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Regulatory Readiness Level: a Tool to Enhance Early Regulatory Adoption in Academic Discovery

Eamonn McGowran
Technological University Dublin

Elaine Harris
Technological University Dublin, elaine.harris@tudublin.ie

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Regulatory Readiness Level
A tool to enhance early regulatory adoption in academic discovery

Authors

Eammon McGowran, TU Dublin & PRST

Elaine Harris, TU Dublin & PRST

Abstract

The development of pharmaceuticals products is a complex and arduous process. It requires significant investment (both financial and time). The costs of developing products range from $314 million to $2.8 billion, with the time of bringing a new drug to market up to 15 years. The overall probability of success from phase 1 to approval is estimated at between 9% to 12%. Concerns have been raised in the fall off of new approvals and the decreasing number of innovative therapies coming through pharmaceutical R&D divisions. Academia is recognised as a source of such new therapies, but their strengths do not lie in successfully getting product to market. Difficulties arise in the academic setting, due to their lack of understanding and knowledge of the rigorous regulatory requirements that are needed to gain clearance to market pharmaceutical products. Additional tools are needed to aid academic researchers navigate the necessary regulatory pathways. Whilst Technology Readiness Level (TRL) tools exist, they are simplistic in nature and do not provide the necessary detail to facilitate this process. An expansion of the TRL is proposed as one such solution, in the form of a Regulatory Readiness (RRL) tool. This tool will serve as a suitable method to ensure academics have the knowledge and skills to incorporate regulatory science into their product development processes.

Introduction

The development of products in the life science sector (Pharmaceutical and Med Tech) is multifaceted and complex, with inherent risk that a product in development will not succeed, even after very substantial financial and time investment (Zurdo, 2013; DiMasi, 2016; Eilat, 2018). Data shows that in the United States the overall success rates from Phase 1stage to a successful US FDA approval is roughly 9-13% (Hay, 2014; Thomas, 2016; FDA, 2017; Takabe, 2018; Wong 2019). The challenges related to drug development include scientific, technical,

and regulatory issues and as the industry has developed over the years, the complexities of development have increased, with the results that companies are channelling their Research and Development (R&D) into areas such as Biopharmaceuticals and Advanced Therapeutic Medicines, with associated high failure risks (PhRMA, 2015). This has added to increasing timelines to take products from initial inception to the market. Drug development costs have steadily increased since the 1950s; with a doubling of costs approximately every 9 years (Scannell, 2012). In the recent years there has been an increase in expenditures on research whilst the number of compounds in late-stage development has declined. The time to bring a new drug to market ranges from 10 – 15 years with estimates of the cost to bring a new drug to market vary with figures of $314 million - $2.8 billion being calculated (DiMasi, 2016; Takabe, 2018). Woulter *et al* (Woulter, 2020) put this cost per product at $985 million, counting expenditures on failed trials. Late-stage failures remain a major cost in any drug development programme (Yildirim, 2016). In research millions of molecules are tested, thousands are selected and moved to development where most fail to progress in preclinical or clinical settings (Shannon, 2007; Mohs, 2017; Toriesen, 2015). The progression of novel therapeutics from the laboratory to the clinic is poor, with a success rate of less than 10%, with safety and poor efficacy cited as the main causes of attrition (Yildirim, 2016; Lowe, 2019). The number of compounds being brought from development to successful launch decreases as they progresses though the clinical development phases, with the likelihood that for every 10,000 compounds identified at the pre-clinical evaluation stage only one succeeds to market approval. Until recently it was quoted that once in the clinical phase there is approximately a 20% success rate from the start of the clinical trials to marketing approval (DiMasi, 2016; Wong 2019) but Woulter *et al* (Woulter, 2020) reviewed the aggregate success rates across a number of studies and reported the overall probability of clinical success (the success rates for a drug entering clinical testing to approval) is estimated to be between 9% -12%. Data presented in 2019 from the Centre for Medicines Research (CMR) International, consortium (Dowden, 2019) indicate success rates in the later stages of development improve with a 66% chance of progression from phase III through to launch whilst for drug candidates in phase II the probability of successfully progressing to phase III is approximately 25%. Paul *et al* (Paul, 2010) estimate that to yield a single New Molecular Entity (NME) launch per annum, then at least 9 molecules must enter clinical development every year. As most large companies aspire

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for 2–5 launches per year approximately 18–45 Phase I starts would be required annually to generate this rate of progression based on previous experience.

