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A new model for product development

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ABSTRACT: The familiar multistage model of drug discovery and development has been in place for decades. Attrition rates under that model have been and still are frighteningly high. The associated debilitating issues, such as weak patient engagement, limited involvement of key stakeholders at critical stages and slow routes to market, are clear for all to see. This article argues that the time is nigh to consider a new approach, based upon what has been learned from other industry sectors developing products for customer markets. The regulators are demanding it through modernisation initiatives, but industry has, to date, been tardy in its response. The suggestion here is that is because it is holding grimly on to the 'tried and tested' old method. The new approach suggested is based on a broad two stage model, comprising design/prototyping as stage one and manufacture for patient supply (including commercial) as stage two. Almost every other industry sector develops its products this way, devising predictive methods (eg wind tunnels to examine thermodynamic characteristics of aircraft) before exposing customers to their final marketed product. The article proposes how this could work in pharmaceuticals, together with an exploration of some supporting organisational and mindset changes needed to support. The challenges of devising and implementing such an approach are enormous, but so are the potential benefits. For those benefits to accrue, it is argued that a fundamental shift in perception needs to take place at the most senior levels in this industry. This means accepting that extra time taken at the early stage of drug development creates a vastly improved value: cost relationship. In other words, the extra costs incurred in terms of time and resources early on are greatly outweighed by reduced attrition rates and time to market.

WHY DO WE NEED A NEW MODEL?

Fundamentally, the current drug development model is no longer "fit for purpose". Why do I say this? There are a number of reasons. Firstly, there is a welter of evidence that points to abysmal success rates in bringing drugs through to market approval. A US Government Accountability Office (GAO) (1) report dated November 2006 makes chilling reading. The figures quoted there tell us that 245 out of every 250 compounds selected for preclinical development fail to make it into the clinic. Of the five that get through, only one makes it to approval. That leads to a sickening cost of failure. Between the discovery and clinical phases, all the combined time and effort of highly skilled scientists and technologists, together with multiple service providers and support staff, goes up in smoke 98 percent of the time. During the clinical phases, the statistic is healthier - only 80 percent down the drain this time! Sobering thoughts, don't you think?

Secondly, the world has moved on since the early days of drug discovery. In those days, there was an urgent need to cure diseases with the potential to wipe out or debilitate whole populations. There was an obligation on discoverers to move prospective medicines forward to human administration as swiftly as possible. Current day capabilities in molecular analysis and predictive methods were not available to those developers. Now that science is unrecognisably advanced from those days, shouldn't we be sure that the science is used to the full before progressing prospective drugs into safety and efficacy testing, both in animals and humans? For example, a key reason why drugs fail is because preclinical models can be poor at predicting responses in patients. Logic therefore dictates an important need to be able to model a drug's effect on the human biology at the preclinical stage. Technology is growing rapidly to be able to do this, but for it to really work there must be a steely determination in the industry to transition away from the traditional trials in humans as the main source of data.

The other question prompted by the concept of a changing world is whether it is now possible for Pharma companies to operate over so many diverse disease areas. The emergence of stratified medicine is set to demand ever deepening knowledge banks of people's biological characteristics with respect to particular diseased states. The company critical mass required to build these knowledge bases is likely to severely restrict the coverage across multiple therapeutic areas.

Thirdly, the Japanese revolution in production systems hadn't taken place. When it did, the world learned that taking more, not less time in the early stages of product development delivered tremendous benefits in time to market, cost and quality. Finally, there is evidence that patients are starting to develop drugs for themselves, in frustration at the slow pace and "one size fits all" nature of drug trials. In an article entitled "A New Rx for Medicine" in the Wall Street Journal (2), October 2 2010 (kindly posted on LinkedIn by Steven Spear, author of Chasing the Rabbit (3)), cancer patients describe how they are designing and running their own clinical trials in collaboration with industry professionals. For these reasons, I believe there is a dire need to review and improve the way this industry discovers and develops products for commercial markets. We start that review with a critique of the current, staggered approach to product development. I should preface this by declaring that I am a non-scientist, so may be regarded by some as an interloper without proper understanding

of the issues. In counter to that, it may be possible that someone asking searching questions without a scientist's training or thinking processes may shine some helpful light on the situation. Readers should judge for themselves.

