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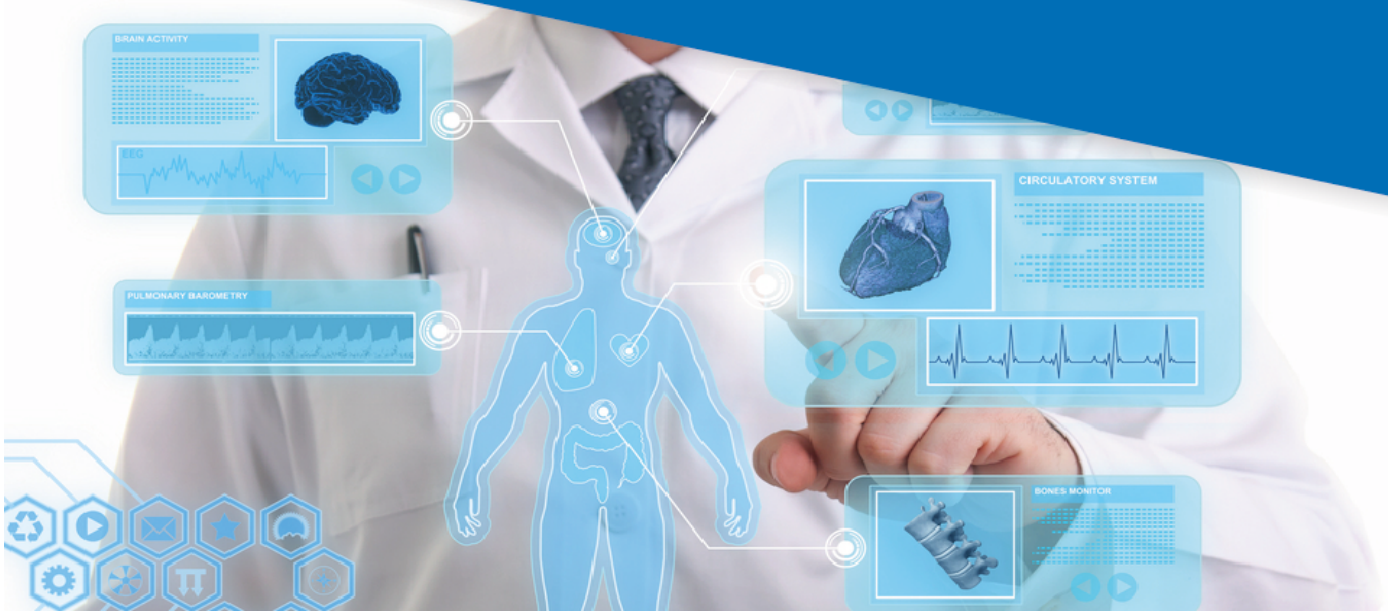
The Potential Role of Virtual Trials in Early Medicines Development: Beyond Pharmacology to Mechanisms

Adriano Henney



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21st Century Healthcare: The Status Quo is Unsustainable

- Ageing population
- Chronic disease
- Limited therapeutic efficacy
- Increasing cost of innovative therapies
- Time to market increasing
- Tendency to focus on "personalisation"
- Limited success
- Exponential increase in budgets

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The *Status Quo*

FINANCIAL TIMES

ORLD US COMPANIES MARKETS OPINION WORK & CAREERS LIFE & ARTS

AstraZeneca PLC + Add to myFT JULY 27, 2017

AstraZeneca shares tumble 15% on big drug trial setback

Flagship lung cancer treatment failed to show benefits hoped for by pharma group

The AstraZeneca study setback is 'a significant blow' for the company © Bloomberg

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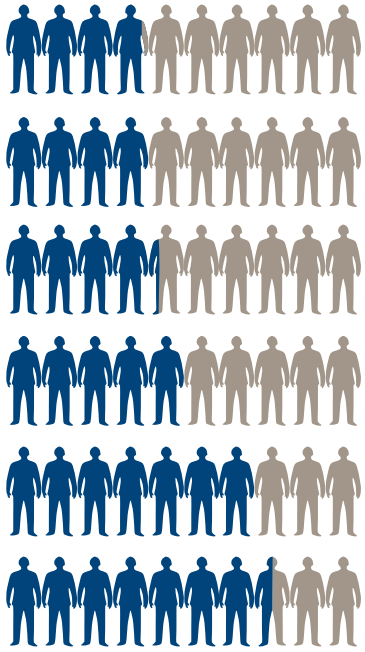
The *Status Quo*

One Size Doesn't Fit All

PERCENTAGE OF THE PATIENT POPULATION FOR WHICH A PARTICULAR DRUG IS INEFFECTIVE, ON AVERAGE

ANTI-DEPRESSANTS (SSRIs)	38%
ASTHMA DRUGS	40%
DIABETES DRUGS	43%
ARTHRITIS DRUGS	50%
ALZHEIMER'S DRUGS	70%
CANCER DRUGS	75%



Source of data: Brian B. Spear, Margo Heath-Chiozzi, Jeffery Huff, "Clinical Trends in Molecular Medicine," Volume 7, Issue 5, 1 May 2001, Pages 201-204.

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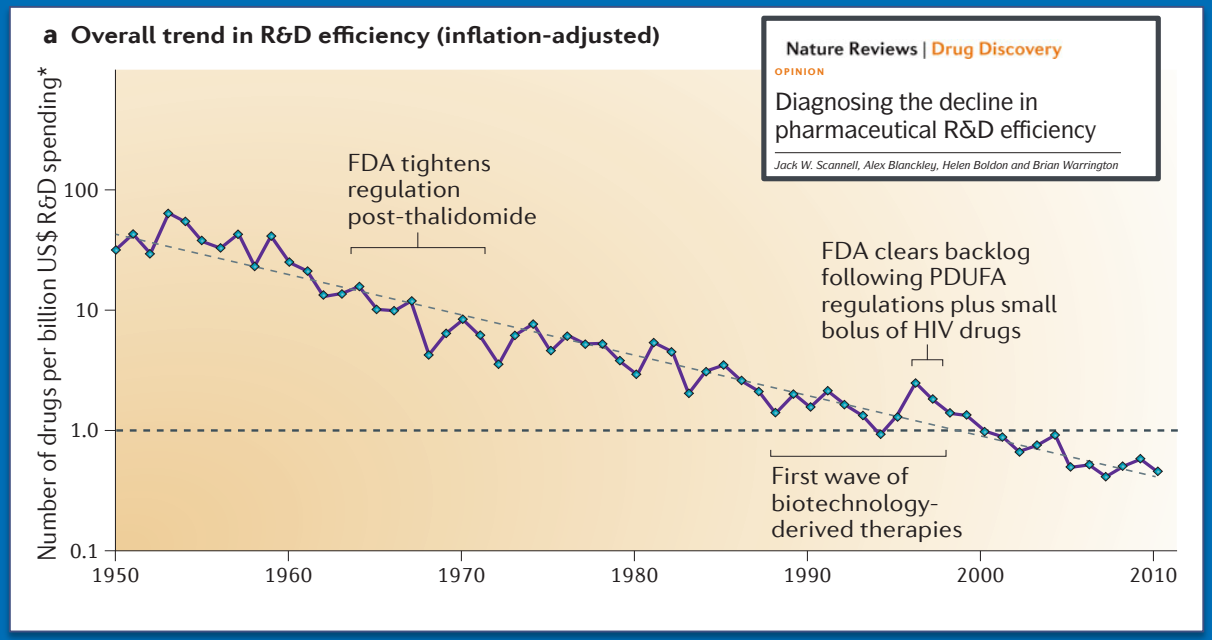
The *Status Quo*