Regardless of the exact proportion of compounds finally achieving launch at a commercial level, the process has rightly been described as a "leaky sieve". Indeed if one is to bench mark the healthcare industry success rates against other industries for given the levels of expenditure then such a high rate of failure (9 in 10) warrants investigation. As one industry commentator has observed "*no other major business type operates under such a high failure rate (> 90%) in the central, crucial process of the whole industrial drug discovery business. Fix that and everything changes*" (Lowe, 2019).

Over the past decade concerns have been raised over the fall off in new approval. Whilst the much lauded 21-year high in approvals of NMEs in the US in 2017 and 2018 is welcome, such approvals have still remained at low levels since the 2000s. (Takabe, 2018) with fewer novel drugs (48) approved by the US Center for Drug Evaluation and Research in 2019 compared with 59 in 2018 (Challener, 2020).

In 2018, the Congressional Budget Office (CBO, 2018) calculated that due to high failure rate, biopharmaceutical companies would need to earn a 61.8 percent rate of return on their successful new drug R&D projects in order to match a 4.8 percent after-tax rate of return on their investments.

Kneller (Kneller, 2010) analysed the origins of 252 drugs that received FDA approval between 1998 and 2007. Up to 24% were transferred from universities to either biotechnology companies (16%) or pharmaceutical companies (8%) showing that universities made a substantial contribution to the discovery phase of innovative drugs over the period.

An analysis undertaken by the European Medicines Agency (EMA) (Lincker, 2014) of approvals by the EMA over the period 2010-2012 noted that for innovative medicine in EU more than 40% of marketing authorisation originated from small or medium-sized enterprises (SMEs), academia or public bodies and public-private partnerships. Of these 27% originate from SMEs with 17% originating from academic institutions, public bodies and public-private partnerships

Whilst basic research in the context of pharmaceutical R&D, is a strength of academic institutions, the ability to translate this research into a successful product is not necessarily the forte or driver in the academic environment. The translation of research findings into medicinal products suitable for use in the clinic requires detailed knowledge, skills and facilities that are typically not located in academic setting (Hait, 2005, Bhavna Chawla, 2018). Pharmaceutical companies have the resources to develop products complying with the complex quality and manufacturing standards, whilst also compiling the regulatory dossiers sufficient to meet requirements for regulatory submission and approvals (Starokozhko, 2020). Furthermore there is an inherent conflict in that academic research is primarily measured and valued by peer reviewed publications and success in obtaining grants (Frye, 2011). This leads naturally to stronger interest in fundamental research rather than meeting the needs of the industry (Huryn, 2013),

Although academic institutions as well as SMEs, public bodies and public-private partnerships bolster the product pipelines of larger companies, academics are not typically seen to be experts at bringing their product through the later stages of development and obtaining a marketing authorization/ marketing approval. For many in the academic arena there is lack of understanding of the specific regulatory requirements that are involved in drug development and obtaining a successful approval.

In a European survey undertaken by the EMA (EMA, 2016) education on the role and activities of regulators was highlighted as necessary in order to increase academia's engagement in regulatory science activities and research. The provision of education, training to academics as well as the need for increased regulatory support were seen as important aids to help in translating academic research into novel methodologies and medicinal products.

In the words of the EMA survey*"understanding the factors that could affect drug innovation, such as the nature of the organisations involved, could help in developing strategies to catalyse further advances"* (Lincker, 2014)**.**

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There are initiatives being undertaken at a European level to bridge the gap between academic researchers and their understanding of the regulatory pathway. The EMA have set out their vision in their 2025 strategy (EMA, 2020a) with the aim to "catalyse and enable regulatory science and innovation to be translated into patient access to medicines in evolving healthcare systems". In their planning the EMA seeks to help regulatory science develop and use it to ensure that advances in knowledge translate in a timely way into new, safe and effective treatments for patients.

In a 2018 study, Takebe *et al* investigated up to 800 drug discovery projects that took place between 1991 and 2015 at 36 academic institutions in the United States and examined the influence of industrial collaboration on the success rate of the academic projects. The authors concluded what is needed is *"closer industry-academia collaborations and integrated computational– i.e. big data – experimental and clinical drug repurposing approaches are needed to tackle the challenges and seize the opportunities in drug development*"(Takabe, 2018). With the increasing awareness of pipeline stagnation, pharmaceutical companies globally are turning their attention to universities conducting fundamental research in order to acquire drug discovery "seeds" that originate in academia.

