another parameter is the exposure in efficacy target tissue and major organs. Human PK prediction takes into consideration bioavailability of a drug candidate, allometric scaling and physiologically-based PK (PBPK) modeling. Prediction of human dose can involve aspects regarding efficacious exposure, biomarkers and pharmacokinetic/pharmacodynamic (PK/PD) modeling.

Safety-related aspects include selectivity regarding the drug candidate's action and can be ascertained using *in vitro* counter screen against unwanted receptor, ion channel, and enzyme interactions. The drug candidate's cardiovascular safety may be assessed *in vitro* using the human Ether-à-go-go-Related Gene (hERG) functional assay and action potential determinations, and *in vivo* by employing anesthetized guinea pig and/or dog or conscious dog model.

Toxicological studies include target assessment (e.g., studying physiological function, potential undesirable effects, tissue distribution, and cross-species comparison); *in vitro* genetic toxicity screening [Ames test (screening version); with and without metabolic activation to detect base pair and frame shift mutations, and micronucleus test (screening version); with and without metabolic activation to detect chromosomal breaks and aneuploidy]. The toleration studies include use of rodents (mouse or rat) or non-rodents (dog or monkey).

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The studies determine if a molecule has an adequate safety profile/margin to support NME nomination (primary objectives) and inform on dose level selection for GLP studies (secondary objectives). Toxicological study design considerations include species selection (default to rat and dog) and pharmacological considerations, compound metabolic/PK profile; testing of the quality of the drug candidate; formulation; dose-exposure linearity information; study duration; clinical endpoints (clinical observations, body weight, food consumption); pathology endpoints (clinical pathology and gross and histopathology) and toxicokinetics.

Discovery phase outcomes are with respect to drug metabolism/pharmacokinetics (e.g., preliminary disposition in toxicology species; predicted human metabolism; potential human drug-drug interaction (DDI) liabilities, and predicted human PK and efficacious dose) and safety pharmacology/toxicology (preliminary safety margins, initial understanding of safety liabilities and sufficient information to design quality good laboratory practice (GLP) studies). Partnership with DMPK scientist and toxicologist may be harnessed to design the best NME candidate.

Preclinical studies to support phase 1 include *in vitro* metabolism studies (using microsomes/S9/hepatocytes) and species comparison); *in vivo* metabolism studies (absorption/excretion/metabolism in Tox species), and CYP-mediated DDI. Additional aspects include bioanalytical method development for Tox species and human (perhaps including key metabolites); documentation regarding toxicokinetics/exposure documentation (such as that involving safety pharmacology, genetic toxicology and repeated-dose toxicology)and human PK prediction (including bioavailability, allometric scaling and physiologically based pharmacokinetic (PBPK). First in Human (FIH) dosage form PK assessment may also be ascertained.

Good Laboratory Practice (GLP) is a vital consideration in that pivotal safety pharmacology/toxicology studies need to be conducted under GLP conditions in order to support clinical trials. The GLP guidelines require the identity and purity of test article; analysis of dosing formulations; adherence to protocol and amendments; integrity of raw data; quality assurance audit of experimental phase and final report, and a final report that describes all the experiments and findings.

The GLP safety studies can include a core battery of tests pertaining to the cardiovascular system, central nervous system and respiratory system. Supplemental studies may include renal/urinary system, autonomic nervous system, gastrointestinal system and other such as skeletal muscle and endocrine health.

GLP genetic toxicity testing involves Ames test (regulatory version) [with and without metabolic activation to detect base pair and frame shift mutations]; *in vitro* micronucleus (regulatory version) [with and without metabolic activation to detect chromosomal breaks and aneuploidy]; *in vivo* rat bone marrow micronucleus test [for the detection of chromosomal breaks and aneuploidy]. GLP repeated-dose toxicity studies focus on the identification of target organs of toxicity; endpoints for clinical monitoring; no observed adverse effect level (NOAEL) doses, and estimation of safety margins based on systemic exposure. The design of the repeated-dose toxicity studies can include rodent (generally rat) and non-rodent (dog or monkey) species. The study duration is at least as long as intended clinical treatment (according to The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) M3R2) (generally up to 1 month for investigational new drug (IND) phase I studies). The NOAEL is specific to each study and the doses selected, and is used to establish safe starting dose for phase 1. The safety margins compare drug Cmax/AUC exposure at NOAEL with predicted efficacious Cmax/AUC exposure in humans. Acceptable safety margins can vary and depend on the indication, nature of the adverse effects and the ability to monitor in humans.

