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Regulatory Science as a Means to Respond to EU Healthcare Challenges and Global Market Needs

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Abstract

The current regulatory approval system for the placing of healthcare products at the disposition of patients is essentially a binary exercise (approval/disapproval) and is a costly, long and tortuous process. Regulations that primarily reflect patient concerns and that facilitate product entry to market are needed. The process requires a pooling of resources on an unprecedented scale from widely differing sectors, both within industry and outside of it. The needs exist to establish open transparent and intense dialogue between regulators and the regulated, to bring the fruits of innovation to patients at an affordable price and to expedite the innovation process.

Keywords: Regulatory Science, Innovation, Healthcare, Lifecycle management, Regulator, Research

1. Regulatory Science

The purpose of the regulatory approval system for the marketing of healthcare products is to protect the public. At the same time, it must ensure access to the latest products and interventions in a timely a manner. Yet despite significant increases in research and innovation expenditure in healthcare, there has not been a concomitant surge in output at the end of the pipeline resulting in new innovative products for patients. This is due to an escalation in costs, additional regulatory hurdles and the sector being severely impacted by austerity measures resulting from the economic crisis in Europe since 2010.

At the same time, healthcare interventions as well as new drug developments and have become increasingly complex not only from a scientific but also from several other perspectives, including those of a strategic, financial and ethical nature.

The rapid evolution and convergence of different sciences and novel technologies in the healthcare sector require the constant addition and adaptation of involved stakeholders, including drug regulators. This is partially due to the need, both commercial and clinical, to modify, extend the uses of and sometimes combine different healthcare interventions into one functioning entity. The data required are complex and interlinked with one another and are accompanied by high public expectations. An additional complexity is the inherent uncertainties associated with science and its continuous evolution. In order to ensure public protection while at the same time ensure that the best possible healthcare interventions remain affordable, a solid scientific and technical foundation is required, which is referred to as regulatory science. Regulatory science aims to harness science in evolution resulting in better policies, in a transparent and open way so as to achieve this objective.

2. Definitions

Even though there is no official definition for regulatory science, a number of citations reflect the need for better policies. One is provided by the United States Food and Drug Administration (FDA) : "the development of new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products" [1]. This definition lists a series of priorities, which reflect multidisciplinary nature of regulatory science. A more recent definition describes three distinct phases of regulatory science in the human health field. This first of these consists of an initial phase when decisions are taken on the basis of incomplete or inadequate scientific information. This is followed by an *exploratory phase* when various tools or models are developed and eventually lead to a standard operating phase when sometimes new or improved measuring instruments are used to re-evaluate decisions taken and even implemented at the beginning. The need for transparency is emphasised by identifying all assumptions, judgments, and related practices that go into defining regulatory science and its outputs [2].



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ATMP Advanced Therapy Medicinal Product CAT Committee for Advanced Therapies CERSI Centers of Excellence in Regulatory Science and Innovation Committee for Human Medicinal Products (European Medicines CHMP Agency) COMP Committee on Orphan Medicinal Products (European Medicines Agency) EFTA European Free Trade Association EMA European Medicines Agency EU European Union FDA Food and Drug Administration HTA Health Technology Assessment Innovative Medicines' Initiative IMI MAA Marketing Authorisation Application NCA National Competent Authorities PDCO Paediatric Committee (European Medicines Agency) PRAC Pharmacovigilance Risk Assessment Committee (European Medicines Agency) Small and Medium-Sized Enterprise SME TRL Technology Readiness Level

Abbreviations

Another citation considers regulatory science to be the acquisition and analysis of data sufficient to inform decision making pertinent to the approval of safe and effective therapeutics, devices and cosmetics and ensuring the safety and nutritional value of the food supply [3]. Importantly it also sets out what regulatory science is not: it is not a new set of regulations and nor is it an attempt to establish cutting edge expertise in regulatory agencies.