It has been established that the success rates for early development to successful launch is less than 10%. The majority of these failures (75 to 80%) are mainly due to problems with efficacy and/or safety (Dowden, 2019). Regulatory authorities have taken steps to mitigate against these issues by the introduction of guidelines for the development of products. For example the EMA have set up electronic guidance on their website in the section on clinical efficacy and safety guidelines (EMA, 2020b). The aim of these guidelines are to help applicants prepare marketing authorisation applications. The guidelines reflect a harmonised approach of the EU Member States and the Agency on how to interpret and apply the requirements for the demonstration of quality, safety and efficacy set out in the Community Directives and the agency actively encourages applicants and marketing authorisation holders to follow these guidelines. To further advance the supports the agency has introduced dedicated structures to support human medicines R&D development and offers new platforms for engagement with the academic world such as the establishment of innovation offices and scientific advice services.

As noted above there is a need to enhance the awareness of the role and activities of regulators as a means to increase academia's engagement in regulatory science activities and research in order to translate academic research into novel methodologies and medicinal products. It was identified that what is needed is for academics to have appropriate tools at their disposal to allow them navigate the rigorous road of product development and the stringent regulatory requirements, in short a regulatory tool to help identify where they are in the process.

One tool already in use by academia is the Technology Readiness Levels (TRL) tool. The TRL originated in NASA in the 70s, where it began as a means of measuring how far a technology was from being deployed in space (Héder, 2017). The NASA researcher, Stan Sadin, conceived the first scale in 1974. It had seven levels which were not formally defined until 1989. In 1990s NASA adopted a scale with nine levels which gained widespread acceptance across industry and remains in use today (Olechowski, 2015). The US Department of Defense (DoD) and the Commonwealth of Australia and NATO require the use of TRL in defence technology acquisition. The usage of the TRL tool has spread among other governmental and military organizations including the European Space Agency which in turn has led to its incorporation in the EU Horizon 2020 programme and will also be used in its successor Horizon Europe 2021-27 (European Commission, 2020). In the EU the High-Level Expert Group on Key Enabling Technologies (HLG-KET) built TRL into the foundation of its new public innovation policy (see Figure 1). The universal usage of TRL in EU policy was proposed in the final report of the first HLG-KET (HLG-KET, 2011).

The TRL model is a relatively simple model categorising the nine stages from basic research to a proven deployment. The model is designed to be concise and easy to communicate. It acts as a means to identify the stages that a technology is at and principally estimates the maturity of that technology. Use of the tool to assess maturity of healthcare products, is however somewhat limited, given that it was specifically designed for engineer-based products. The US Army Medical Research and Materiel Command (AMRMC) have attempted to address this and mapped the TRL descripts to the development of health care products (US Department of Defense, 2009). A simplified TRL example for a therapeutic candidate would progress through TRLs 1 to 4 involving basic technology research and preclinical studies, cover clinical trial application (TRL5), to clinical trials (TRL6-8) and submissions for a product

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approval from the agencies (FDA or EMA) and then to product launch (TRL9) followed by post-marketing studies and surveillance. It spans the whole innovation process, from basic research activities to product launch and post-marketing activities. So whilst the AMRMC TRL offers a useful tool to estimate the stage of development of a medicinal product, it is lacking the degree of detail necessary to allow academic researchers to navigate the complex regulatory routes to market. It does not contain the necessary granularity and depth that covers the quality requirements for pharmaceutical products and the clinical guides needs for bringing a product thought the complex development routes necessary for a successful submission and ultimate approval. Most notably within the TRL level 4 to 7 (the development stages that can be equated to "the Valley of Death" where initial research do not successfully cross over to allow for a product to attain its commercial potential). It is claimed that this lack of detail explains its relatively low uptake within the pharmaceutical and academic development programmes (Webster, 2019).

An adaptation of the TRL approach which emphasises the detailed steps required on the regulatory pathway would add substantially to the armoury of the researcher. An approach would be to expand the TRL tool methodology to capture a pharmaceutical products regulatory readiness. In doing so the regulatory gaps that prevent a pharmaceutical product moving to the next stage are identified and the necessary remediation actions to be implemented are indicated.

