

**The Escher project: Science-driven drug
regulation and innovative research
throughout phased drug development**

Index

1.	Introduction.....	3
2.	Overview.....	4
3.	Regulatory barriers.....	6
4.	Innovative models.....	8
5.	Knowledge preservation.....	11

1. Introduction

Main Goal

Drug innovation is in need for regulatory reform. This project aims to energize pharmaceutical R&D by identifying, evaluating and removing regulatory barriers to bring efficacious and safe medicines to patients in an efficient and timely fashion.

Summary

The pharmaceutical arena is one of the most regulated sectors in our society. However, there is increasing concern that apart from all the benefits of drug regulation (e.g. improving pharmacotherapy, protecting patient safety, enterprise stimulation, affordable access to medicines), the balance sheet may have shifted towards over-regulation with apparent threats to drug innovation in general. A major goal of regulating marketing authorization of medicines is to secure safe and effective drugs, but such regulations are also driving high costs of drug development; regulations affecting reimbursement and access to the market are key to cost-containment but may also provide major barriers for investors and industry to stimulate innovation. Various analyses (Rawlins Nat Drug Discovery 2004, FDA Critical Path, EMEA Roadmap, EU Innovative Medicines Initiative, WHO Priority Medicines) have provided evidence that the current system of pharmaceutical innovation is not sustainable anymore, both from an economic point of view and from the perspective of unmet medical needs, therapeutic gaps and access to medicines. At the same time, lack of efficacy (25%) and clinical safety (12%) are still major reasons for drug development projects to be stopped prematurely. Insufficient predictive capability, complexities in assay sensitivity, lack of validated and accepted biomarkers are important hampering factors across virtually all the discovery, pre-clinical and clinical phases of drug development. Key objectives of this project are to identify, evaluate and remove regulatory (related to clinical evaluation, marketing authorization, pharmacovigilance and access) bottlenecks hampering the efficiency in pharmaceutical innovation. The proposed project encompasses three synergistic areas of research directed at: [1] Regulatory barriers and opportunities in drug innovation [2] Innovative models of testing and monitoring efficacy and safety of new drugs, and [3] Knowledge management, learning and education.

2. Overview

The proposed project encompasses a series of synergistic research activities addressing the questions:

1. What kind of regulatory barriers (e.g. legislative, ethical, economic, political) can be identified in bringing medicinal products to the market, are there scientifically sound alternatives, and how can these contribute to science based regulatory reform?
2. What are the foundations of current research designs for testing the efficacy and safety of new drugs, are there scientifically sound alternative models, both in terms of design, statistical analyses and outcomes definition (including proxy-outcomes and biomarkers), and how can these add to efficiency in drug development?
3. What can we learn from the accumulated regulatory and drug development data, is scientifically valid information management feasible, and how can these add to better 'learning'[\[1\]](#) on the interface between drug development, regulatory affairs and clinical use of medicines.

We aim to address these questions both from a theoretical and a practical perspective, with a strong focus on delivering evidence and credibility for regulatory reform and policy recommendations. Actual cases of molecules in the various stages of drug development will be factored in. The research group includes representatives for the universities of Utrecht, Groningen and Rotterdam, and the pharmaceutical companies Organon, Merck, GSK, WINAp, and is organised into three work packages.

<u>Regulatory barriers and opportunities in drug innovation</u>	<u>Innovative models of testing and monitoring efficacy and safety of new drugs</u>	<u>Knowledge preservation, management and learning</u>
Drug regulation on the edge of ensuring and protecting public health	Advancements/innovation in (trial) design, conduct and statistical data analysis	Streamlining data management in regulating pharmaceutical products
Development of models for accelerated, fast-track conditional approval of medicinal products	Translational/methodological research on biomarkers, proxy-outcomes, genomics/proteomics, patient targeting	Beyond regulatory compliance, fostering a culture of science driven drug regulation
Regulatory improvement of the reimbursement and diffusion trajectory	Proactive and balanced risk assessment and management of medicinal products in pre- and postmarketing phases	Regulatory and drug development data as intelligence system fuelling pharmaceutical innovation

Work package 1	Work package 2	Work package 3
UU/UMCU (Leufkens, Schellekens, Hoes, Pieters, v Delden), Erasmus MC (Rutten, Koopmanschap), Organon (Broekmans), GSK (Raaijmakers), MEB (Kalis)	UMCU/UU (Grobbee, Hoes, de Boer, v Delden, Egberts), UMCG (de Zeeuw), Organon (Roes, Broekmans), EMC (Stijnen), Merck (van Leijenhorst), MEB (v Zwieten, Kalis), WINAP (vd Vaart, Smet)	RUG/UMCG (Hillege, de Graeff, Stolk, de Brock), UU (Leufkens, Schellekens, Veen), MEB (Kalis, v Zwieten, v Belkum), Organon (Roes, Broekmans)
Principal Investigator: Leufkens		

