Remodelling pharmaceutical R&D
and the role of regulatory affairs

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Abstract
This article summarises the results of exploratory regulatory research undertaken for a TOPRA MSc dissertation. The research investigated declining productivity in pharmaceutical R&D; the reasons behind this, the various initiatives and potential solutions to reverse this trend, and the implications for the regulatory function.

Background and conceptual setting
Drug discovery and development (R&D), as an interdisciplinary task with an industrial base, has only existed for around a hundred years. In that time, the pharmaceutical industry has played a significant role in transforming the lives of millions and improving human life expectancy globally. But the industry model is challenging, as typically only one in 10,000 molecules make it to market,¹ and only three in ten of those marketed products generate enough revenue to surpass R&D costs.² Further, the duration from initial discovery to sale of a new drug can take at least 12 years,³ with the cost per new molecular entity estimated to exceed one billion dollars.⁴ Despite these adversities, the industry has traditionally been successful, generating approximately 30 new drug approvals per year.⁵

However, in recent years a gradual decline in R&D productivity has been observed.⁶⁻¹⁰ This has been defined as a decline in “the number of new molecular entities (NME) versus R&D cost on an annual basis”⁶⁻¹¹ – a phenomenon herein termed the “Pharmaceutical Industry R&D Slow-Down” (PhIRD-SD).

The PhIRD-SD was first highlighted to the regulatory community in 2004 by Dr Janet Woodcock (then Chief Medical Officer at the US FDA) in a seminal paper titled “Innovation or Stagnation – Challenge and Opportunity on the Critical Path to New Medical Products”.¹² In this document, Dr Woodcock asserted that the drug development path had become increasing challenging, inefficient and costly and that regulators were seriously concerned with the declining number of new registrations. Dr Woodcock called for new tools for drug development and started the Critical Path Initiative (CPI) where industry, the FDA and academia work together to identify key bottlenecks in the drug development pathway. Similarly, many other initiatives involving regulatory professionals as a key stakeholder (eg, IMI,¹³ NEWDIGS¹⁴) have begun to investigate new paradigms for R&D and to facilitate transformational change in the innovator pharmaceutical industry.

Since 2004, the PhIRD-SD phenomenon has been extensively referenced in publications⁶⁻¹¹ and a general concern expressed that the current pharmaceutical R&D model will not be sustainable beyond the next decade. The exploratory research undertaken in 2011 involved investigating the view of this phenomenon in the regulatory community and understanding how changes impacting the pharmaceutical industry may also impact the regulatory affairs discipline.

Research findings
Research data collection involved three forms of methodology; an extensive literature review (more than 300 literature articles), a questionnaire (270 pharmaceutical participants) and in-depth interviews with ten senior pharmaceutical respondents. All interviewees were director level or higher with more than 15 years’ experience in the industry. A range of sectors was represented, including academia, generics, large and small to mid-sized biotech companies, innovator SMEs, privately owned mid-sized innovators, and two interviewees from “Big Pharma” and contract research organisations (CROs). Insights detailed below are based on the findings of this research.

Factors impacting the PhIRD-SD
The drivers for the current issues and the key factors attributed as impacting the PhIRD-SD are as detailed in Table 1.

Of these, the overall root causes link to the lack of complete understanding of disease pathophysiology and poor translational science, which give rise to the high attrition rates. There are also a number of other factors which create a further slow-down for the industry, which are linked as interdependencies. Some are obvious, such as the publicised safety issues and the growing complexity of clinical trials. However, many are connected to corporate culture and shareholder expectations, and will take a major shift in thinking to modify. Further, the key driver of urgency at this time is patent expiries accompanied by an ever-decreasing period of market exclusivity for the innovator industry products.
The blockbuster model has been used to counterbalance high attrition rates while also keeping shareholders satisfied. This concept was termed the “blockbuster lottery” model by one survey respondent, and noted as a fundamental flaw for business strategy moving forward.

Overall, it was recognised that pharmaceuticals is a maturing industry and shareholder expectations need to align with this, given that the blockbuster model is unlikely to survive in the evolving new paradigm.

Regulators were also factored in as being overly bureaucratic, providing excessive administrative burden (rather than leading from a “science base”) and not always working in partnership with industry for medicines development as a societal need. Importantly, it should be recognised that as events unfold for the industry, the regulatory affairs profession will also need to adapt to the new industry paradigms.