Taking all of the above into consideration, regulatory science may be defined as the acquisition and combination of scientific, technical and socio-economic data in a way to enable appropriate decision-taking regarding the marketing and use of innovative and cost-effective healthcare interventions by patients. This must happen in a safe and effective manner for patients' best benefit.

Why Regulatory Science?

The most pressing need for the emergence of regulatory science is the shift in the role of regulators from being solely gatekeepers towards maintaining the balance between public safety and facilitating the needs of innovation. Regulations should therefore not be considered in isolation, but as contributing to the acceptability of healthcare products by healthcare systems. Requirements for quality, safety and efficacy should therefore not just come from regulators but also from consumers and healthcare providers. For patients, the major questions relate to the capability of a new intervention to change life quality and affordability. The approval process is in transit from the present form of a binary yes/no approach towards the concept of an evolving lifecycle management. Lifecycle management necessarily means a concrete action plan of integrative support to, allowing for more efficient interaction between regulators, academia and industry throughout the lifetime of products. It would take account of the flow information on efficacy and safety that arises after market launch, as well as having a bearing on pricing and reimbursement decisions to be taken around that time.

The second major need for the development of regulatory science is to facilitate crossing the socalled "valley of death" between pure laboratorybased, or "basic" research and the ideal method of clinical testing, in which research targets population, efficacy and safety profiles. This "valley of death" can exist for a wide variety of reasons : a lack of definition of the final target patient population, incomplete technical data (quality, toxicity, etc.) before clinical testing begins and appropriate definition of endpoints to a clinical trial. in their full expression, these factors may individually or collectively comprise surrogates or proxies for true end points. A need exists for better large scale testing that is more economical, efficient and representative of reallife postmarketing clinical practice. Translational Medicine refers to the process of applying the knowledge gained from basic biomedical research into clinical practice so as to close this gap leading to final application. New research findings, scientific discoveries and improved techniques to prevent, diagnose and treat human disease become standard practice. It includes drugs, devices, biomarkers, treatment methods or combinations of thereof. The ultimate goal is the patient's health [4].

The key to the success for translational medicine, in which promising developments in the laboratory can be translated into the clinic is twofold. The first element for success is a close partnership between the various stakeholders in the research and development pipeline. It is also necessary to find the right balance among various commercial and financial interests, along with input from ethics, health economics and patient organisations. The integration of these different resources from research to innovation and market placement can close the existing gap by sharing resources, mitigating risks, and optimising the use of available knowledge. A potentially great achievement could be a reform of Intellectual Property with a shift from the initial composition of constituent entities in a product to the final and approved product itself [5] similar to that in which printed matter can be copyrighted, although this does not mean patenting the alphabet. The integration will provide better long term industry coordination, a better alignment of industrial capacities with clinical needs and maximise patient benefits.

The second element for success is better education and training facilities to produce individuals who understand not only science and medicine, but also related commercial or nonscientific aspects. Examples of these skills of a nonscientific nature comprise healthcare economics, ethics, management, business administration, and law. Modelling systems that harness datasets from these domains would need to be devised as part of regulatory science. In this way, translational scientists and regulators will gain a better understanding of the challenges faced by each and thereby encourage stronger innovation.

Obstacles that need to be overcome in the education field comprise [6]:

- The design of appropriate curricula with appropriate opportunities for interdisciplinarity to make maximum use of scientific advice procedures from regulators, as well as to make research a longterm career option
- The modernisation of resources and strategies to reflect new developments and challenges related to healthcare systems
- Facilitation of the mutual recognition of degrees and diplomas, thereby fostering better international collaboration and yet maintain the highest possible clinical and quality standards
- The improvement of cooperation between academic, industrial and clinical sectors to facilitate practical handson training, especially for those coming from laboratorybased backgrounds and wishing to transit their findings into the clinic

Many relevant university education programmes now exist in the US as collaborations between the FDA and academic institutions to advance regulatory science through innovative research, education, and scientific exchanges (CERSI Centres for the Advancement of Regulatory Science and Innovation). In this way, new medical technologies for healthcare can be harnessed in collaboration with academia, industry, and other governmental agencies to develop the tools, standards, and approaches required to assess the safety, efficacy, quality, and performance of innovative products [7].

