Pharmaceutical Quality by Design: the Economic Stakes.

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This short article addresses the economic issues of implementing the QbD approach for the development of new drugs.

1 Introduction.

In Pharmaceutical industry, from 10,000 molecules screened to 10 which will be the subject of a patent application and 1 which will pass all the stages of tests and clinical trials to become a drug, the path from innovation to the market is long (twelve years on average). In 2012, a study had estimated that the development of a new molecule represented an investment of approximately 900 million dollars, and even 1.5 billion dollars taking into account the cost of capital (Mestre-Ferrandiz, Sussex, and Towse, 2012) This cost is of the same order as the average budget ($1.2 billion) estimated in Avellanet, 2008.

The financial amortization of this work can only be done at the global level, which is complicated by the late arrival of drugs on the market and early competition from generics. The patent, essential to the financing of research, makes it possible to protect innovation for twenty years. It can be extended for a maximum period of five years by a supplementary protection certificate. As illustrated in Figure 1, the patent begins as soon as the molecule is identified. This will then undergo a series of preclinical and clinical tests, which extend over ten years, before going through the stages of marketing authorisation. Given the complexity of this process, innovation only benefits from effective commercial protection for an average of ten years. Moreover, a new product only gradually (in two or three years) reaches its therapeutic target population, whereas at the end of the patent or data protection, the arrival of generics has become very rapid.

- In this context, the reduction of the development timeline becomes a critical economic issue.
- A second challenge deals with the optimization of the product quality from the early steps of development since it directly impacts on the added value of the candidate drug.

The good development practice of "Quality by Design" (ICH Q8-Q11) was recommended by FDA and EMA to comply with those two objectives. The key stages of the testing and development phases make it possible to check the efficacy of the molecule and to find out about any side effects. Many drug candidates are thus ruled out because they do not present a positive risk/benefit ratio. The drug candidate first goes through a series of so-called “preclinical” tests. These tests are obligatory passages before any stage of testing on humans.

2 Drug Genesis.

The riskiest and costiest phase of drug lifespan occurs during new product development. In this section we recall the main stages of the preclinical and clinical development phases.

2.1 Preclinical studies

Preclinical studies must be carried out in compliance with the ICH Q8(R2) guideline (ICH Expert Working Group, 2009) This guideline describes the suggested contents for the 3.2.P.2 (Pharmaceutical Development)

