



The paradigm shift to an “open” model in drug development



Regina Au*

Strategic Marketing Consultant, BioMarketing Insight, Boston, MA, United States

ARTICLE INFO

Keywords:

Drug development
Systems biology
Open model

ABSTRACT

The rising cost of healthcare, the rising cost for drug development, the patent cliff for Big pharma, shorter patent protection, decrease reimbursement, and the recession have made it more difficult for the pharmaceutical and biotechnology industry to develop drugs. Due to the unsustainable amount of time and money in developing a drug that will have a significant return on investment (ROI) it has become hard to sustain a robust pipeline. The industry is transforming its business model to meet these challenges. In essence a paradigm shift is occurring; the old “closed” model is giving way to a new “open” business model.

© 2014 The Author. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/3.0/>).

Contents

1. Introduction	86
2. Drug development—then and now	86
2.1. Drug development—then	86
2.2. Drug development—now	87
3. How systems biology is accelerating drug development and drug approval	87
4. The new business model: pharma/biotech is going “open”	88
5. FDA is going “open”—what does this mean for drug approval?	88
6. Conclusion	89
Acknowledgment	89
References	89

1. Introduction

Scientific advances, such as the relatively new field of systems biology are revolutionizing drug development. Thanks to systems biology, biomedical informatics systems and convergent technologies such as the ‘omics’, our ability to understand diseases and develop safe and effective drugs has never been better. This review will cover: 1) Development factors engineering this paradigm shift; 2) How systems biology is accelerating drug development and approval; 3) The definition of an open Pharma/Biotech and how it works; and 4) How the FDA is going “open”, what does this mean for drug approvals. Although the old model is broken, the key question is will the new “open” model be successful?

2. Drug development—then and now

To understand the paradigm shift that is taking place and why, it is useful to understand how drug development was traditionally done and the factors that have impelled this shift that took place over the years affecting drug development.

2.1. Drug development—then

As depicted in Fig. 1, pharmaceutical companies used to develop small molecule drugs focusing on the chemistry of drugs where majority of the pathways are well known, such as the renin–angiotensin system that regulates blood pressure and water used to control hypertension. This approach made drug development predictable because a chemical reaction would occur the same way each time.

The majority of the development was done via a “trial and error” method where scientist started with 1,000+ compounds and through process of elimination pared it down to about 50–100 compounds.

* Strategic Marketing Consultant, BioMarketing Insight, United States. Tel.: +1 781 935 1462.
E-mail address: regina@biomarketinginsight.com.
URL: <http://www.biomarketinginsight.com>.

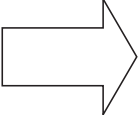
Factors that Affected Drug Development			
	Then		Now
Type of drug	Small molecule		Large molecule
	Chemistry		Biology
	Known pathways - Easier Science		Unknown pathways - More complex science
Time	8 - 10 years		10 - 15 years
Cost	Average - \$800 million		Average - \$1.65 billion
Pipeline	Internal		Internal + more external
Drug Discovery methodology	"Trial and Error" - start with 1,000 compounds and narrow it down		More targeted pathways - need to understand biology better
Clinical Trials	Compared to placebo		Comparative Effectiveness, to similar or other drugs on the market
	High failure rate in Phase II and III		High failure rate in Phase II and III
Drug Approvals	FDA non-communicative		More communicative - ongoing
Intellectual property	Patent protection		Shorter patent protection and numerous drugs going off patent - patent cliff
Reimbursement	Formulary		Superiority + decreased reimbursement
Funding	Plentiful - many investors in life sciences		Risk adverse investors, fewer investors in life sciences - funding is tight
Obamacare	Didn't exist		Life science companies footing the tab for everyone to have access to healthcare and drugs

Fig. 1. Factors that affected drug development.

The clinical trials for drug approval experienced a high failure rate in Phase 2 and Phase 3, primarily because they did not have the benefit of knowing how factors such as co-morbidities, lifestyle and environment influenced individual variation in drug responses. The entire development process would take anywhere from 8–10 years and cost about \$800 million.

Further, the development process was entirely off limits. The Pharma/biotech industry has been long criticized for keeping its research and clinical data closed to the outside, and notably so for negative results or when a serious side effect results in death. Their rationale for keeping all information confidential are:

1. Intellectual property (IP) protection. If someone steals your research there is no legal recourse until after the competitive product is on the market to show damages from patent infringement. But a court battle could drag on for months and even years which is detrimental particularly to a small company who may not have the monetary resources to legally stop their competitor from selling their product.
2. Fierce competition to be first in the market place. Disclosure of data can increase competition and threaten market share.
3. Patient privacy or HIPPA for clinical trials. Patient data is confidential, unless subpoenaed by a court order.