In a separate paper in this publication (O'Reilly, 2020), a survey of academic researchers and relevant subject matter experts indicated there is a willingness among academic based researchers to embrace a regulatory tool as part of their development strategies. In the study the authors gauged the awareness and knowledge of academics and early stage researchers in regards to the regulatory requirements to commercialise academic research and sought to determine the interest in the use of a regulatory pathway tool (based on the TRL tool). It was established that such researchers do not have the necessary training, knowledge, or experience to enable them to engage in the regulatory pathways and there is a lack of clarity around the regulatory requirements associated with commercialisation of basic scientific research. It was identified that a simple, easy-to-use tool to guide early stage researchers

along this regulatory pathway would be very useful. The introduction of such a tool would be timely given the increased interest in academic settings to commercialise research.

This paper introduces a Regulatory Readiness Level (RRL) tool, developed by the author that can confirm what stage of a process a technology is at and what are the steps needed to complete the regulatory steps to advance development of the product and move to the next TRL. This RRL tool can be used from early development work in academic laboratories to commercial release (gauging the status /level the technology is currently at). The tool would allow researchers to map to the next key stages whilst identifying the gaps and areas to focus on and build strategies to reach RRL goals-milestones.

Early work conducted by the authors led to the creation of a simplified tool that outlines an RRL based on a set of reached development milestones (see Figure 2). This tool also contained 9 levels (RRL 1 to 9) with an expansion of the TRL definitions to introduce scientific requirements to be met at each of the regulatory readiness levels. This tool was subsequently beta tested with a review group of industry based professional and an academic group focussed on commercialisation of innovative products. Feedback on the tool was positive, with constructive suggestions provided to enhance the workability and usefulness of this tool. These included a further expansion of the RRL levels to give more detailed information on the steps expected at each RRL and the introduction of an interactive element with provision of hyperlinks to relevant regulatory agency guidance's (e.g. Quality, Preclinical, Clinical and ICH guidance).

The tool is now being further developed into a RRL model within a Microsoft Excel programme, with the inclusion of series of questions (Yes/No) on the stage of development allowing for an evaluation of the RRL level reached. An added functionality is included so that where gaps in the RRL are identified, a mapping to suitable regulatory agency guidance is available. As the same set of questions are answered each time in the tool, it provides researchers a standardized, repeatable process for evaluating the status of a product under development.

Conclusion

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The development of a medicinal product is a complex and time-consuming process with numerous scientific, technical, and regulatory hurdles. Coupled with this is the increasing costs associated with R&D, the reduction in product approvals and a shrinking pharmaceutical industry pipeline. Academia has long been seen a source of innovative products that feed into the pharmaceutical and biotechnology sectors. Whilst industry is well placed with to meet the increasing challenge the academic arena struggles with this complex regulatory environment and this is often cited as one of the barriers to translation of scientific research to use in the clinical setting. It is now recognised that those is the academic sector have a need for greater understanding of the regulatory requirements in place to achieve a successful approval of a product.

The use of a Regulatory Readiness Level tool as envisaged by the authors will greatly facilitate the increased awareness and advance the incorporation of regulatory science in the academic sphere. The work on the further development, validation, and implementation of the RRL tool in academic settings, followed by investigations into application and usefulness of the RRL tool in a real-world setting in ongoing.

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FIGURE 1 - The TRL scale and EU HORIZON 2020 definitions