The components of the programme are interrelated and their implications are complementary as well as overlapping. A series of PhD-projects will be dedicated to the theoretical and empirical advancement of the main components. There will be ample emphasis on conceptual and theoretical research. As far as empirical testing and modelling of concepts is concerned, data will be used from 'real life' completed drug development and regulatory dossiers and population-based data from the TI Pharma Mondriaan-project. As it is of critical importance that eventually conclusions and directions will be provided that integrate the different specific components, post-docs will be made responsible to promote and monitor the interaction and exchange of evolving insights across the projects.

The projects will be carried out in close collaboration with partners from the pharmaceutical industry, which will allow immediate feedback and input from running drug development processes. The latter will require appropriate measures to guarantee confidentiality and commercial interest. This will be further supported by frequent feedback and discussions with the multidisciplinary programme committee. Eventually, apart from the results of the separate PhD-projects, the programme will produce an integrated overview of innovation in models of testing and monitoring the efficacy and safety of new drugs with an emphasis on improved speed and cost-containment, while maintaining individual and societal responsibility for safety. Given the inherently broad scope of the programme, focus will be guaranteed by using case studies as themes and frame of reference throughout the research. These case-studies will be selected in the initial phase of the research and will cover at least examples of a regular drug development and approval scheme, examples involving conditional approval and continued post-marketing research and examples of an emerging 'breakthrough' compound for which fast and timely release is considered. Moreover, we aim to add 'blue sky' models for drug regulation, particularly in the fields of CNS, cardiovascular and biologicals.

[1] Sheiner L. Learning versus confirming in clinical drug development. *Clin Pharmacol Ther* 1997; 61: 275- 91.

3. Regulatory barriers

Regulatory barriers and opportunities in drug innovation

Since the early 60s of the last century virtually all countries have installed systems for regulating the quality, efficacy and safety (and increasingly also reimbursement and access) of medical products. From the very start of regulating drug development and market authorisation, there has been an ongoing debate about finding the right balance between regulation and stimulating drug innovation [\[1\]](#). Overall, drug regulation has definitely made substantial contributions to public health, although we still lack a systematic analysis of the effects of regulating marketing authorisation of medicinal products as already proposed by Dukes and Lunde in the late 70s of the last century [\[2\]](#). A series of recent analyses (Rawlins Nat Drug Discovery 2004, FDA Critical Path, EMEA Roadmap, EU Innovative Medicines Initiative, WHO Priority Medicines) have fuelled a renaissance in looking at regulatory barriers to drug innovation. All these reports unanimously share the conclusion that 'something should be done'. They share also the awareness that the current drug regulatory system is more procedure and compliance than science driven, most likely affecting the efficiency of drug development in a negative fashion. Both regulators and industry acknowledge that today's drug regulatory systems have been marinated with a myriad of 'rituals', adding probably a lot that is 'nice to know', but not always 'necessary to know'. Moreover, although decision making about reimbursement and patient access to medicines is not part of the formal market authorisation process in most countries, it is affecting the continuum of bringing molecules from the bench via clinical evaluation to the patient in various, and not always productive, ways as well.

The conceptual basis for the current drug regulatory process will be revisited and challenged in terms of effects on quantitative output, consequences for individual (neglected) disease categories and drug innovation in general. A comprehensive inventory of current and forthcoming drug approval regulations in the EU and the US will be made and differences and similarities examined both from a historical and contemporary perspective. This will focus on regulations pertinent to the research questions at hand. Consistencies and discrepancies will be spelled out as well as their respective origins. The requirements of specific aspects of drug approval regulations and the relation these have with existing and alternative phases of drug research, both pre- and post-marketing, will be analysed from a legal and ethical perspective. This will include both the scientific as well as the societal and ethical outlook. Moreover, the role and responsibilities of the individual stakeholders (e.g. pharmaceutical companies, regulatory authorities, policy makers, patient groups, etc) will be examined. This part of the project aims to fuel trust building among the different

stakeholders involved. Given the strong political nature of the drug regulatory environment, we aim to add to a more efficient system of bringing drugs the patient through scientific evidence and data supported recommendations. This applies both to the direct marketing authorisation as well the reimbursement phase.