- Late stage failures
- 45% R&D cost associated with Phase II and III (~$1Bn)
- Safety
- Efficacy:
  - Poor trial design
  - Failure of compound
  - Failure of mechanism: target lacks relevance to the pathophysiological system -> clinically ineffective



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Gene-centric doesn't work

JCI The Journal of Clinical Investigation

Promises, promises, and precision medicine

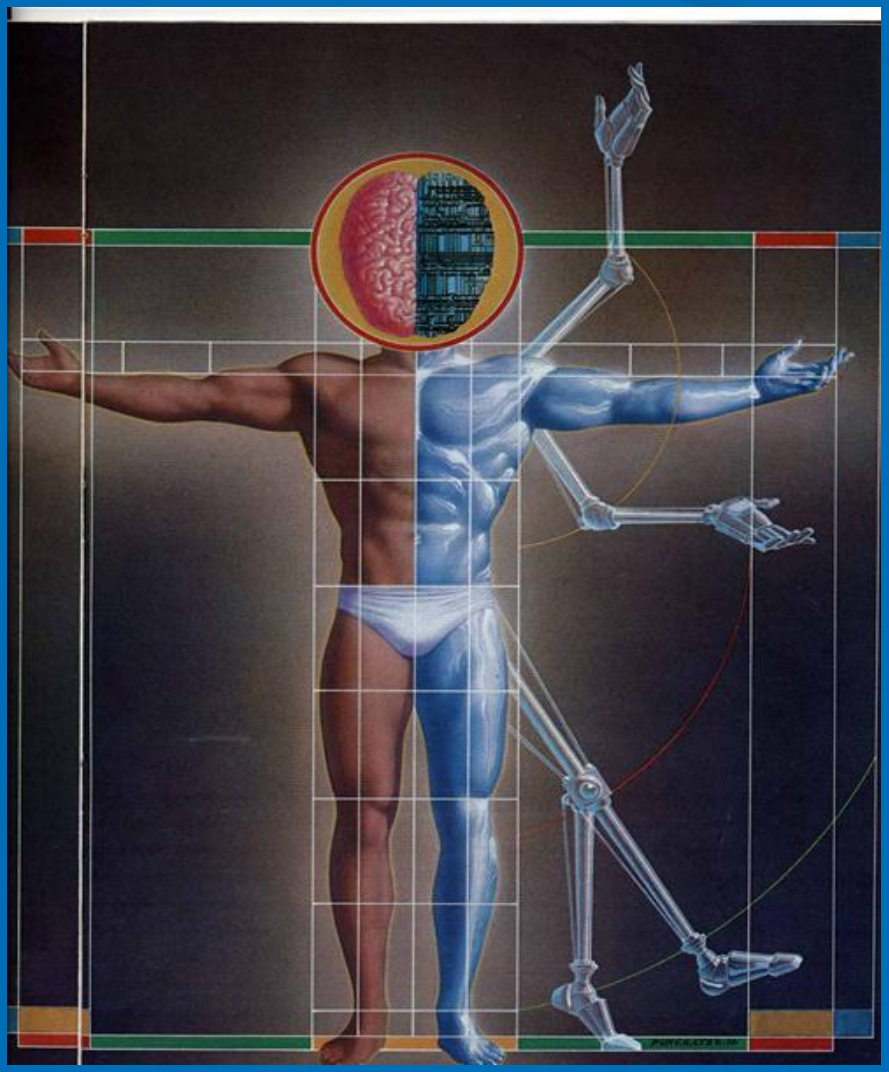
Michael J. Joyner, Nigel Paneth

J Clin Invest. 2019;129(3):946-948. https://doi.org/10.1172/JCI126119.

However, nearly two decades after the first predictions of dramatic success, we find no impact of the human genome project on the population's life expectancy or any other public health measure, notwithstanding the vast resources that have been directed at genomics.

Exaggerated expectations of how large an impact on disease would be found for genes have been paralleled by unrealistic timelines for success, yet the promotion of precision medicine continues unabated.

- Human body ≡ machine
  - Engine, Communication, motion, Computation and Control
- Self-organised, not built to a standard blueprint, like a Ferrari or Jumbo jet
  - Conception/ genetics/ environment ➛ development
  - Stochastic variability
- Function emerges from dynamic network interactions
- Understanding complex system dynamics needs **computer modelling**



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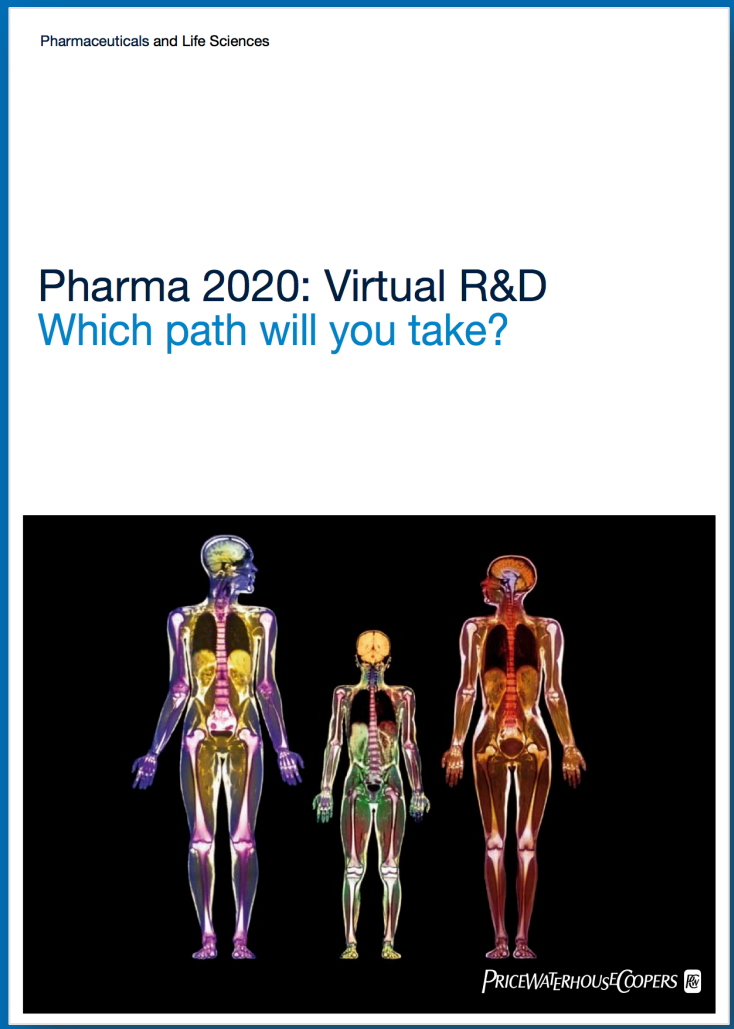
2008: Virtualisation is a solution

We believe that, if the industry is to become more innovative and cut its R&D costs, four features will be vital:

- A comprehensive understanding of how the human body works at the molecular level
- A much better grasp of the pathophysiology of disease
- Greater use of new technologies to "virtualise" the research process and accelerate clinical development
- Greater collaboration between the industry, academia, the regulators, governments and healthcare providers.