Appropriate mentoring in a workbased environment, so as to facilitate the acquisition of practical experience as outlined above can then enable better use the scientific advice procedure described above. The final element essential for the success of translational medicine is appropriate policy development and implementation [4]. This consists of the evolution of current regulatory control from a binary approval/disapproval mechanism towards a system of continuous management throughout the product life cycle, taking account of scientific developments and data availability. The scientific advice procedure can begin with the first contacts between regulators and applicants in order to determine the appropriate regulatory path for the final marketing of products.

3. Overview of European Regulatory Approval Procedures

All healthcare products must be authorised before they can be placed on the market in the EU. The European system differs with regard to the nature of products that are marketed.

For human medicines, pharmaceutical companies submit a single marketing-authorisation application to the European Medicines Agency. Its Committee for Medicinal Products for Human Use (CHMP) carries out a scientific assessment of the application and gives a recommendation on whether or not to grant a marketing authorisation. If granted by the European Commission, the centralised marketing authorisation becomes valid in all European Union (EU) Member States. This also extends to those from the European Free Trade Association (EFTA) states (Iceland, Liechtenstein and Norway) which are affiliated to this process.

A decentralised procedure also exists for the simultaneous authorisation of a medicine in more than one EU Member State if it has not yet been authorised in any EU country and if it does not fall within the mandatory scope of the centralised procedure. Similarly, a mutual-recognition procedure allows for medicines authorised in one EU Member State to be extended to other EU countries. In this way, Member States can rely on each other's scientific assessments.

The centralised marketing authorisation process is compulsory for all medicines derived from biotechnology and other high-tech processes. It is also required for human medicines for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, immune dysfunctions, and viral disorders. This is of particular importance to Advanced Therapy Medicinal Products, which has its own scientific committee at the European Medicines Agency, the Committee for Advanced Therapies (CAT) and which operates along similar lines to the CHMP.

The centralised procedure is also open to products that bring a significant therapeutic, scientific or technical innovation, or is in any other respect in the interest of patient or animal health. As a result, the majority of genuinely novel medicines are authorised in this way through the European Medicines Agency (EMA).

The EMA also offers scientific advice to prospective applicants involved in the development of medicines. This is an important tool to facilitate the development and availability of highquality, effective and safe medicines, for the benefit of patients. Various incentives exist to encourage the use of this facility by small and mediumsized enterprises (SMEs). Scientific advice can also be given by national competent authorities (NCAs).

Medical Devices are marketed in the EU subject to the awarding of the CE mark from Member States' Notified Bodies. These entities are officially accredited to determine whether products conform to EU Medical Devices Directives, for which revisions have been proposed [8–11] and if so, that they can then be marketed in the EU.

3.1. Scientific Advice Procedure

The scientific advice procedure is an almost essential consultation process before submission of a Marketing Authorisation Application (MAA). The Scientific Advice Working Party is responsible for the coordination of this exercise to ensure consistency with productrelated procedures. It is to ensure that appropriate tests and studies are performed according to standard recognised operating procedures (Good Clinical Practice, Good Laboratory Practice etc.) and to fine-tune development plans to make sure data generated is in compliance with regulations. In this way, major objections regarding their design and content are less likely during the review of the marketing authorisation application. These can significantly delay the marketing of a product, and even result in its refusal. The effectiveness of scientific advice procedure has been demonstrated recently [12].

3.2. Data Certification

A useful but under-used regulatory procedure that has resulted from the scientific advice procedure is the acknowledgement of the acceptability of research data as part of a marketing authorisation application. This data certification does not mean acceptance and approval of the data per se, but rather an acknowledgement that it has been generated according to scientifically sound methodologies based on standard acceptable clinical practice. The specific provisions governing the certification procedure were adopted by means of Commission Regulation (EC) No 668/2009 [13]. Such certification can demonstrate that given Technology Readiness Level (Table I) has been attained in the path to market

Only three data certification requests have been received by mid-2013 by the European Medicines' Agency. Two of the requests concerned exclusively quality data, while the third request related to quality and non-clinical data. Certification was granted in all three cases.