Project	Title	Topics
Project 1.1	Scientific and political drivers of the current drug regulatory system, perspectives for improvement	Foundations of drug regulation, protection public health vs enhancement innovation, regulatory compliance vs science
Project 1.2	Facilitating drug development, the ideal regulatory context	International comparisons, EU vs FDA, IND vs scientific advice, EU clinical trial directive, development guidance documents
Project 1.3	Development of accelerated, fast-track conditional approval of medicinal products	Regulatory barriers, consequences for reimbursement, ethical and liability issues, balancing patient interests and evidence based
Project 1.4	Restoring societal trust in drug development	Towards a new 'social contract' between industry and society, commonalities of interest, precautionary principle as two-sided sword,
Project 1.5	Improvement of access and reimbursement trajectories and beyond	Decision making on reimbursement in EU, required data, impact of pharmacoeconomic evaluation, conditional reimbursement

[1] OECD. Gaps in Technology: Pharmaceuticals, 1969.

[2] Dukes MNG, Lunde I. Measuring the effects of drug registration. Pharm J 1979; 223:

4. Innovative models

Innovative models of testing and monitoring efficacy and safety of new drugs

Accelerated, but thoughtful and responsible, evaluation of new medical products in humans is warranted for current and future drug innovation [1]. Since the streptomycin trials in the mid-20th century, continuous evolution and progress of clinical development methods have promoted scientific evidence as a basis for the benefit-risk assessment of new drugs. However, further innovations are needed, particularly in the advent of complex, sophisticated biologicals, long-term chronic therapy, and mechanism-driven, rather than indication-driven, therapeutics (e.g. immune modulation). Furthermore, improved prediction of safety risks by detecting vulnerable subgroups is mandatory. In addition, valid and intelligent use of proxy outcomes and biomarkers of drug main and side effects may make pre-marketing research more efficient and post-marketing research more feasible. In this part of the project, the methodological principles of the classical phase II to IV are addressed and put in perspective of recent advances in both experimental and non-experimental research. The primary intention is to improve the scientific quality and efficiency of late phase drug research. As a consequence, time to registration may be reduced while maintaining the safety of new registrations. To reach this objective three complementary approaches are chosen: [1] Innovative research design, [2] Innovation in biomarkers and surrogate endpoints, [3] Innovative data analysis and statistical modelling.

This will include an assessment of weaknesses and strengths of randomised and non-randomised cohort studies, case-control studies and their variations such as case-cohort and case-crossover studies. The specific characteristics, requirements and deliverables of alternative research designs in view of the objectives of subsequent phases of accumulating knowledge on benefits and risks of drugs are determined and weighted. Alternative schemes are formulated and their impact is estimated using data from existing drug development processes. Moreover, ample translational research concentrating on the continuum of research results across phases II to IV with a special emphasis on the use of proxy-outcomes and biomarkers is anticipated. There will be special focus on the validation of biomarkers against established clinical endpoints that adequately express patient benefit or harm. Scientifically it is clear that proper clinical validation of biomarkers and other proxy-outcomes will require a multiple trial approach and will most likely entail disease (model) specific and treatment specific components. It is very attractive to use the opportunity of (experimental) research across early clinical development, full development and post-registration systematically as a framework for biomarker validation as well. Design options to incorporate this and validation criteria will be investigated and (additionally) developed. These will involve parties across drug development projects and across company components. To evaluate scenario's use will be made of modelling and simulation based on actual data (and disease models) from real, ongoing, drug development projects. In particular, applications in the development of cardiovascular and CNS drugs will be addressed.



Project	Title	Topics
Project 2.1	Innovation in the design of research on efficacy and safety of new drugs	Concepts, design and conduct of phase II, III and IV research; SWOT analysis and positioning of different study designs
Project 2.2	The (future) post-marketing phase: requirements and opportunities.	Theoretical and regulatory basis for phasing drug research, alternative designs, off-label use, vulnerable populations, ethical aspects; multi-variate prediction of safety risks.
Project 2.3	Advancements in the design, conduct and analysis of randomised trials on drug effects	Recruitment and follow-up patient populations; primary, secondary and composite outcomes; stopping trials early; Bayesian approaches
Project 2.4	Connecting biomarkers and proxy-outcomes across different phases of drug development	Methodological and design options for validated biomarkers and proxy-outcomes used across biological systems (in vitro, vivo and human)
Project 2.5	Use and validation of biomarkers and proxy-outcomes in pre- and post-registration setting	Validation principles versus different research designs (series of clinical trials, case control studies, cohort studies), Bayesian approaches
Project 2.6	Optimising the benefits and safety of new drugs: prospects of pharmacogenetics and pharmaco-genomics and safety monitoring	Molecular/omics strategies in patient selection, enrichment, depletion of susceptibles, efficiency, statistical and ethical aspects
Project 2.7	Ethical dilemmas and prospects in the timely and safe availability of new drugs to individuals and the society	Individual, societal and industry perspectives on clinical drug development, pushing market release forward, breakthrough drugs