PricewaterhouseCoopers Report

http://www.pwc. com/gx/en/pharma-life-sciences/pharma-2020/pharma-2020- vision-path.jhtml.



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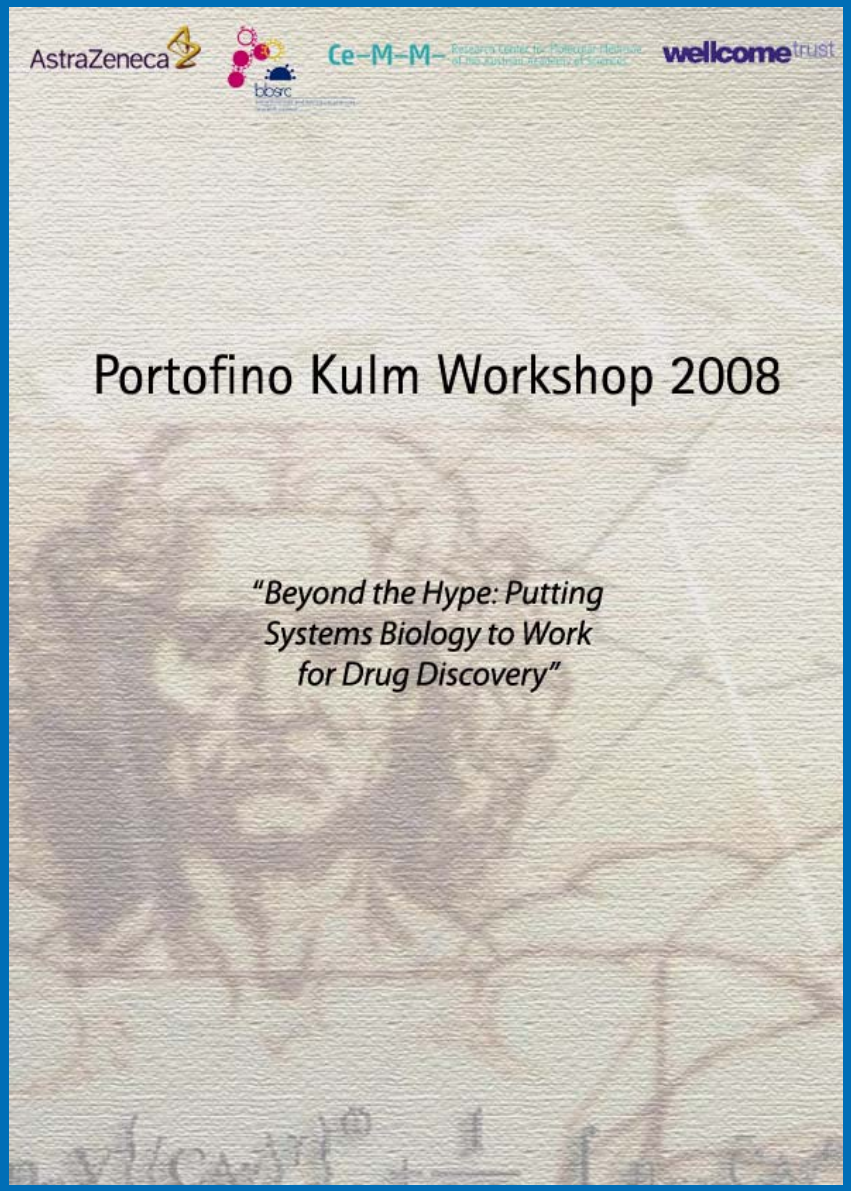
2008: Portofino Workshop



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2008: Portofino Workshop

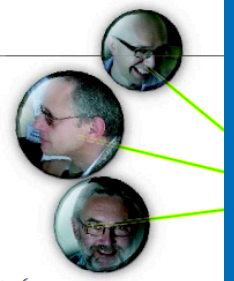
nature

Vol 455|9 October 2008

COMMENTARY

A network solution

With the right plan, systems biology can empower drug discovery, say **Adriano Henney** and **Giulio Superti-Furga**. Field leaders have contributed and now the authors want to hear from you.



Systems biology focuses on interactions within and between the mechanisms that combine to give rise to the function and behaviour of a biological system. To some it is the logical and inevitable next-level understanding that will propel drug discovery from empiricism to mechanism-based rational design. Countless column inches in the scientific press hail systems approaches as the latest weapon to tackle the major challenges of modern medicine. But to others, it is an ill-defined pile-up of '-omics' approaches that in terms of usefulness for drug discovery represents the culmination of all delusions. So it is not a suprise that the pharmaceutical industry remains unconvinced, fearing parallels with the genomics hype and considering the approaches currently impractical.

Can we realistically expect systems biology to have a tangible effect on human health in the near term? In June, at a workshop in Portofino, Italy,[1] a representative group of the community of academic, biotechnology and pharmaceutical scientists active in systems biology gathered with the goal of presenting a set of recommendations that, if implemented, would represent a coherent, structured route to demonstrate the

and often semi-quantitative data that are hard to integrate into biological models. Additionally, there are multiple gaps in the data stream linking experiment to clinical outcome. For the field to advance effectively, we need to find new ways to create a reliable data pipeline that is compatible with the needs of systems biology. This pipeline can only be achieved realistically by the establishment of a consortium to set appropriate standards, quality-control metrics and processes on behalf of the community. How best to achieve such standardization procedures remains to be seen, but as soon as they are established, initial efforts should focus on closing the data gaps and on acquiring multiple data types on a limited number of standard models and samples. Lastly, it is of paramount importance to concentrate on the creation of necessary computational tools to provide a streamlined and standardized framework for handling and sharing large quantitative data sets efficiently. Interactions at Portfino highlighted a broad community willingness and motivation to apply self-discipline and adopt standards.

Modelling drug actions

Molecular pathways and networks have already

response to combination therapies[6].

Although they are already being used extensively post-hoc in an explanatory mode to rationalize specific outcomes, these models and approaches have not yet been integrated routinely as tools in early drug discovery. Concentrating on the development and refinement of these approaches, and finding opportunities to apply them in areas, such as solid tumours and inflammation, in which other methods have proven inefficient, would help to build confidence in the ability of systems-based approaches to make predictions. We think that this step represents a good opportunity to provide early evidence of systems biology's value.