Under this closed model, many drugs that decreased morbidity and mortality and increased patients quality of life, have been developed. However, developing drugs for known pathways offered little room for innovation so researchers looked to large molecules (proteins).

With the birth of the biotechnology industry development became more complex and difficult.

The challenges biotechnology companies face in developing large molecule compounds are:

- 1) The biology is more complex and we don't understand it well.
- 2) The targets are more difficult, new and unproven, therefore more risky.
- 3) A delivery system is needed to get large molecules to the desired area.
- 4) The FDA mandated that drugs be compared to existing drugs on the market vs. placebo.

Therefore, the development time is longer and more costly.

2.2. Drug development–now

The sequencing of the whole human genome led to the field of systems biology. Today, some define systems biology as the “fifth prism”, where every life form is a complex system formed by interacting genes and macromolecules that underlie most biological processes (1). (Vidal, 2009) Systems biology promotes the understanding of how networks in the biological system interact to produce the behavior of that system and how proteins interact with each other inside a cell in response to hormones or other external stimuli (2). (Trafton, 2011) This approach has enabled development to target segments of the population based on biological processes, rather than one size fits all.

3. How systems biology is accelerating drug development and drug approval

Systems biology investigates interactions at the macro- and cellular levels of biological networks and the interplay between

the two levels to explain why cells behave the way they do (3). (Ferrell, 2009).

Mathematics and computational modeling capture the complexity of many variables in systems biology.

If one views human diseases as perturbations of highly interlinked cellular networks, then diseases are highly interconnected and not independent of each other. Therefore, it can be theorized that molecular defects responsible for one of the pair of diseases can spread along the edges of cellular networks and affect the activity of related genes or diseases and cause or affect the outcome of the other disease (4). (Vidal et al., 2011) Most diseases can't be explained in terms of one genetic deficit or one molecular impairment, said Douglas Lauffenburger, head of MIT's Department of Biological Engineering (2). We need to understand how many molecular components are involved, how they work in concert, and how cells and tissues are formed, either properly or improperly.

The systems biology approach is benefiting drug development in six (6) ways:

- 1) More precise understanding of diseases and disease processes.
- 2) Faster discovery of biomarkers, companion diagnostics and therapeutic drugs—Microarray models (DNA proteomics) can identify subsets of phenotypes, and pharmacogenomics can explain why certain drugs will work on certain gene expression patterns but not others give rise to personalized medicine.
- 3) Improved pre-clinical trials—By combining computational modeling and a pilot animal study, one can better predict what will happen in mice rather than conducting animal studies to determine efficacy and safety parameters.
- 4) Improved efficacy—Identifying biomarkers in diseases and then developing drugs that target these biomarkers results in better efficacy and minimal side effects. In addition, computer modeling will predict how cells react with related co-morbidities in helping to predict efficacy.
- 5) Smaller clinical trials and reduced drug development cost—Personalized medicine makes a strong case for the FDA to require fewer homogenous patients than the 1000s of patients enrolled in standard trials of heterogeneous patients. If the number of patients required for all trials are smaller, the trial costs will be significantly less and the time to recruit, conduct the trials and submit results will be significantly shorter.
- 6) Drugs available to patients sooner—Drugs are held at a higher standard because we have better drugs (standard of care) on the market. Using the systems biology approach, drugs have a higher probability of being approved because efficacy and safety would not be an issue, even if the time frame for drug development remained the same.

4. The new business model: pharma/biotech is going “open”

Despite reservations, noted above, the pharma/biotech industry is moving towards favoring an “open access” to their anonymized clinical trial data for researchers who request it. They now believe that sharing information can help other researchers and themselves better understand disease progression, accelerate drug development or design more efficient clinical trials for faster drug approval thus accelerating “the time to market” for drugs (5). (Pogorelc, 2014) There is a lot of clinical trial data locked away which could be useful to other researchers who have the time to analyze the data, when Big pharma may not be due to other priorities. A number of pharma companies have formed independent companies to manage the data and address prior obstacles to sharing clinical trial data.

Thus, a new business model has evolved. Features are:

- 1) Abandon the “internal” development only philosophy to include more external developments (more early stage collaboration, M&A and licensing).