These innovations in design and conduct require statistical and methodological advancements. Emphasis will be on randomised trials and comparative population-based studies. The rate-limiting factors of generic randomised trials in view of pre-marketing requirements will be examined and innovative data-analytical approaches will be explored and developed. This will particularly comprise the biostatistical aspects of planning research, including sample sizes and randomisation schemes, estimating level of knowledge on effects and risks during trial progress, different approaches to terminating trials at the time of maximal informativeness. Apart from conventional statistical techniques this will involve Bayesian approaches and concomitant modelling of effects using both new and external data. The rationale is that currently trials are not designed, conducted and analysed in the most efficient and expeditious manner, because the accumulating information is not (systematically and quantitatively) used to improve design and/or interpretation of results. Apart from bringing new medicines faster to clinical practice there will be also strong focus on keeping good drugs on the market in terms of clinical risk management of drug therapy-related risks: [1] risk identification and assessment, [2] development and execution of risk reduction strategies, [3] evaluation of risk reduction strategies. This part of the project will involve health professionals (e.g. WINAP, GPs) and is strongly embedded in the Mondriaan-project, entailing the richness of Dutch healthcare databases in an innovative fashion.

[1] Lesko LJ et al. Optimizing the science of drug development: opportunities for better candidate selection and accelerated evaluation in humans. *Pharm Res* 2000; 17: 1335-44.

5. Knowledge preservation

Knowledge preservation, management and learning

Effective knowledge access, management, exchange and sharing are key conditions for regulating medicinal products. Unfortunately, decision making in the pre- and post-marketing evaluation of medicinal products is still largely based on simple document management technology and deals with extremely extensive, often inconveniently arranged, and by times incomplete information that all contribute to information stagnation. There is a strong need for evidence-based medicinal product repositories in which different regulatory and drug development research questions can be answered in an efficient, transparent and accountable way. A central thesis for this part of the project is that efficient management of regulatory data provides ample opportunities, not only to speed up the regulatory process itself, but also to serve as a rich resource for learning and education in drug development (e.g. regulatory science). So far little scientific research has been performed on regulatory data, mainly because of confidentiality and other strategic reasons. However, regulatory data can, if the relevant stakeholders are willing and able to find a common ground in terms of confidentiality, competitiveness etc, be developed as a learning system fuelling pharmaceutical innovation in creative way. The public-private nature of TI Pharma, with ample attention to ensure confidentiality of regulatory data by the different stakeholders, provides the challenge to invest in such a platform.

As the completing requirement of the current programme we propose to build a web-based knowledge system (Drug Information Opinion System) that will provide us with comprehensive drug efficacy and safety information for a broad audience including laypersons, patient organizations and pharmaceutical researchers. A cornerstone of drug information sources for DIOS will be, among others, available scientific literature, the summary of product characteristics (SmPC), tabulated formats and the clinical written summaries of the electronic common technical document (eCTD) of the applicant and the clinical assessment reports of the regulatory authorities (E(N)PARs). Using state of the art data standards and technologies, the information will be stored in a systematically organized relational database of drug information. This information will be made available in a secured web-based knowledge system that will provide, comprehensive drug efficacy and safety information using online analytical processing, tabular and graphic reporting and data mining features for a large group of potential users of different professions. Here we particularly anticipate a strong contribution by WINAp.

The repository will include information about exposure, characteristics of the study populations dose-response, short and long-term efficacy, and efficacy in population subsets, and the safety profile of the drug. The application will be based on state of the art data interchange standards (Clinical Data Interchange Standards Consortium (CDISC), Study Data Tabulation Model (SDTM) and will be

implemented using XML technology. To make the whole system as secure as possible, authentication, authorization, access control and an extensive audit trail will be implemented. DIOS is based on collaborations between university, regulatory bodies and pharmaceutical industry and will act as a tool for the other two research activities (regulatory barriers and innovative models) to determine their research needs. Besides preservation of knowledge, DIOS will promote medicinal product knowledge growth and communication. It will help regulators, healthcare professionals, medical decision makers and patients, in the improvement of interpretation of the benefit-risk assessment of medicinal products and the decision process leading to marketing authorisation and clinical use in the post-marketing phase.

Project	Title	Topics
Project 3.1	Streamlining data management in regulating pharmaceutical products	Kinetics, dynamics, efficacy and safety extent of population exposure, ICH and EMEA guidelines, balance benefit-risk, comparability, assay validity
Project 3.2	An intelligent, automated learning, knowledge system to recognize patterns in regulatory and drug development data	Pattern analyses, data mining, closed loop Business Intelligence in regulatory and drug development data across Phase II-IV studies