Predictive toxicology

The evaluation of drug safety and toxicity is largely empirical, expensive and error prone, relying on proprietary data and often on chemistry-centric evaluations. Integrating biological data and applying quantitative modelling

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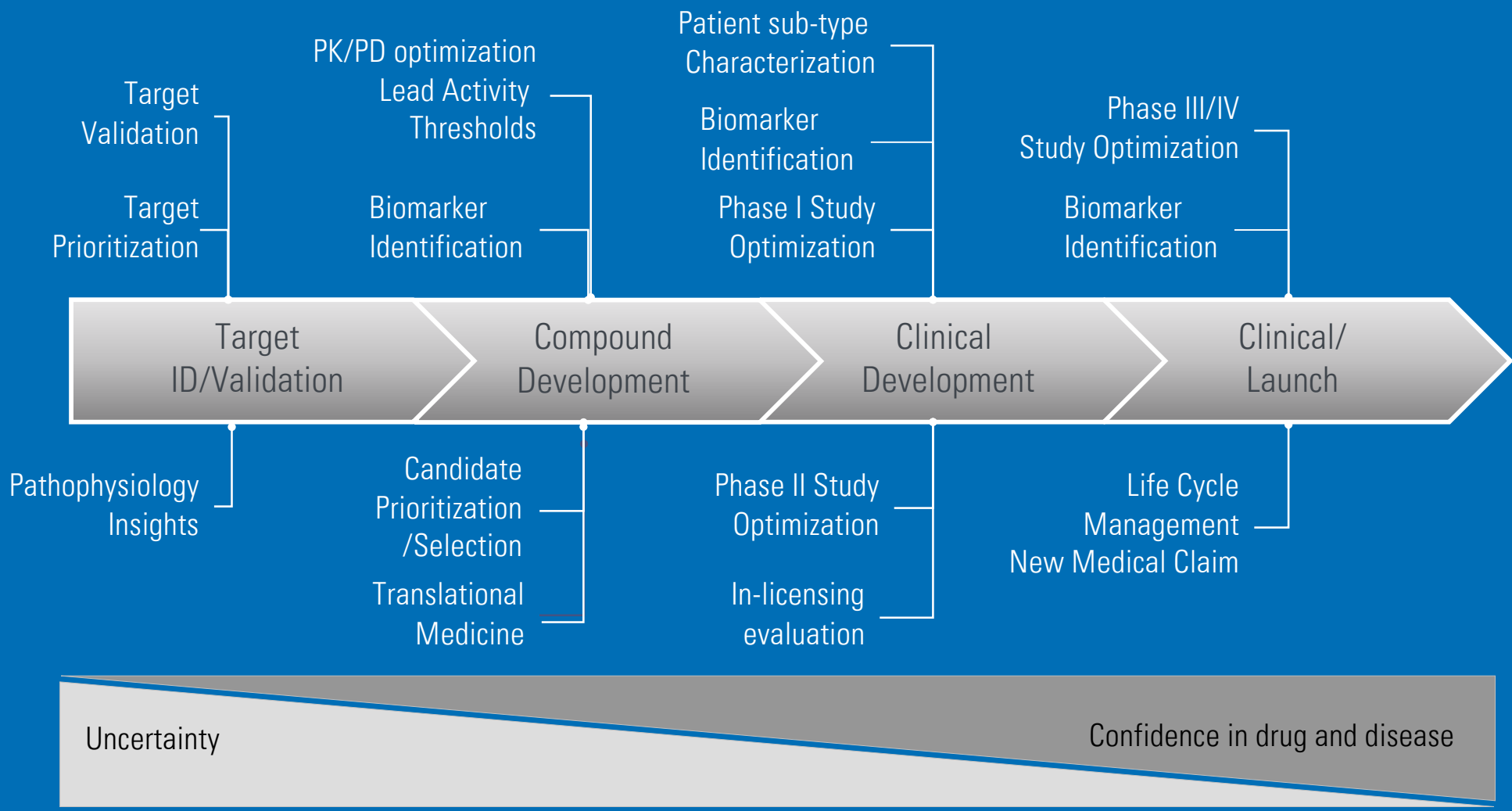
Pharma R&D Pipeline: CM&S potential



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Modelling and pharmacometrics

- Physiology Based Pharmacokinetic (PBPK) modelling and simulation mechanistically relates a patient's physiology to the emerging pharmacokinetic pro- file. PBPK models explicitly include physiological information quantifying, for example, blood flow rates or relative tissue-specific gene expression.
- It can be used to predict the pharmacokinetic behaviour of drugs in humans using preclinical data.
- It can also explore the effects of various physiologic parameters such as age, ethnicity, or disease status on human pharmacokinetics, as well as guide dose and dose regimen selection and aid drug–drug interaction risk assessment

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OPEN ACCESS Freely available online

PLoS one

Evaluation of the Efficacy and Safety of Rivaroxaban Using a Computer Model for Blood Coagulation

Rolf Burghaus[1], Katrin Coboeken[2], Thomas Gaub[2], Lars Kuepfer[2], Anke Sensse[3], Hans-Ulrich Siegmund[2], Wolfgang Weiss[2], Wolfgang Mueck[1], Joerg Lippert[2]*

1 Bayer Schering Pharma AG, Wuppertal, Germany, **2** Bayer Technology Services GmbH, Leverkusen, Germany, **3** Bayer Schering Pharma AG, Berlin, Germany

Abstract

Rivaroxaban is an oral, direct Factor Xa inhibitor approved in the European Union and several other countries for the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery and is in advanced clinical development for the treatment of thromboembolic disorders. Its mechanism of action is antithrombin independent and differs from that of other anticoagulants, such as warfarin (a vitamin K antagonist), enoxaparin (an indirect thrombin/Factor Xa inhibitor) and dabigatran (a direct thrombin inhibitor). A blood coagulation computer model has been developed, based on several published models and preclinical and clinical data. Unlike previous models, the current model takes into account both the intrinsic and extrinsic pathways of the coagulation cascade, and possesses some unique features, including a blood flow component and a portfolio of drug action mechanisms. This study aimed to use the model to compare the mechanism of action of rivaroxaban with that of warfarin, and to evaluate the efficacy and safety of different rivaroxaban doses with other anticoagulants included in the model. Rather than reproducing known standard clinical measurements, such as the prothrombin time and activated partial thromboplastin time clotting tests, the anticoagulant benchmarking was based on a simulation of physiologically plausible clotting scenarios. Compared with warfarin, rivaroxaban showed a favourable sensitivity for tissue factor concentration inducing clotting, and a steep concentration–effect relationship, rapidly flattening towards higher inhibitor concentrations, both suggesting a broad therapeutic window. The predicted dosing window is highly accordant with the final dose recommendation based upon extensive clinical studies.

Dosing Schedules

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frontiers in PHYSIOLOGY

ORIGINAL RESEARCH ARTICLE
published: 07 November 2014
doi: 10.3389/fphys.2014.00417

Computational investigation of potential dosing schedules for a switch of medication from warfarin to rivaroxaban—an oral, direct Factor Xa inhibitor

Rolf Burghaus[1], Katrin Coboeken[2], Thomas Gaub[2], Christoph Niederalt[2], Anke Sensse[1], Hans-Ulrich Siegmund[2], Wolfgang Weiss[2], Wolfgang Mueck[1], Takahiko Tanigawa[1] and Jörg Lippert[1]*

[1] *Bayer HealthCare, Wuppertal, Germany*
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The long-lasting anticoagulant effect of vitamin K antagonists can be problematic in cases of adverse drug reactions or when patients are switched to another anticoagulant therapy. The objective of this study was to examine *in silico* the anticoagulant effect of rivaroxaban, an oral, direct Factor Xa inhibitor, combined with the residual effect of discontinued warfarin. Our simulations were based on the recommended anticoagulant dosing regimen for stroke prevention in patients with atrial fibrillation. The effects of the combination of discontinued warfarin plus rivaroxaban were simulated using an extended version of a previously validated blood coagulation computer model. A strong synergistic effect of the two distinct mechanisms of action was observed in the first 2–3 days after warfarin discontinuation; thereafter, the effect was close to additive. Nomograms for the introduction of rivaroxaban therapy after warfarin discontinuation were derived for Caucasian and Japanese patients using safety and efficacy criteria described previously, together with the coagulation model. The findings of our study provide a mechanistic pharmacologic rationale for dosing schedules during the therapy switch from warfarin to rivaroxaban and support the switching strategies as outlined in the Summary of Product Characteristics and Prescribing Information for rivaroxaban.