In realistic terms, data certification would correspond to a Technology Readiness Level (TRL) of at least 5 out of a possible 9 on the TRL scale.

3.3. Further Developments

As an extension to the foregoing, the EMA decided in 2007 to set up a procedure, whereby novel methodologies for drug development in specific areas would provide greater certainty about their acceptability for regulatory purposes. This originated in its collaboration with the Innovative Medicines' Initiative (IMI) [14] as well as in the now current "Scientific Advice" process described above.

The procedure looks ahead from the experience thus gained to future methodologies for product development in general. What is sought is a "qualification opinion" determining on the acceptability of novel drug development methods based on results available. In this way the novel methodology is determined to be acceptable or not from the regulatory point of view. Once approved, the new methodology is available to all stakeholders, including industry, publicprivate partnerships, research consortia, and academia and thus can function for those outside mainline pharmaceutical companies, such as medical device manufacturers.

The qualification exercise can thereby serve as a template for future procedures for emerging scientific fields. A further long-term goal is to examine legal and policy aspects related to these licensing measures. Better legislation and new consolidated guidelines are expected, especially for current products that were not developed based on this new way. More systematic regulatory participation in product development can now be institutionalised and serve as the basis for future regulatory science.

4. Health Technology Assessment

Another major development that follows the scientific advice procedure is the harmonisation of scientific advice with that of Health Technology Assessment (HTA) bodies. Health Technology Assessment is the systematic and multidisciplinary evaluation of the properties and effects of a healthcare product or service, addressing its direct and indirect, intended or unintended effects. Since one of its major uses is to determine reimbursement policy on a casebycase basis and coverage decisions, Health Technology Assessment must include a risk-benefit assessment and an economic evaluation. The overall objective is to formulate safe, effective, health policies that prioritise patient benefits and maximise economic gains. Despite this policy goal, HTA must be firmly rooted in research and robust science. It therefore provides a bridge between clinical research and economic decision-taking, which affects patient access to healthcare products.

It is necessary to harmonise not just scientific requirements but also HTA considerations, so that patient access to products is not compromised. The development of a regulatory science as a discipline can help to overcome this hurdle, since it must consider national as well as international concerns.

Without such harmonisation, Health Technology Assessment bodies may lack vital information to decide whether or not to reimburse a new healthcare intervention. Alternatively, they may decide to restrict its access to a subpopulation, before granting wider access to broader patient groups. A further complication consists of regional variations in clinical practice within larger countries. The decision to reimburse may only be possible via more formal postmarketing surveillance studies, which is part of various aspects of progressive or staggered approval procedures. This might be expected to comprise epidemiological, statistical, ethical and even genetic profiling aspects that are not available at the time of initial product launching. The development of regulatory science as a new specialist

TABLE	1
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Level	Definition	Explanation
1	Basic Principles Observed and Reported in the Context of a Military Capability Shortfall	Potential scientific application to defined problems is articulated.
2	Technology Concept and/or Application Formulated	Hypothesis(es) generated. Research plans and/or protocols developed, peer reviewed, and approved.
3	Function and/or Characteristic Proof of Concept	hypotheses tested, alternative concepts explored. Initial characterization of candidates in preclinical studies.
4	Component and/or Breadboard Validation in Laboratory/Field Environment	Non GxP laboratory research to refine hypothesis and identify relevant parametric data required for technological assessment in a rigorous (worst case) experimental design
5	Component and/or Breadboard Validation in a Relevant (Operating) Environment	Intense period of nonclinical and pre-clinical GxP research studies involving parametric data collection and analysis in well-defined systems.
6	System/Sub-System Model or Prototype Demonstration in a Realistic (Operating) Environment or Context	Phase I Clinical Trials
7	System Prototype Demonstration in an Operational Environment or Context (e.g., Exercise)	Phase II Clinical Trials
8	Actual System Completed and Qualified through Test and Demonstration	Phase III Clinical Trials
9	Actual System Operationally Proven through Successful Mission Operations	Post Marketing Studies

Technology Readiness Levels as applicable to Healthcare

area could facilitate Health Technology Assessment decisions being taken earlier, particularly since it aims to bring together widely differing disciplines and at the same time reflect patient concerns.