- 2) Incorporate system's biology in drug discovery to understand diseases better.
- 3) Include other scientific expertise such as immunology, bioinformatics and mathematics to keep up with advancement in technology.
- 4) Actively pursue basic research collaboration with academic and private research institutions to understand diseases better.
- 5) Lobby for more open communication with FDA with respect to guidance and support in the drug approval process.

The industry would also like to collaborate and in so doing open up research to get more input from fellow scientists in a “precompetitive space.” The partnership of GlaxoSmithKline (GSK), European Bioinformatics Institute (EMBL–EBI) and The Wellcome Trust Sanger Institute to form the Center for Therapeutic Target Validation (CTTV) is trying to accomplish this. The goal is to mine the combined sources of genomics, proteomics, chemistry and disease biology data to find new therapeutic targets (6). (Taylor, 2013) This information will be shared publicly. Patrick Vallance, Head of R&D at GSK believes that the more knowledge or data obtained, the more it de-risk things (6). This is true in discovering biomarkers. However, it is the interpretation of this information that's the innovation. Vallance hopes more drug companies and academic institutions will participate in CTTV.

The following companies, or Big pharma consortiums have “opened” their clinical trial or research databases to scientists who request access:

- 1) Roche—clinical trial (7) (RocheMedia Release, 2013).
- 2) GlaxoSmithKline—clinical trial (8) (Press Release, 2013).
- 3) Center for Therapeutic Target Validation (CTTV)—research (6).
- 4) Structural Genomics Consortium (Wellcome Trust and GSK)—European Database (6).
- 5) Project Data Sphere (AstraZeneca, Bayer, Celgene, Johnson & Johnson (J&J), Pfizer, Sanofi and Memorial Sloan Kettering Cancer Center)—cancer research (5).
- 6) TransCelerate BioPharma (Eli Lilly, J&J and Merck)—clinical trial.

5. FDA is going “open”—what does this mean for drug approval?

The FDA has been criticized in the past by industry for being non-communicative with input and guidance in clinical trials and the low number of drugs being approved due to delays when the FDA requests for more data on safety and efficacy as patients are awaiting for life savings drugs to be approved. The current administration is trying to change this negative image by incorporating an “open model” to establish rapport and work with industry by having more open dialog between both parties to make the drugs approval process go more smoothly.

The FDA has allowed and provided guidance for “clinical trials (to) be designed with adaptive features (i.e., changes in design or analyses guided by examination of the accumulated data at an interim point in the trial) that may make the studies more efficient (e.g., shorter duration, fewer patients) and more likely to demonstrate an effect of the drug if one exists, or more informative (e.g., providing broader dose-response information)(9)” (FDA, 2010) This includes both well-established low risk designs as well as methodological designs with less experience. These “adaptive” clinical trial designs could certainly aid in demonstrating better efficacy, or reduce cost with the reduction in trial length and patients.

Implementing an adaptive trial requires open dialog and discussions upfront and throughout the trial such as interim analysis on how to best proceed forward which can make the studies more efficient.

For the first time, the FDA and European Medicines Agency (EMA) have given “open” access to their clinical trial database and sequencing information of drug submissions to the public for anyone to use. The goal in sharing this information is to help accelerate drug development and navigate through the approval process more efficiently by seeing

what has worked, mistakes to avoid, and improve upon existing clinical trial design and technology.

- 1) NIH 1000 Genome Project—the world's largest set of data on human genetic variation in identifying biomarkers (10). ([National Institute of Health, 2012](#)).
- 2) OpenFDA—3 million records that cover medication errors and side effects, from 2004 to 2013. The program will eventually expand to include product recalls and labeling problems (11). ([Lee, 2014](#)).
- 3) FDA NextGen Sequencing—next generation sequencing information for drug approvals (12). ([Taylor, 2014](#)).
- 4) EU Clinical Trial Registry—clinical trials for medicines authorized in the 27 EU Member States and Iceland, Liechtenstein and Norway (13). ([EMA, 2011](#)).

FDA's trend towards this model of open data sharing will have a positive impact in the long run as it will establish a collaborative working relationship between FDA and industry in developing better drugs and a quicker approval process.

6. Conclusion

The industry is adopting a new “open” business model because they realize that the only way to develop drugs faster is to put our collective minds together; researchers, clinicians, and patients. Companies have been doing research for decades on disease such as Alzheimers, Dementia and Parkinson and have not scratched the surface to understanding why these diseases occur and how to treat it because they are so complex. With open collaborations this promises to change. The trend towards personalized medicine also forces the industry to adopt new strategies for success. Companies can't develop drugs alone and they need to pull all resources together to figure it out. Many companies are collaborating with other companies (for example diagnostic companies with therapeutic companies) to develop therapeutic drugs in hopes of getting to market faster and sharing the wealth, and expanding the market.