Keywords: coagulation, combination therapy, mathematical modeling, pharmacodynamics, rivaroxaban, simulation, warfarin

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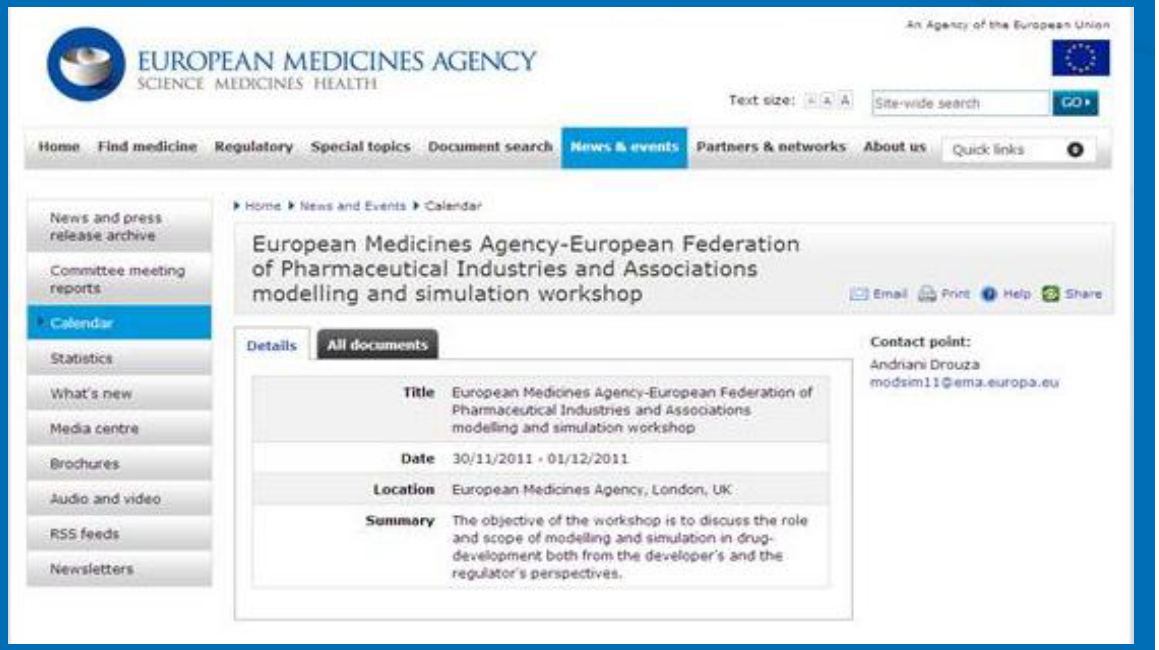
Model Informed Drug Discovery & Development (MID3)

- Quantitative modelling aiming to integrate knowledge of drug, disease, and mechanism of action to allow prediction (interpolation or extrapolation) of new outcomes under new conditions, such as untested doses, regimens, populations, or disease factors.
- Approaches include empirical, semi-mechanistic, or quantitative systems pharmacology techniques



White Paper

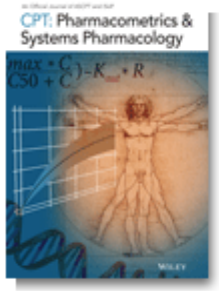
Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation

OPEN

EFPIA MID3 Workgroup, SF Marshall[1,*], R Burghaus[2], V Cosson[3], SYA Cheung[4], M Chenel[5], O DellaPasqua[6], N Frey[3], B Hamrén[7], L Harnisch[1], F Ivanow[8], T Kerbusch[9], J Lippert[2], PA Milligan[1], S Rohou[10], A Staab[11], JL Steimer[12], C Tornøe[13] and SAG Visser[14]

Version of Record online: 14 MAR 2016
DOI: 10.1002/psp4.12049

Issue



CPT: Pharmacometrics & Systems Pharmacology
Volume 5, Issue 3, pages 93–122, March 2016

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Quantitative Systems Toxicology (QSTS)

- A multidisciplinary approach bringing together Systems Biology, Toxicology and Chemistry
- Integrates classical toxicology with quantitative analysis of the molecular and functional changes that occur across multiple levels of biological organization.
- QSTS aims to characterize ADRs by describing modes of action as adverse outcomes pathways and perturbed networks versus conventional empirical end points and animal-based testing

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Quantitative Systems Toxicology (QST): Industry needs

- Models (biological and computational) that:
  - Inform mechanisms of toxicity of existing and new drugs
  - Identify mechanistic differences between preclinical species and human
  - Differentiate between adaptive/benign and progressive/toxic events
  - Aid interpretation of complex 'omics data sets to predict toxic phenotypes
  - Help minimise false negatives/positives during drug safety assessment
  - Support key risk assessments (e.g. safety margins) ahead of first-in-human trials
  - Are straightforward to use within industry

efpia imi innovative medicines initiative transQST

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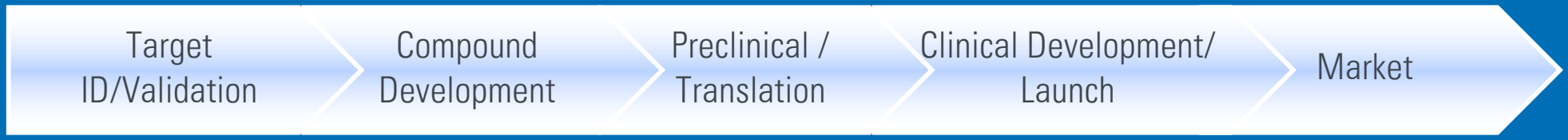
Quantitative Systems Toxicology (QST)



- To aid in molecular design to differentiate toxicophores
- Early read on compound liabilities and disposition
- In vitro screening models

- Supplement to traditional preclinical studies
- Mechanistic interrogation
- Early estimate on human safety margins (translational)
- Species sensitivity
- Differentiate between adaptive and progressive events
- Links to biomarkers

- Retrospective analysis of failed compounds
- Unexpected findings
- Translation of preclinical species to humans
- Links to biomarkers

efpia imi innovative medicines initiative transQST

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Towards Mechanisms…

- Safety
  - QST
- Efficacy:
  - Poor trial design
  - Failure of compound: characteristics (ADME) ineffective
  - Failure of mechanism: target lacks relevance to the pathophysiological system -> clinically ineffective
- Need mechanistic models
  - Heart, Liver, Kidney, Lung, Gut…..