**Impact of PhIRD-SD on the industry and the regulatory affairs function**

Patent expiries and the additional factor of requiring “outcomes-based medicine” are putting extreme pressure on an already sub-optimal model. The research work predicted that severe industry disruption may occur, with significant down-sizing of large pharmaceutical companies, consolidation and general industry fragmentation. In turn this is expected to be replaced by a new industry paradigm (“New Pharma”) and various new players. New drug development is likely to slow with the shrinking R&D pipeline. Work will be more limited in scope by performing clinical trials in patient sub-populations (based on genotype), and focus on disease areas where value is more easily demonstrated (eg, orphan drugs and oncology therapeutics). Overriding themes for new business models feature collaborative working (in various forms). In addition, smaller companies or the formation of smaller autonomous business units within a larger company are believed to provide the best innovative environment. The traditional industry model is expected to disappear over the next 20 years, to be replaced by an approach based on networks and scientific centres for development.

The regulatory affairs function is inextricably linked to the business model changes and the paradigm shifts which will be taking place in the industry. As a result, the regulatory framework is expected to undergo radical modification. Flexible regulatory mechanisms will be needed as industry transforms, and regulatory affairs staff will be expected to challenge requirements as work in new areas evolves. Competency frameworks will be important for the function in the future, especially as the industry moves toward a network base. Individual knowledge across a wide range of regulatory topic areas will be key, as regulatory affairs professionals adapt to the new working environment. Self-sufficiency will be an important theme for the future, and a generally fluid movement of regulatory staff across companies is predicted. Regulatory knowledge and education will therefore be of high value.

Regulatory affairs will be a pivotal group to work with regulators in facilitating partnerships and to provide influence via trade associations.
Focus – Drug development

and with R&D disciplines. Regulatory affairs can also act as a bridge to aid balanced requirements versus support for innovation – a fulcrum for change. To do this, regulatory staff must be creative and collaborative, but also challenge both internally and externally, and be able to move forward in new areas which do not fit current regulatory pathways.

Globalisation will be fundamental to the future, with key growth markets outside the EU/US, and global harmonisation groups will be necessary beyond the boundaries of ICH. There is a real need to push for true harmonisation to support the industry and medicines development for the benefit of patients.

Potential solutions to PhIRD-SD

The 2011 research also explored ideas for potential solutions to aid reverse the PhIRD-SD. A key overriding factor noted was the need for a “safety culture” in the industry. Safety culture refers to a blame-free culture which allows mistakes (to stimulate innovation), but has appropriate layers of vigilance in place to monitor for unintended consequences. It does not just apply to pharmacovigilance, but to all areas within the industry. Further, by acknowledging how mistakes happen, organisational learning is promoted. This, coupled with standardised policies, procedures and competency frameworks, could enhance efficiency within the industry, enable a new collaborative paradigm (as networks evolve) and, importantly, regain trust for the industry, thereby facilitating future partnerships. Table 2 details the summary of potential solutions to reverse the PhIRD-SD.

Ultimately, innovation will be needed to turn the industry around, but this will only come with time through nurturing the innovative environment. Innovation will only occur at the juxtaposition of many different disciplines, therefore to encourage this, smaller business models and collaborative working across companies, with academia and with the healthcare community will be needed. This will be supplemented by our increasing knowledge via genomics and through the various ongoing initiatives. However, as this work will take time, shorter-term wins to sustain the industry must also be undertaken. These involve modified R&D models, modified company business models and working with product areas where differentiation

Table 2: Analysis of potential solutions to reverse PhIRD-SD

| Improved knowledge of disease pathophysiology and translational science | • Various initiatives  
• Collaborations across industry and across sectors (academia/regulators/industry/healthcare sector)  
• Consortia and public-private partnerships  
• Open innovation. |
|---|---|
| Support “innovative environment” | • Smaller companies or smaller autonomous units within larger organisations noted as improving the innovative environment  
• Improved multi-disciplinary interactions also noted as supporting the innovative environment  
• Let the scientists lead the science (remove overly bureaucratic control). |
| Build more slowly for long-term success | • Eliminate blockbuster focus, educate shareholders – pharmaceuticals is a maturing industry  
• Clinical trials in sub-populations – build knowledge and safety information over a longer time period  
• Focus on specialised areas where “value” can be more easily demonstrated – eg, orphan products, oncology  
• Build set of recognised common standards and policies and overall governing body/build “safety culture” and address “trust issues” (airline industry is an example)  
• Improve stakeholder interactions – provide disease area service. |
| Regulatory | • Better partnership between regulators, industry and healthcare professionals – medicines development is a societal need  
• Improved regulatory framework aligned with current science and removing unnecessary administrative burden  
• New flexible R&D processes aligned with science and “disease need” developed in collaboration between industry and regulators  
• Separate regulatory assessment and health technology assessment (HTA) needs to be addressed. |
| Globalisation | True harmonisation needed (regulatory and HTA) – progress toward the global filing – national boundaries should not impact medicines development or delivery to the patient. |
| Overall industry changes | New business models for industry, various sized companies, federated or diversified models.  
Devices and diagnostics becoming part of the value chain. |
| Incentives | National governments need to provide better support for innovator R&D, otherwise the industry and the academic base around it will be lost. Medicines development is a critical industry to be maintained. |
| Longer term – scientific advances over time | • Advances in “omics” research – genomics, proteomics, metabonomics, epigenetic factor analysis  
• Mass sequencing across both human and animal species/various disease states and time-points in disease progression  
• Bioinformatic progress to handle extensive data generated. |
and value can be shown. Most importantly, policies, procedures and frameworks should not stifle innovation through excessive bureaucracy; support for the innovative culture is paramount.