However, the “open” business model must be balanced against the ability to compete and profit in order to develop and maintain a robust pipeline. The industry has partnered with others to form independent institution to help define a “precompetitive space” where everyone can gain information from a single source. Whether these open models will work is too early to tell.

As medicine and technology advances, development will increasingly require experts from disparate domains; mathematics, bioinformatics, computer science, thus reinforcing the need for precompetitive open collaboration. Once the industry figures out how best to work in the new open environment, development should be faster, more successful

and less costly. Then negative issues that have significantly impacted the industry; the patent cliff, shorter patent protection, generics and biosimilar competition, rising cost of healthcare and decreased reimbursement for drugs, would be less impactful.

Acknowledgment

I would like to express my gratitude to Dr. Carol Isaacson Barash (Founder & Principal, Helix Health Advisors, Adjunct Prof. Personalized Medicine, Regis College, Graduate Program Science, Nursing & Health Professions, Boston, MA USA) for her support and helpful comments on this article.

References

- EMA, 2011. EU Clinical Trials Register goes live, EMA Press Release 3/22/11. (Visit: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/03/news_detail_001228.jsp&mid=WC0b01ac058004d5c1).
- FDA, 2010. Guidance for Industry—Adaptive Design Clinical Trials for Drugs and Biologics, FDA Website, February 2010. (February, Visit: <http://www.fda.gov/downloads/Drugs/Guidances/ucm201790.pdf>).
- Ferrell, J.E., 2009. Q&A Systems Biology. *J. Biol.* 8 (1), 2. <http://dx.doi.org/10.1186/jbiol107> (Published online Jan 26, 2009. doi: 10.1186/jbiol107, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2656213/>).
- Lee, T., 2014. OpenFDA a Boon to Medical Device and Drug Startups, San Francisco Gate, July 11, 2014. (<http://www.sfgate.com/business/article/OpenFDA-a-boon-to-medical-device-and-drug-startups-5616336.php>).
- National Institute of Health, 2012. 1000 Genomes Project Data Available on Amazon Cloud, NIH Press Release, March 29, 2012. (Visit: <http://www.nih.gov/news/health/mar2012/nhgri-29.htm>).
- Pogorelc, D., 2014. To Spark Cancer Discoveries, Several Big Pharma Companies are Sharing Idle Clinical Trial Data, MedCity News, April 8, 2014. (<http://medcitynews.com/2014/04/sanofi-pfizer-ji-astrazeneca-share-clinical-trial-data/>).
- Press Release, S.A.S., 2013. SAS leads the charge for pharmaceutical data transparency. DIA 2013 49TH ANNUAL MEETING, BOSTON, June 27, 2014 (http://www.sas.com/en_us/news/press-releases/2013/june/clinical-data-transparency.html).
- RocheMedia Release, 2013. Roche Launches New Process for Accessing Clinical Trial Data, Roche Media Release, Basel, 26 February 2013. (http://www.roche.com/media/media_releases/med-cor-2013-02-26.htm).
- Taylor, N.P., 2013. GSK Teams Up to Apply Big Data to Target Validation, FierceBioIT, March 30, 2014. (http://www.fiercebiotechit.com/story/gsk-teams-apply-big-data-target-validation/2014-03-30?utm_medium=nl&utm_source=internal).
- Taylor, N.P., 2014. FDA Informatics Chief: NGS is an Immediate Priority for the Agency, FierceBioIT, March 10, 2014. (<http://www.fiercebiotechit.com/story/fda-informatics-chief-ngs-immediate-priority-agency/2014-03-10>).
- Trafton, A., 2011. Vivo Systems Biology—Using Computer Models, Systems Biologists Can Predict Complicated Behavior of Cells in Living Animals. MIT News Office (March 23, 2011, <http://newsoffice.mit.edu/2011/vivo-systems-biology-0323>).
- Vidal, M., 2009. A unifying view of 21st century systems biology. *FEBS Lett.* 583 (2009), 3891–3894 (http://ccsb.dfci.harvard.edu/web/export/sites/default/ccsb/publications/papers/2009/Vidal_FEBS-Lett_12-09.pdf).
- Vidal, M., Cusick, M.E., Barabási, A.L., 2011. Interactome networks and human disease. *Cell* 144 (6), 986–998. <http://dx.doi.org/10.1016/j.cell.2011.02.016> (18 March 2011, <http://www.cell.com/abstract/S0092-8674%2811%2900130-9>).