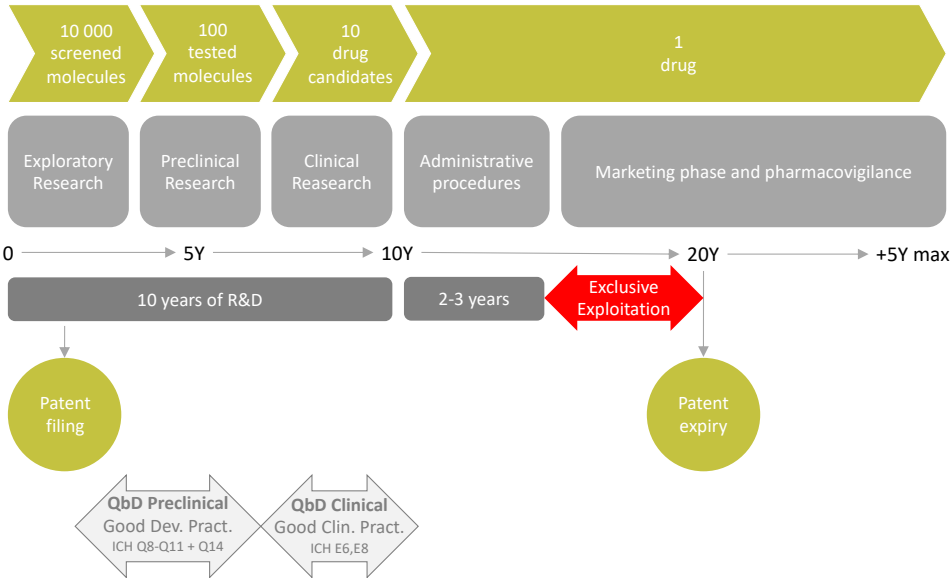

Figure 1: *Drug Lifecycle (LEEM report, 2021)*

section of a regulatory submission in the ICH M4 Common Technical Document (CTD) format. The Pharmaceutical Development section provides an opportunity to present the knowledge gained through the application of scientific approaches and quality risk management (ICH Expert Working Group, 2005) to the development of a product and its manufacturing process. It is first produced for the original marketing application and can be updated to support new knowledge gained over the lifecycle of a product. The Pharmaceutical Development section is intended to provide a comprehensive understanding of the product and manufacturing process for reviewers and inspectors. The guideline also indicates areas where the demonstration of greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches. The degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided.

Experimental pharmacology. Efficacy trials are carried out on inert molecular systems, on cells and cultures and, finally, on animal models to get the first proof of concept.

Toxicology. These studies evaluate the risks of side effects of future drugs.

Pharmacokinetics and metabolism of the drug. These studies relate to the pharmaceutical properties of the molecule such as absorption, metabolism, distribution and elimination. But they also aim to prove the pharmacological properties.

If the results of these studies are positive, the drug enters the human clinical trial phase.

2.2 Clinical studies

Only 1 in 10 drug candidates will reach this stage. These studies are carried out in three main phases, which must be carried out according to good clinical practice, ICH E6(ICH Expert Working Group, 2016) and E8(ICH Expert Working Group, 2021). They are carried out in a hospital environment or in a doctor's office, under the responsibility of expert doctors: the investigators.

Phase 1 : Tolerance. Increasing quantities of the new molecule are administered to healthy volunteers, under close supervision. This phase makes it possible to evaluate the main lines of the product's tolerance profile and its pharmacological activity.

Phase 2 : Product efficacy on small populations. This phase considers a small number of hospitalized patients. The aim here is to define the optimal dose, that is to say the one for which the therapeutic effect is the best with the least side effects. Proof of concept studies are used to validate a new treatment hypothesis for the patient.

Phase 3 : Pivotal study. Under conditions as close as possible to the usual conditions of use of the treatments, the efficacy and safety are studied in comparison with the reference treatment. This is verified on a large group of patients. Precautions for use and risks of interaction with other products are identified. Trials can cover from several hundred to several thousand patients.

when they are successfully completed, these three steps will be integrated into the file that will be presented to the health authorities to receive, with official

approval, the marketing authorization. The drug will then be made available to patients.

2.3 Submissions for Market Approval

Submissions based on Quality by Design have more scientific information on the product, its process and controls (Avellanet, 2008). This allows faster reviews. The FDA's own internal analysis has shown that QbD-based applications are processed 63% faster than traditional submissions.

3 R&D Expenses and CDMO implementation

Therapeutic innovation presents both a high cost and a major financial risk: the time required for research (preclinical and clinical studies) mobilizes significant capital over a long period, for an uncertain result. Few drugs generate sufficient earnings to cover all the research and development costs incurred. In addition, companies can only rely on a limited number of drugs to finance their future R&D activity. The diversification of the companies' product portfolio makes it possible to minimize the risk associated with each drug. This phenomenon explains recent mergers, thanks to which companies achieve economies of scale. Today, the protection of molecules by a patent is one way to guarantee the financing of future research, and therefore the development of new vital drugs with the best cost/effectiveness ratio. The drug industry is one of the economic sectors with the greatest research effort. It represented 10% of the turnover of pharmaceutical companies in 2017. (LEEM : les entreprises du médicament, 2021)

Figure 2 shows four main evolutions of the drug development process since 1980s:

- Faster distribution
- Faster entry of generics
- Increase of R&D costs
- Delayed market entry

Although the benefits of QbD are obvious, the industry has been relatively slow in adopting the concept because QbD often falls low on the list of immediate priorities. With product development and manufacturing increasingly being outsourced to contract development and manufacturing organisations (CDMOs), however, a strategic partnership between the sponsor and a CDMO can help realize the benefits of QbD (Kane, 2012).