5. Combination of Pharmaceuticals With Biomaterials, Medical Devices and Advanced Therapies

The development of a standardised regulatory science (rooted in science and thereby closing knowledge gaps therein) is especially needed to bring together the various disciplines related to healthcare products and implicates technology convergence. Examples would include where a medicine, a Medical Device or an Advanced Therapy Medicinal Product (ATMP) have to be combined. Products could include drug-eluting stents, whereas a device combined with an ATMP might be an artificial bone scaffold seeded with autologous stem cells. The device part is regulated by the Competent Authorities or Notified Bodies, which are designated by individual Member States. Approval is denoted by the award of the CE marking. That approval is based on the results of clinical data, scientific in vitro testing or comparison with a competitor medical device. Advanced Therapies are regulated centrally by the European Medicines Agency and in particular, the Committee for Advanced Therapies (CAT).

A review of the Advanced Therapy Medicinal Products Regulation [15, 16] has demonstrated new challenges. The first and most significant observation is the classification of a product as ATMP. Although the centralised approval system can provide standards, the authorities of the Member States often cannot seek the view of the European regulator when they have to decide themselves whether a product should be considered as ATMP or otherwise. Scientific progress is rapid and regulations must keep up with developments, but unfortunately the academic sector with spin-off SMEs lack exposure to the complex regulatory system that governs this area. Indeed, scientific evaluation of ATMPs involves up to five specialist committees at European level :

- The Committee for Advanced Therapies (CAT) which reviews the initial marketing authorisation application and transmits its opinion to the Committee for Human Medicinal Products (CHMP)
- The CHMP adopts an opinion which is transmitted to the European Commission
- The Pharmacovigilance Risk Assessment Committee (PRAC), which issues an opinion to the CHMP on pharmacovigilance-related topics
- The Paediatric Committee (PDCO), whose brief is related to obligations imposed under the Paediatric Medicines Regulation [17]
- The Committee on Orphan Medicinal Products (COMP), which provides scientific opinions to the Commission on potential designation of orphan status (only if this has been requested)

These procedures can be daunting for stakeholders involved in combined ATMPdevice research, especially whose objective



Figure 1: The integration of knowledge from widely differing domains within the healthcare sector can lead to the next generation of technologybased innovations

is to market their products. In these circumstances, the cost can be prohibitive, especially to the academic and SME sectors. This is reflected in the low numbers of applications for data certification, which covers nonclinical aspects and is presently available only to SMEs at a discount price. These low numbers are also due the current arrangement in which even if an ATMP is approved by Committee for Advanced Therapies, an assessment from a notified body is additionally required for the device part and this may not be readily available in all Member States. A potential solution to this impasse might be the mutual recognition of health technology assessments from one Member State by other Member States.

6. Patient Participation in Regulatory Activities

The need to ensure patients participation in the scientific dialogue around marketing approval of healthcare products is now fully recognised and regulatory agencies have introduced various initiatives to address this need. Patients can be the drivers, initiators and funders of new types of research, better advocate their needs and act as advisors for clinical trials. Effective measures to ensure patient participation include providing information on clinically meaningful endpoints and appropriate endpoint measurement, provision of informed consent, selection of recruitment centres, data interpretation and the dissemination of results to regulatory authorities, especially to ethics committees. Patient input stimulates and challenges the research and innovation process as well as enriching and instructing it. In this way, societal objectives and concerns can become central to regulatory science and ensure that healthcare products are approved primarily on the basis of the needs of patients. Debate still exists as to whether or not this is attainable.