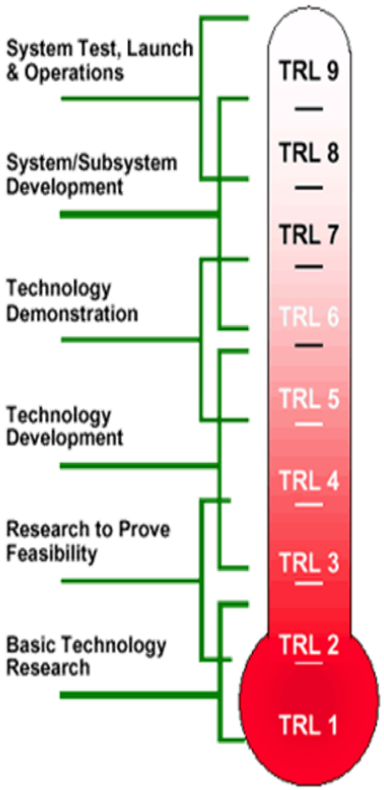
Standard TRL	***HORIZON 2020 Definitions***			
	***TRL-1*** ***Ideation***	***Basic principles observed*** ***Initial scientific research has been conducted. Principals are qualitatively postulated and observed. Focus is on new discovery rather than applications.***	**TRL-6** **Early stage validation (Continued)**	**Technology demonstrated in relevant environment (industrially relevant environment in the case of key enabling technologies)** System/process prototype demonstration in an operational environment (beta prototype**)**
	TRL-2 ***Proof of Principle***	***Technology concept formulated*** *Initial practical applications are identified. Potential of material, process to solve a problem, satisfy a need or find application is confirmed*	TRL-7 **Late stage Validation**	**System prototype demonstration in operational environment** System/process prototype demonstration in an operational environment (integrated pilot system level)
	TRL-3 ***Proof of Concept demonstrated***	***Experimental proof of concept*** *Applied research advances and early stage development begins, Studies and laboratory measurements validate analytical predictions of separate elements of the technology*	***TRL-8*** ***Pre-commercialization***	***System complete and qualified*** ***Actual systems/process completed and qualified though test and demonstration (pre commercial demonstration)***
	TRL-4 ***Proof of concept established***	***Technology validated in lab*** *Design, development and lab testing of component/processes. Results provide evidence that performance targets may be attainable based on projected or modelled systems*	*TRL-9* ***Commercialization and post market studies***	***Actual system proven in operational environment (competitive manufacturing in the case of key enabling technologies; or in space)*** *Actual system proven through successful operations in operating environment and ready for full commercial deployment*
	TRL-5 ***Early stage validation***	***Technology validated in relevant environment (industrially relevant environment in the case of key enabling technologies)*** *System component and/or process validation is achieved in a relevant environment*		

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FIGURE 2 – Relationship between TRL and RRL scales.

TRL	Expansion of Activities	RRL Level
TRL 1	• Scientific findings reviewed characterizing new technologies.	RRL 1
TRL 2	• Generate research ideas "paper studies" • Developing research plans • Hypothesis are formed & identify candidate concepts &/or therapeutic drugs	RRL 2.1 – 2.3
TRL 3	• Test hypothesis -evaluate technologies supporting drug development. • Initial synthesis of candidates, limited in-vitro and in-vivo research models - initial proof of concept. • MOA & characterization of hits in preclinical studies	RRL 3.1 – 3.3
TRL 4	• Demonstrate proof-of-concept & safety of candidate drug formulations • Preclinical studies (animal models) to assess potential safety & toxicity problems, adverse events, & side effects. • Exploratory studies of hits/leads to set: formulation; routes of administration; method of synthesis; physical & chemical properties; metabolic fate & excretion/elimination; and dose ranging	RRL 4.1 –4.3
TRL 5	• Non-clinical & pre-clinical research studies • Parametric data collection and analysis in well-defined systems. • Pilot lots drug candidate are produced for further development & provide the basis for a manufacturing process tranferrable to cGMP-compliant pilot lot production. • GLP safety & toxicity studies to evaluate PK/PD of candidate drugs. • Data package compiled of animal pharmacology & toxicology studies, proposed manufacturing information, and clinical protocols for Phase 1 clinical testing.	RRL 5.1 –5.5
TRL 6	• Phase 1 trial application submitted and approved • Phase 1 Clinicla Trial (CT) conducted • Production technologies demonstrated through production-scale cGMP plant qualification. • PK & PD data to meet clinical safety requirements generated to support design of Phase 2 CT l	RRL 6.1 – 6.4
TRL 7	• Phase 2 CT conducted (initial efficacy & further safety, toxicity & immunogenicity data. • Product final dose, dose range, schedule, & route of administration established. • End of Phase 2 CT • Pre-Phase 3 meeting with agencies to discuss results of Phase /Phase 2 & clinical endpoints and/or surrogate efficacy markers & test plans. • Phase 3 CT or surrogate test plan prepared • Application, & clinical protocol to support Phase 3 CT trials or surrogate test plan submitted	RRL 7.1 – 7.5
TRL 8	• Safety & effectiveness in Phase 3 CT or surrogate tests. • Evaluate overall risk-benefit of administering candidate product & provide basis for drug labelling. • Process validation completed, followed by lot consistency and reproducibility studies. • Dossier prepared & submitted to agency	RRL 8.1 – 8.3
TRL 9	• Approval Received • Product launch and monitoring in the market.	RRL 9.1 – 9.2

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