In the context of the IND submission, the Food and Drug Administration (FDA)/ The Center for Drug Evaluation and Research (CDER) has 30 days to assess safety. If there are minor or no comments, then the phase I trial may proceed. However, clinical hold may be experienced due to some reasons; for example, the duration of toxicology studies could be insufficient to support proposed clinical duration; doses/exposures may not be high enough in toxicology studies (according to ICH M3R2), or NOAEL not established in toxicology studies.

Preclinical studies to support phase IIa [proof-of-concept (POC)] studies can involve 3-month toxicity studies if the human POC study is more 1 month of treatment. Embryo-fetal developmental (EFD) toxicity studies involve rat and rabbit. These are treated during critical period of organogenesis and soft tissue and skeletal evaluation of the fetuses is performed. The need for EFD toxicity studies varies and includes considerations such as if patient population includes women of childbearing potential; duration and size of trial; regional differences related to US vs. EU/Japan and if they are preliminary versus definitive studies.

Preclinical tox programs regarding biologics differ from those for small molecules. Drugs of the latter type (sizes less than 1000 Da) can diffuse across membranes and in and out of cells. Antibodies on the other hand, are larger in size (e.g., 150,000 Da) and are largely confined to the blood volume. Both types of drugs can exhibit high specificity for their respective pharmacologic target and potential toxicity can be associated with

exaggerated primary pharmacology. In case of small molecules, potential toxicity can also be associated with off-target activity (e.g. hERG) and chemical toxicity (e.g., via a reactive metabolite). For the preclinical tox programs pertaining to biologics, ICH56 is of relevance, immunogenicity determinations are performed, route of administration is intravenous or subcutaneous, and the dose frequency may be 1-2 times per week. In case of small molecules, ICH M3, S1, S2, S3, S4 are of relevance, metabolism and mutagenicity/toxicity are studied, administration may be oral and the dose frequency may be daily.

Dr. Snook also discussed the factors influencing contract research organization (CRO) partner selection. Among these are the CRO's capabilities (with respect to conducting studies on drug metabolism/PK; bioanalysis (preclinical and clinical); and genetic toxicity; repeated-dose toxicity and reproductive toxicity determinations). Other factors are whether the CRO is a boutique one or an bigger entity; type of facility and staff; the CRO's GLP track record and geographical location and time zone the CRO may be in. Keeping oversight of The CRO is a critical factor.

An additional event held by JLABS was entitled, "Between Two Benches: Leading a Legacy in Life Sciences" (November 12, 2015). This featured Pablo J. Cagnoni, M.D. (Managing Director, MPM Capital) and Diego Miralles, M.D. (Head, Johnson & Johnson Innovation) as the interviewer.

Among the points discussed were the considerations for venture investment. These included: The length of potential investment and exit strategy; the potential outcome (within 5-7 years), management team, and the company's culture. In drug development process, even if a good p-value is obtained, but the progression-free survival may be enhanced by only a few months, then the potential drug candidate may still not be worth pursuing. Thus such a company may still not necessarily be deemed an investment opportunity. When pursuing a theme, a company should emphasize what makes it differentiated as compared to others in that same space. Also, the market size although important, cannot be impressive by itself and a company seeking venture capital should demonstrate the market opportunity in a clear and concise manner. Different types of therapeutic areas have distinctive challenges and it may be helpful for different parts of a company to have the freedom to conduct functions that are necessary. Looking forward, of importance would be faster recruitment of many more patients for clinical trials and generation of tests that could allow faster early stage determinations regarding the potential usefulness of drug candidates.

The two events by JLABS provided insights for the benefit of young companies/early stage inventions. One of the presentations recognized the rigors associated with moving a program from discovery through development whereas the other discussion provided some considerations pertaining to investment by a venture firm.

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