The key question that must therefore be addressed is how to harness patient knowledge and experience into the scientific process. How can patients' perspectives be rooted in scientific format? What methods can be used to quantify and qualify patient feedback? Should this come from their own individual experiences or should this act as an advocate for others? What transmitted information is relevant to decisiontaking and what is not? What will the outcomes be? An appropriate framework is needed to assure structural outcome assessment of initiatives to involve patients and citizens [18, 19]. This will not only strengthen the evidence for patient and citizen involvement, but also justify policy making and necessary expenditures. Critical scrutiny of initiatives would not only involve description and effect measurement, but also a cost-benefit assessment.

Key objectives might comprise :

- i. *Representation* : which should take stock of different types of representation in a particular process (e.g. geographic, demographic or political)
- ii. Structure of the process or procedures : with procedural aspects of a consultation process that are legitimate, reasonable, responsive and fair. Inclusion/exclusion mechanisms for participation will have a major impact on outcomes and final decisions.
- iii. Information : determining what and how information is selected, presented and interpreted. The healthcare domain differs from others in that professionals have control over how patients, citizens and nonprofessionals are involved. The knowledge and language shared by them does not reflect the views of patients whose preferences are not always sufficiently incorporated in the scientific discourse. This may have implications for patients to bring about fundamental change in their own best interests. Clearly, information should be given to patients in a clear, unbiased and straight forward manner.

iv. *Outcomes and decisions arising from the process* : The evaluation principles need to consider the various outcomes from the public participation process. Participants must be satisfied with the process which shall lead to a better understanding of the issue. Another important outcome is the achievement of consensus, better decision-taking and improved policy making.

7. Template for Regulatory Science

Regulatory science is therefore needed to cross the divide between laboratory-based science on the one hand and the bedside on the other. It will facilitate better informed decisiontaking regarding healthcare products and their market position. Lifecycle management of products is needed for a maximal protection of the public with evolving science along the following lines :

- Harmonisation of various regulations and other legislative provisions that govern pharmaceutical products, Advanced Therapy Medicinal Products and Medical Devices to facilitate new product innovations. This will eliminate misinterpretations between different regulatory bodies regarding the nature of healthcare products, especially combination therapies and facilitate a new generation of technology opportunities (Figure1)
- Facilitating of constructive dialogues between key stakeholders in the above process. These comprise *inter alia* centralised and Member State regulators, notified bodies, marketing authorisation applicants, Health Technology Assessment bodies ,pricing and reimbursement bodies, and health insurance bodies. The objective is to harmonise risk-benefit requirements and relevant postmarketing obligations
- Developing and piloting new science-based methods for evidence generation and risk-benefit assessment that keep patient needs uppermost in mind
- Consideration of those measures that are urgent and necessary to avoid disparities in the classification of various healthcare products in the EU
- Extension of data certification procedures to all parts of the research pipeline and solidify links with marketing authorisation procedures as value-added milestones in the process
- Centralisation of patients' contributions to the definition of efficacy and safety criteria that are needed for marketing authorisations

8. Conclusions

The time is mature to transform the regulatory process from the present yes/no approach to a science-based life-cycle management strategy. That is to say it must cover all aspects of product development from the laboratory to the clinic. By doing so, innovation can be promoted but the challenges that must be overcome are considerable. These comprise organisational responses to new and traditional data models that should offer a better prediction of clinical performance to cross the "Valley of Death" between the laboratory and the clinic. Considerable human and capital resources will be needed to deploy these new information sources. Other challenges relate to access to data, its ownership and the associated costs. Innovation needs to be balanced with scientific rigor to enhance the efficiency, accuracy, and applicability of clinical testing, without compromising safety and therefore obtain the most effective and reliable strategies for human healthcare.

In this way, new innovative products will reach the bedside sooner and attain the highest standards of safety and efficacy at a much lower cost.

9. Disclaimer

The views expressed in this article are the personal views of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the European Commission or one of its committees or working parties.

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