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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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

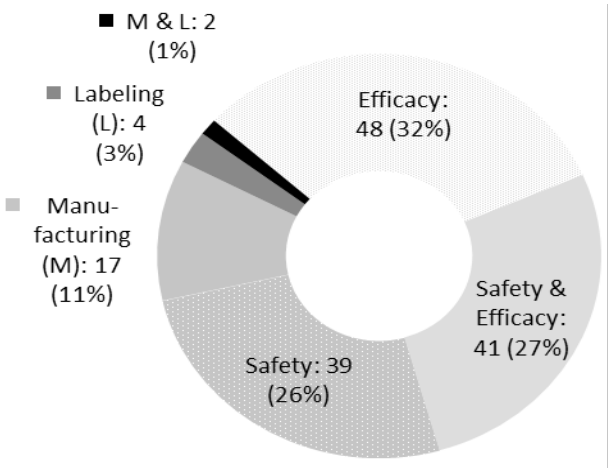

Figure 1: Reasons for FDA NDA refusals (n=151)

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 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	

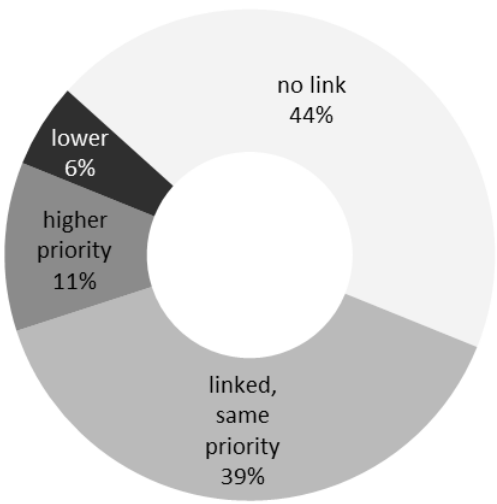

Figure 2: Linkage of IP and regulatory strategy

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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