**Regulatory framework**

As discussed earlier, the regulatory framework is also predicted to need radical change. General themes from the research are shown in Table 3.

An important theme mentioned by respondents was the need for true partnership between the industry and regulators to further medicines development as a societal need. In general it was felt that a revised, more flexible, regulatory framework is needed, aligned with current science, and improved in terms of the overall review timeframe. Further, the current regulatory system is overly bureaucratic and this aspect is overruling the science, along with an excessive administrative burden.

The need for formal competency frameworks for both regulators and regulatory affairs professionals was also highlighted by respondents. It was emphasised that relationships with regulators should be broadened to include key R&D discipline personnel along with regulatory affairs to facilitate more in-depth scientific discussions. Finally, mechanisms for informal regulatory advice were noted, and will be important in the changing industry paradigm with increased numbers of small start-up companies needing advice in new innovative areas.

Harmonisation was also an important theme among respondents, both in terms of regulators and HTA bodies. For regulatory affairs, the cost implications of non-harmonisation (directly and indirectly through inefficiency) as the emerging markets grow will be enormous. Already, the issue of different timelines for clinical trial application approvals is adversely impacting development programmes, and more should be done to address this. Regarding HTA, specifically within the EU, harmonisation is critical and is having a serious impact on drug development programmes. However, these areas need review above national governance, which is another important theme moving forward and impacts on many facets of the global pharmaceutical industry.
Strategic options for industry

In summary, for the industry to move forward, it is clear that one size will not fit all, and there will likely be many variations across the industry according to company size and focus. Interactions with stakeholders will be critical, and companies may change to a disease state lifecycle approach. However, while there is much talk of smaller companies being the solution, there is also a need to have considerable scale to bring a drug through Phase III to market. Therefore, there will always be a key role for Big Pharma. In terms of the regulatory function (both industry and regulators), engagement in further collaboration at all levels (with each other, with R&D, in consortia, through initiatives, etc) will be a key trend. Challenging requirements to align with science, to work in new disease areas and to adapt across various fluid R&D and business models will be key for regulatory. Major changes to the current incentive framework will also be needed in order to foster the type of collaborative work needed for the future. This is likely to involve a variety of different models and players. Importantly though, this major disruption to the industry may lead to great opportunities for some companies and regulatory affairs groups who are nimble enough to adapt in the evolving paradigm. Therefore, the overall view is that pharmaceutical companies and their regulatory groups will need to be flexible and adaptable regarding strategies moving forward.

From the research work undertaken it appears that a pivotal change across the industry needs to take place, with an increased focus on science and technology to fuel innovation through collaborative associations. Fundamentally, the pivotal change will be to new types of R&D and industry business models, heavily linked to the science and academic collaborations, highly supportive of the innovative environment and incorporating strategically focused, adaptable regulatory affairs teams. These new models will also link in to the concept of “open innovation” and harnessing ideas from outside of the main company (ie, the “global brain”). Innovation is beyond core regulatory affairs teams. These new models will also link in to the main company (ie, the “global brain”). Innovation is beyond core

Conclusion

We are currently on the cusp of a healthcare transformation which, to reach full potential, will encapsulate not just scientific transformation but also organisational and institutional transformation. Formation of New Pharma, and more importantly the frameworks to support this, will require radical transformation. In conjunction, regenerative growth and transformation of the regulatory affairs organisations will also need to occur, to facilitate support for New Pharma. Traditional boundaries need to be revisited, systems challenged and a new dynamic partnership across sectors established. While this will involve a huge effort, it should only serve to inspire and motivate all within the industry. The search for new medicines to alleviate human suffering is a noble cause, and the advances seen in the past 70 years are a testament to human ingenuity, and the dedication of so many individuals within the industry. As one survey respondent observed: “Necessity is the mother of invention,” and in light of the many economic and political pressures facing the industry, this transformation (in industry and regulatory) may be borne out of necessity to survive these difficult times. However, these changes, coupled with the scientific advances about to dawn, have the potential to mediate extraordinary transformation both for medical science and humankind.

References