4 Costs of poor Quality: the Rule of 10s

In a webinar published in 2016, Craig Gygi illustrated the real cost of poor quality and the importance of planning for quality early in the design stages of any kind of product or service[1]. One of the major elements of his presentation is the Rule of 10s – $1 Issues That Cost You $1,000, Figure 3. Design is the serie of decisions people make to plan and create something new, and those decisions determine how a product is going to perform – from how much it's going to cost, to how much it helps a patient, to its quality, to how long it takes to develop. All of these things are determined in the design process. A typical design process consists of a concept phase, a detailed design phase, a prototype phase and a production phase (or some variation thereof). In each phase, the associated deliverable has a specific Technological Readiness Level (TRL) estimated between 3 and 6. As the product moves through these phases, it becomes more and more finalized and its TRL index is increasing. Gygi explained that as the design progresses over time, the "Rule of 10s" dictates that the cost of fixing issues increases by a factor of 10 for each phase, such that an issue that costs you $1 to fix in the concept phase might cost you $1,000 in the production phase.

According to C. Gigy, *sometimes, even if you want to make a change, you can't. It's just too late, things have gone too far, ... but in the concept stage, virtually anything is possible*. Making carefully considered decisions early in the design stages can help alleviate the need to make late and very costly changes to your product, or worse, to issue recalls, reimbursements or face damaging lawsuits.

To further express the cost of poor quality, Gygi compared it to an iceberg as illustrated in Figure 4. The visible part of the iceberg represents the problems and associated costs that are readily apparent in a company with quality issues, including rework, scrap, noncompliance and warranty claims. Together, these amount to 5-15% of a company's revenue – that's $5-15 million for a company with a $100 million revenue. But this is just the tip of the iceberg. Underneath the surface of these obvious issues lies a much larger problem: things like lost customer loyalty, excess inventory, cost of engineering change orders, extra equipment and extra headcount can claim another 15-25% of a company's revenue. The entire iceberg of quality issues, totaling up to 40% of a company's revenue, can be enough to sink the proverbial Titanic. The only way to fix this issue is the in design phase, it becomes much more difficult to fix it after that.

5 Economic survey

In (Kourti and Davis, 2012), T. Kourti and B. Davis examines the business case for Quality by Design. They carried out a survey of 12 companies[2] about the busi-

[1] https://www.youtube.com/watch?v=yn0_6N07_E4

[2] Abbott (US), AstraZeneca (UK), Bristol Myers Squibb (UK and US), GSK (USA), Jazz Pharmaceuticals Inc. (USA), Eli lilly and Company (USA), Merck (USA and Ireland), Pfizer (USA), Centocor