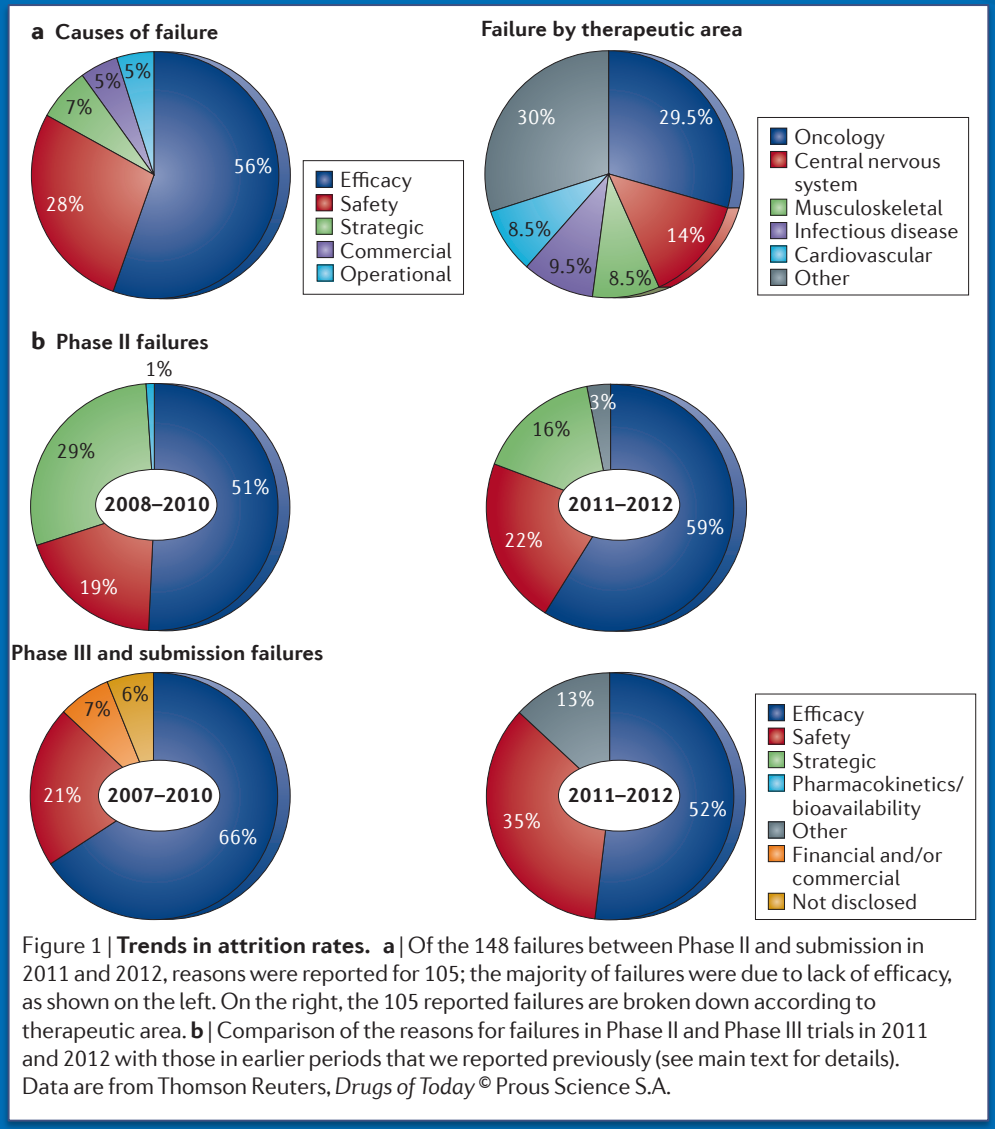

Figure 1 | **Trends in attrition rates.** **a** | Of the 148 failures between Phase II and submission in 2011 and 2012, reasons were reported for 105; the majority of failures were due to lack of efficacy, as shown on the left. On the right, the 105 reported failures are broken down according to therapeutic area. **b** | Comparison of the reasons for failures in Phase II and Phase III trials in 2011 and 2012 with those in earlier periods that we reported previously (see main text for details). Data are from Thomson Reuters, *Drugs of Today* © Prous Science S.A.

Data from Arrowsmith & Miller (2013)
Nature Reviews Drug Discovery 12, 569

Virtual Trials

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RESEARCH ARTICLE

www.ScienceTranslationalMedicine.org 29 April 2015 Vol 7 Issue 285 285ra61

COMPUTATIONAL MODELING

Trauma in silico: Individual-specific mathematical models and virtual clinical populations

David Brown,[1] Rami A. Namas,[2] Khalid Almahmoud,[2] Akram Zaaqoq,[3] Joydeep Sarkar,[1] Derek A. Barclay,[2] Jinling Yin,[2] Ali Ghuma,[2] Andrew Abboud,[2] Gregory Constantine,[4] Gary Nieman,[5] Ruben Zamora,[2,6] Steven C. Chang,[1] Timothy R. Billiar,[2] Yoram Vodovotz[2,6]*

Trauma-induced critical illness is driven by acute inflammation, and elevated systemic interleukin-6 (IL-6) after trauma is a biomarker of adverse outcomes. We constructed a multicompartment, ordinary differential equation model that represents a virtual trauma patient. Individual-specific variants of this model reproduced both systemic inflammation and outcomes of 33 blunt trauma survivors, from which a cohort of 10,000 virtual trauma patients was generated. Model-predicted length of stay in the intensive care unit, degree of multiple organ dysfunction, and IL-6 area under the curve as a function of injury severity were in concordance with the results from a validation cohort of 147 blunt trauma patients. In a subcohort of 98 trauma patients, those with high–IL-6 single-nucleotide polymorphisms (SNPs) exhibited higher plasma IL-6 levels than those with low IL-6 SNPs, matching model predictions. Although IL-6 could drive mortality in individual virtual patients, simulated outcomes in the overall cohort were independent of the propensity to produce IL-6, a prediction verified in the 98-patient subcohort. In silico randomized clinical trials suggested a small survival benefit of IL-6 inhibition, little benefit of IL-1β inhibition, and worse survival after tumor necrosis factor–α inhibition. This study demonstrates the limitations of extrapolating from reductionist mechanisms to outcomes in individuals and populations and demonstrates the use of mechanistic simulation in complex diseases.