A CRITIQUE OF THE CURRENT APPROACH

Figure 1 (below) shows a diagram from the GAO report referenced above. Aside from showing the statistics of attrition and average timelines, it presents the well known staged process of discovery, preclinical and clinical research, regulatory review and approval. When we study this approach in practice, some key issues emerge:

- There is a sharp, organizational divide between discovery and pre-clinical research. Once a development candidate is selected, it is handed-over to a new set of players as the discoverers move on to new areas of research. Does this make sense, given the attrition rates we all live with? Shouldn't both teams work together in an iterative fashion, where the discovery functions and preclinical functions take joint responsibility for what enters the clinic?
- There is very little engagement of stakeholders other than the discovery and preclinical research functions at the critical early stages. This means there is an absence of input from, for example, commercial manufacturing, procurement, marketing… and dare I say, payers and patients! Because of this, we are starting with a "limiting" mindset and left with a dilemma. By not involving these other key stakeholders, decisions to progress a compound forward are based on incomplete data. For example, what are the specific needs of the target patient population? Does the compound have the chemical and biological makeup to be manufactured at a commercial scale? Is the supply base for the constituent materials, as specified, sufficiently robust to support demand from the patient population?
- When these functions do eventually become involved, there is little or no chance to revisit those early trade-off decisions - the pressure is on to get product to market. In practice of course, this means the trade-offs (such as poor solubility of a compound or border line safety profile) lay fallow until they eventually contribute to the attrition statistic.

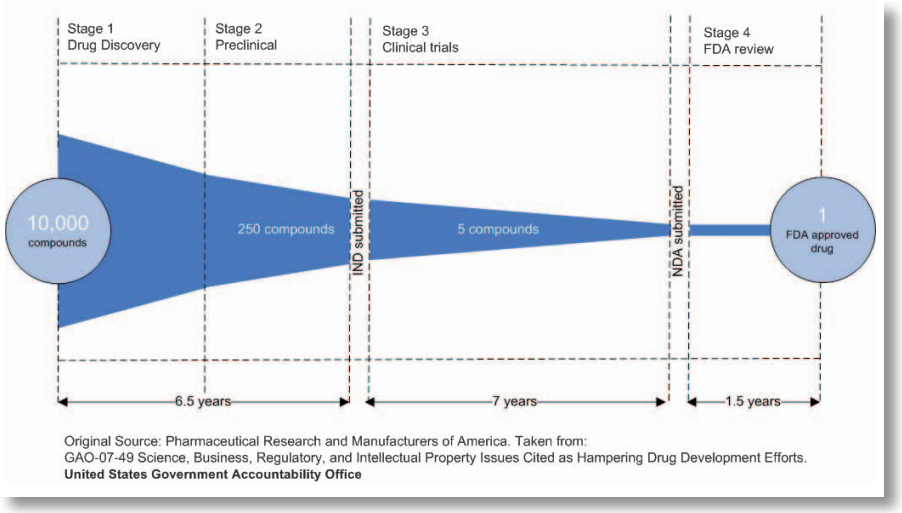
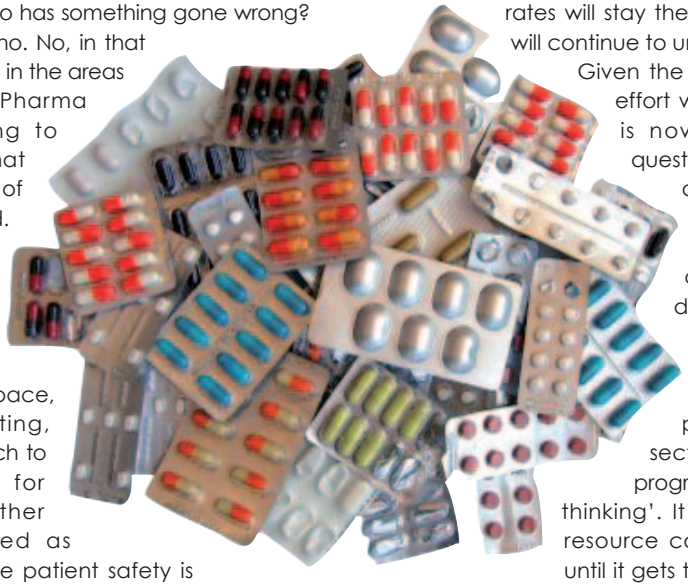


Figure 1. The drug discovery, development and review process.

The points above are made briefly by necessity, but hopefully make the case that there are issues to be resolved. What follows now is a suggested starting point for improvement, more to catalyse debate rather than offer a prescriptive solution.