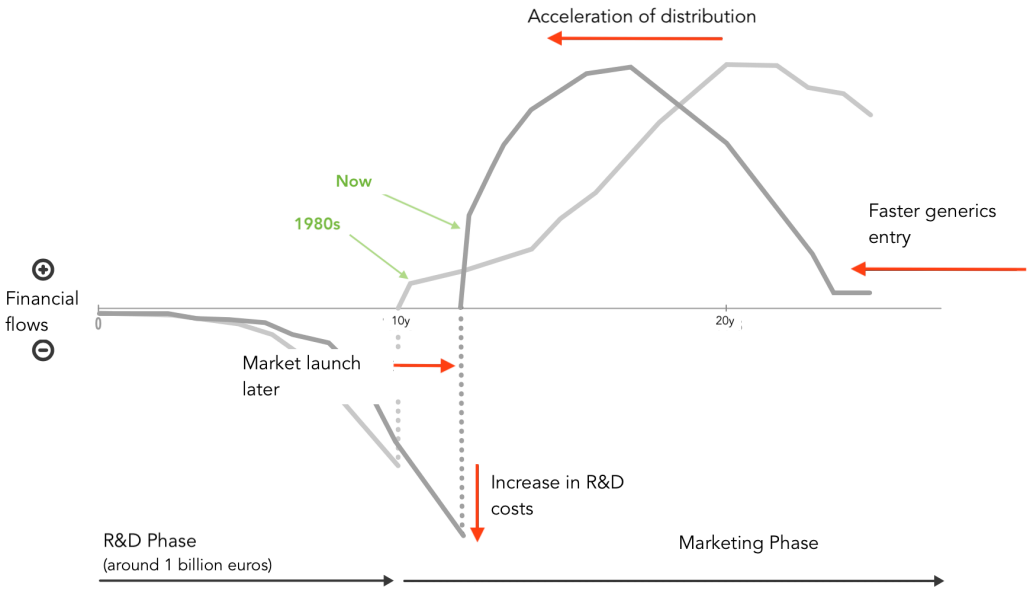

Figure 2: *Evolution of pharmaceutical development costs (LEEM report, 2021)*

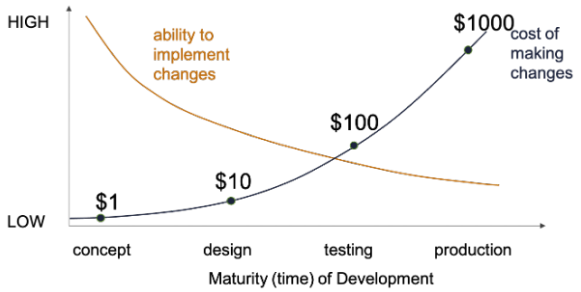

Figure 3: *Quality by Design is all about making quality a proactive process, rather than a reactive one. In this video, best-selling author Craig Gygi describes how Quality by Design doesn't just create a better product, but also saves a company money.*

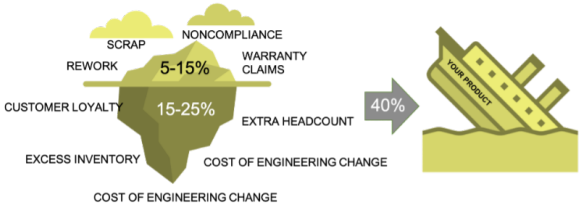

Figure 4: *The "iceberg" of poor quality issues and their associated costs, totaling up to 40 percent of a company's revenue.*

ness benefits of Quality by Design. The questions of this survey were designed to cover a wide range of issues, including the use of modeling and PAT tools. They identified several key benefits including :

- improved process and product knowledge and understanding;
- improvement in product quality and product robustness/reproducibility;
- improved control strategy;
- fast and reliably to market;
- increased process capability/process robustness and reduced atypicals;
- reduced impact of raw materiel variability;
- improved product stability;
- improved scale up efficiency/speed;
- standardize ways of working;
- improved development capability, speed and formulation design;
- cost reduction benefits;
- increased yield;
- engaging science in profitable ways;
- improvement in collaboration between business units and enhanced work practices.

In this study, one of the companies claims to have saved more than $60 million with the QbD approach. In a more recent study (Testas et al., 2021), M. Testas *et al.* have applied a complete QbD to accelerate time-to-market of a drug product. They have showed a significant reduction of 30% in the overall development and validation time was achieved when compared to a traditional approach.

Biologics (J&J) (Ireland), Vertex Pharmaceuticals (USA), United Therapeutics Inc (USA)

Summary 1: Learning Points

- Pharma R&D expenses represent about 10% of the turnover of pharmaceutical companies.
- The cost of fixing issues increases by a factor of 10 for each phase (Technological Readiness Level), such that an issue that costs you $1 to fix in the concept phase might cost you $1,000 in the production phase.
- QbD-based applications are processed 63% faster than traditional submissions
- QbD allows a significant reduction of 30% in the overall development and validation time compared to a traditional approach.
- Some companies have saved more than $60 million with the QbD approach.

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