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Challenges

- Despite evidence indicating potential for computer modelling and simulation to have an impact, uptake has been slow and very limited
- Lack of confidence in "*in silico*" models compared with *in vivo* or *in vitro* models in routine use
  - Familiar uncertainty vs unfamiliar uncertainty
- Regulatory hurdles
  - Verification and validation

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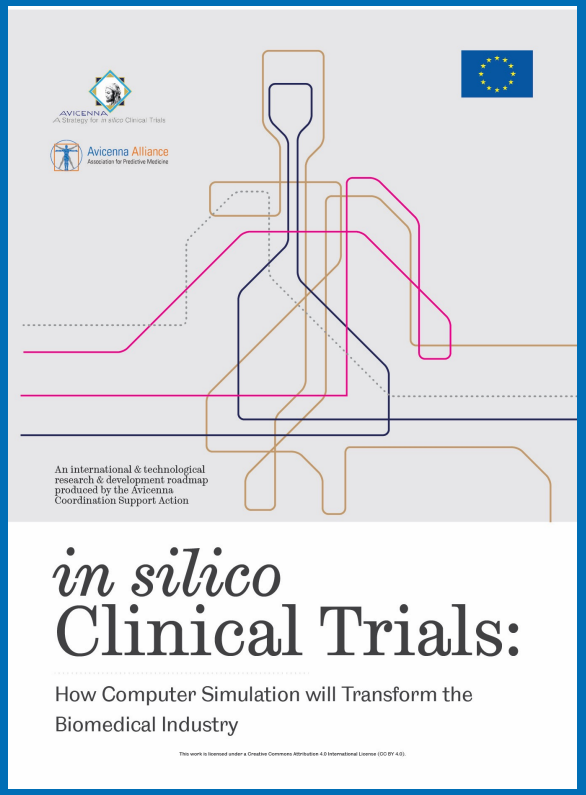
Avicenna Roadmap (2016)

- Total of 36 Recommendations:
- Training & education; validation & reliability; 3Rs; decision making….
- Policy: focus on regulators to embrace CM&S
- Detailed Information:
  - http://bit.ly/Avicenna_Roadmap



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What is the Avicenna Alliance?

A market focused **partnership** of healthcare industries and researchers set up a the *request of the European Commission*

Has its origins in:

1. Virtual Physiological Human Initiative, a research area focusing on computer modeling and simulation
2. Avicenna project which developed a "Roadmap for in silico medicine"

- Address regulatory barriers and develop policies on in silico medicine
- Link healthcare industries with researchers to further accelerate in silico medicine

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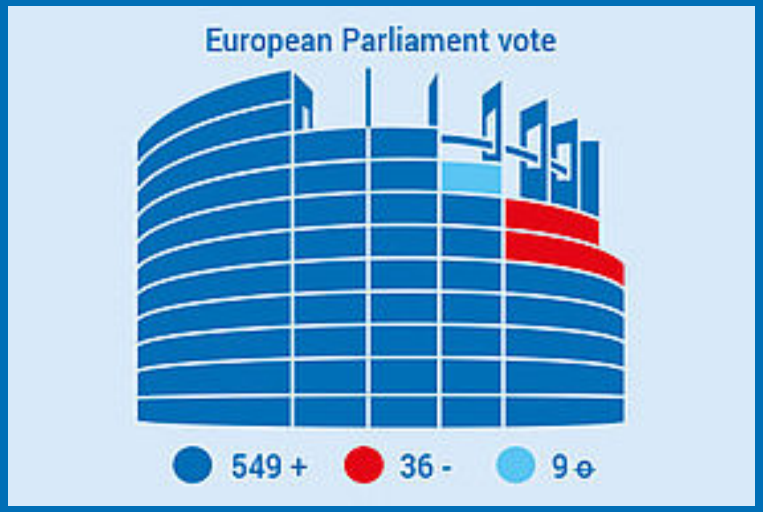

Parliament calls on European Medicines Agency (EMA) to develop a new framework

- "(6a) Advances in alternative testing require the creation of a regulatory framework capable of adapting to new developments in this field, including for example ***the recognition and evaluation of modelling and simulation*** technologies."
- 4b. The Agency shall develop a framework for the regulatory acceptance of alternative models and shall take into consideration the opportunities presented by these new concepts which aim at providing for more predictive medicines. These concepts may be ***based on human-relevant computer or cellular models,*** pathways of toxicity, or adverse outcome pathways."

Momentum is gathering

Avicenna Alliance
Association for Predictive Medicine

A developing collaboration towards harmonization between the US & EU

FDA

Avicenna Alliance
Association for Predictive Medicine

http://avicenna-alliance.com/

Momentum is gathering

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MEMORANDUM OF UNDERSTANDING
BETWEEN THE
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
OFFICE OF THE CHIEF SCIENTIST
AND
THE AVICENNA ALLIANCE FOR PREDICTIVE MEDICINE ASBL

I. Purpose

The United States Food and Drug Administration's (FDA) Office of the Chief Scientist and the Avicenna Alliance for Predictive Medicine ASBL (Avicenna Alliance) share interests in promoting progress in the application of computer modelling and simulation in healthcare through the exchange of knowledge, information, case studies and policy. FDA and Avicenna Alliance foresee benefits from the mutual exchange of knowledge, information, case studies, policy, training and research expertise in computational modelling and simulation as applied to healthcare in its broadest sense. This Memorandum of Understanding (MOU) establishes the terms for collaboration to promote these shared interests. Both FDA and Avicenna Alliance are referred to individually as a "Party" and collectively as the "Parties."

Momentum is gathering

Avicenna Alliance
Association for Predictive Medicine

Avicenna Alliance
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US authorities require the development of "a full human in silico model able to test drugs and devices across the entire body"

Calendar No. 177

115TH CONGRESS *1st Session* | SENATE | REPORT 115–131

AGRICULTURE, RURAL DEVELOPMENT, FOOD AND DRUG ADMINISTRATION, AND RELATED AGENCIES APPROPRIATIONS BILL, 2018

JULY 20, 2017—Ordered to be printed

Mr. HOEVEN, from the Committee on Appropriations, submitted the following

REPORT

In Silico Clinical Trials. – In Silico clinical trials use computer models and simulations to develop and assess devices and drugs, including their potential risk to the public, before being tested in live clinical trials. Advanced computer modeling can also be used to predict how a drug or device will behave when deployed in the general population, thereby protecting the public from the unintended

By understanding the impact a drug or a device will have on the human body immediately and over time, as well as within different populations, millions of dollars in the development costs can be saved. **A mere percent improvement in predicting failures before a clinical trial could save $100,000,000 in development costs per drug.**

predicting failures before a clinical trial could save $100,000,000 in development costs per drug.

As such, the **Committee directs the FDA to expand its use of in silico clinical models through a pilot project** aimed at creation of a full human body in silico model able to test drugs and devices across the entire body, including long-term effects among distinct populations.

If necessary to enact this project, the FDA shall issue a unified guidance to allow the model to be used to test both drugs and devices. The Committee requests a written report outlining the FDA's plans for development of the model within 120 days of enactment of this act.