WHAT WOULD A NEW APPROACH LOOK LIKE?

The following examines a model of drug development based on the approach taken by other sectors when developing products for customer markets. In fact, this IS what the regulators did when they formulated the modernisation guidelines that are embodied in the International Conference on Harmonisation (ICH) documents Q8, Q9 and Q10. For readers not familiar with them, they refer to Pharmaceutical Development (Quality by Design), Risk Management and Quality Systems. These three together provide a framework for a much improved product development process. Nearly a decade after the modernisation guidelines were first penned, there is patchy evidence that anything has changed in the mindset that drives drug development. The issues of concern for stakeholders are still present in terms of high attrition rates and defect levels, together with poor supply chain integrity. So has something gone wrong? The answer is probably yes and no. No, in that the guidelines are basically sound in the areas they cover; but yes, in that Pharma companies are still struggling to understand the essence of what those other sectors did in terms of changing the way they worked. For this reason, I have listed below my own interpretation of the regulators intention. The analysis is based on work researching these other sector's (such as semi-conductor, aerospace, automotive) ways of operating, especially the Japanese approach to systems producing products for markets. Historically these other sectors have been perceived as "different" to this industry, where patient safety is paramount. However, when we compare quality in certain other sectors, when measured in terms of errors and defects produced, Pharma does not stack up well. Similarly, the organisational processes by which they develop "fit for purpose" products for customers are often far better integrated and streamlined than our sector. Why not at least try and learn some different tricks? The points are listed as summary bullets below, and are based on a more detailed account in the end note reference (4).



Companies developing drugs for patient markets should consider:

- Designing molecules based on full and early stakeholder involvement - manufacturing, procurement, marketing, patient and even payers.
- Having only two broad stages - "prototyping" and "commercial manufacture". Whilst there are sub stages, such as initial conceptualization, these two broad categories draw a stark distinction between design (and the eventual prototypes) and manufacture. Design would have the ability to produce options that manufacture would assess for suitability, but nothing would move forward unless it could be manufactured as a commercial product.
- Developing prototypes of molecules in the patient intended dosage form.
- Organising drug development as complete programmes, not a series of phased projects.
- Allocating overall leadership responsibility for the programme.
- Creating an end-to-end value chain with joined-up processes and long-term supply relationships.
- Placing responsibility for defective work on the producers not the quality function.
- Re-defining the role of "quality" towards improvement activities, rather than inspection.
- Building a deep understanding of material and process capability.
- Becoming "business process" oriented and systems aware.
- Institutionalising risk management into development programmes.

WHAT ARE THE BARRIERS TO CHANGE?

Some, all or none of the above may appeal to readers. Most, I believe, will be sceptical if it could ever happen. Why would a company spend valuable time and money on compounds that may never make it past a first-in-humans study?
Good question indeed. I just wonder though, what is going to happen if no-one in this sector does it? The attrition rates will stay the same and our supply chains will continue to underperform.
Given the amount of wasted time and effort we already see, maybe there is now an easy answer to the question - that is, taking more time and effort at the start will save orders of magnitude more money and resources than are currently consumed in drug development.
If this was potentially a convincing argument, however, there is still one all pervading mindset in this sector that stands in the way of progress. It is what I call 'endpoint thinking'. It basically means minimising resource commitment to a compound until it gets through the next endpoint, be that preclinical, or any of the clinical phases. I don't know any other sector myself that designs products ONLY to get through each next phase of testing. Imagine how aircraft would perform if that were the case. Luckily, they discovered their own predictive technologies, such as wind tunnels, a long time ago!
Hopefully then, the foregoing has provided some food for thought to those in the industry keen to progress modernisation as a new way of doing business, rather than a set of regulatory guidelines per se. Let us hope that successes follow on, for the benefit of patients (that includes us) around the globe.

REFERENCES AND NOTES

1. *US Government Accountability Office (GAO), "NEW DRUG DEVELOPMENT, Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts*" November 2006, http://www.gao.gov/new.items/d0749.pdf, accessed Oct 2010
2. R. Winslow, *Wall Street Journal*, October 2 (2010).
3. S.J. Spear, *Chasing the Rabbit: How Market Leaders Outdistance the Competition and How Great Companies Can Catch Up and Win* (2009).
4. H. Rees, *Supply Chain Management in the Drug Industry: Delivering Patient Value in Pharmaceuticals and Biologics*, J. Wiley, NJ, (for release early 2011).