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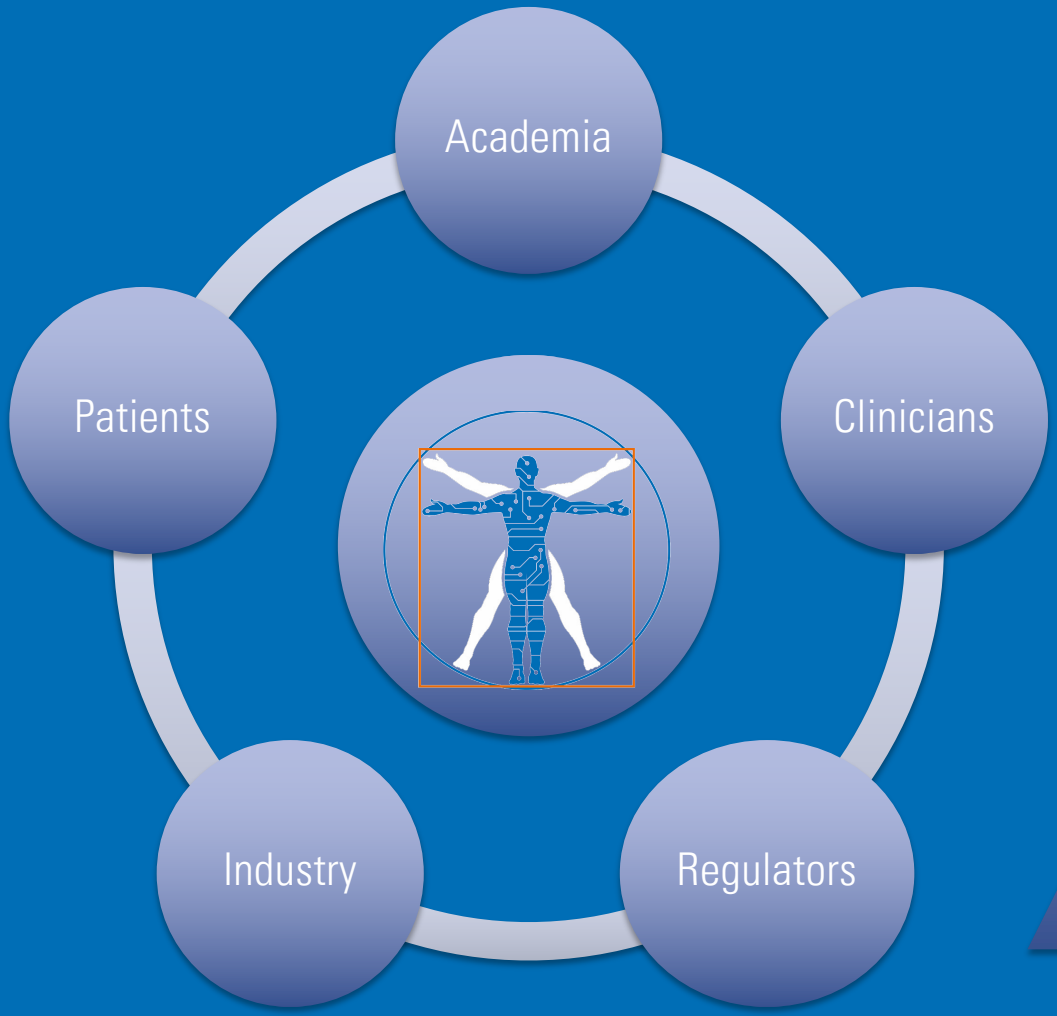
A Framework To Build Confidence



- Adoption
- Validation
- Research
- Policy

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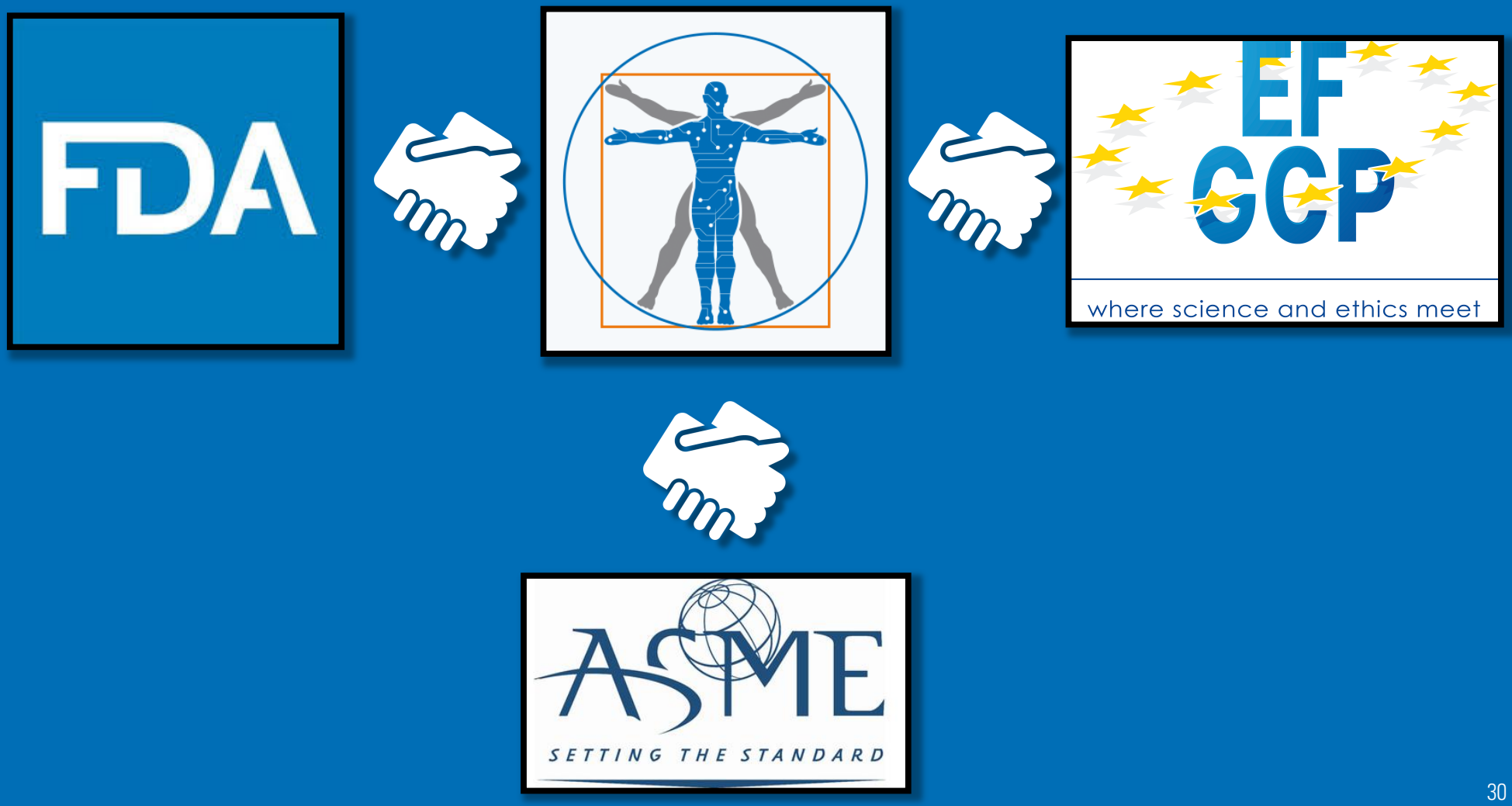

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The NEW ENGLAND JOURNAL of MEDICINE

The integration of data science and medicine is not as far away as it may seem: cell biology and genetics, once also foreign to medicine, are now at the core of medical research, and medical education has made all doctors into informed consumers of these fields. Similar efforts in data science are urgently needed.

Lost in Thought — The Limits of the Human Mind and the Future of Medicine
Obermeyer & Thomas. Perspective, NEJM, September 28, 2017


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Association for Predictive Medicine
Thank you
www.avicenna-alliance.com
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#AvicennaAlliance #InSilico