In Silico Clinical Trials: How Computer Simulation Will Transform The Biomedical Industry

An international research and development roadmap for an industry-driven initiative

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1. A layperson’s introduction

Every product to be distributed commercially undergoes a development and assessment process before entering the market. Biomedical products must undergo a much closer scrutiny before they can be commercialised, in order to ensure that the product does not harm the patient. Also, in many cases, before a widespread adoption of the product, the producing company must demonstrate the efficacy of the product in healing or alleviating the effects of a disease or disability (the intended use).

The only way to ensure the safety and efficacy of a biomedical product conclusively is to test it in humans. This process, known as clinical trial, usually follows three phases: phase I, where the product is tested on a small group of patients or healthy volunteers under strictly controlled conditions, in order to ensure that the product can be used safely without any unexpected side effects; phase II, where the product is tested on a larger group of patients, in order to verify whether it is effective, i.e. if it produces the expected beneficial effect in those patients; and phase III, where the product is distributed to a much larger group of patients, in multiple hospitals and possibly in multiple countries, to evaluate the product in a much larger community, reflecting the population at large, to see whether any less frequent, unexpected safety or efficacy problem emerges.

By the time a clinical trial for a new product starts, the company will have already tested the product exhaustively using laboratory-based tests. Depending on the type of product such tests can be done in vitro (for example looking at how a small culture of cells responds to the product), ex vivo (for example implanting a medical device in a cadaver to verify that it can be safely inserted and firmly attached to the tissues), or in vivo, on animal models (for example creating a special strain of mice that shows a condition similar to that intended for treatment in humans, to see how effective the product is).

The problem is that, due to the huge complexity of human pathophysiology, the significant differences between individuals, and the inevitable variability of how the product is actually administered to each patient (e.g., the patient forgetting to take the pill, or the surgeon placing the devices in slightly different positions in each patient), it is not unusual to find a product that performs exceptionally well in tightly controlled laboratory tests, but shows some serious problems during the clinical trials. The development of a new pharmaceutical product, and its introduction into the market today, is estimated to cost over two billion US dollars; nearly 75% is of this is spent in the various phases of the clinical trials. So every time a product fails late in the process, for example at the end of phase II or even phase III, the company suffers a huge loss.

Whilst clinical trials may tell us that a product is unsafe or ineffective, they rarely tell us why, or suggest how to improve the product in order to solve the problems highlighted by the clinical trial. Therefore a product that fails during clinical trials may simply be abandoned, even if a small modification would make it work properly. This stifles innovation, with a resulting decrease of the number of truly innovative biomedical products presented to the market every year, and a rise of costs to introduce new products. It then becomes increasingly difficult for a company to undertake projects on rare diseases since the limited return on investment can’t justify the costs.

In other sectors, such as aerospace or nuclear industries, similar problems with mission-critical products have been considerably overcome by using Computer Modelling and Simulation (CM&S) during both development and assessment. Can the same approach be used for biomedical products? In addition to in vitro and in vivo studies, might we adopt a third way for developing and testing biomedical products in silico, i.e. through computer simulation?

CM&S is already being used in the development of biomedical products. For example, pharmaceutical companies use computer models to estimate the pharmacokinetics (fate of substances administered externally to a living organism) and the pharmacodynamics (biochemical and physiological effects of drugs on the body, especially in relation to their concentration) of a new compound; medical device companies use computational fluid dynamics to predict how blood or other bodily fluids move inside and around the device being tested, or structural finite element analysis to make sure that the forces exchanged between the body and the device will not damage one another.

While these CM&S technologies are essential, current in silico technologies struggle to help address a number of very difficult questions in the development of a biomedical product, such as: why only some patients react adversely to the drug, while others are fine? Why is it that blood clots form around the
device in few patients only, while in others they do not? What is missing is the ability to assess the individual determinants of this variability, for example by:

- Using a computer model of the patient to take account of his/her particular physiology, the individual manifestation of the disease being treated, his/her life style, the presence of co-morbidities, etc.;
- Using a computer model of the treatment, which accounts for the compliance, or lack thereof, in taking the drug at the times and dose prescribed; or in the case of a surgically implanted device, to account for the variability between surgeons implanting a device because of surgical experience, technique, the particular anatomy of the patient, etc.

If we could develop accurate computer models of the treatment (effect of the drug/device on the organism) and its deployment (administration of the drug, surgical deployment of the device), together with accurate computer models reflecting different patients, we could foresee the use of in silico clinical trials (ISCT) to simulate a number of elements affected by the administration of the candidate biomedical product. In such a scenario, models of many individual patients are treated with the model of the treatment, allowing us to observe through a computer simulation how the product performs and whether it produces the intended effect, without inducing adverse effects that might be potentially dangerous for the patient. We believe that such in silico clinical trials could help to reduce, refine, and partially replace real clinical trials:

- ISCT could reduce the size and the duration of clinical trials through a more effective clinical trial design, for example by identifying characteristics to distinguish patients who might be at greater risk of complications and designing the trial accordingly; or providing ways to confirm earlier that the product is working as expected, thus reducing the duration of the trial, etc.;
- ISCT could refine clinical trials by improving the design through a much clearer knowledge framework for outcomes, and providing greater explanatory power to interpret any adverse observations that might emerge during the trial. ISCT can also be used to improve understanding of how the tested product interacts with the individual patient anatomy, predicting long term or rare effects that clinical trials are unlikely to reveal;
- ISCT could partially replace clinical trials in those situations where the clinical trial is not an absolute regulatory necessity, but only a legal requirement. We already have examples where the regulators have accepted the replacement of animal models with in silico models under appropriate conditions. While real clinical trials will remain essential in most cases, there are specific situations where it is conceivable that a reliable predictive model can replace a routine clinical assessment.

The process that we suggest involves the generation of computer models for each patient enrolled in a trial that simulates his/her pathophysiology and the treatment under test (either pharmacological or surgical), and that predicts the outcome, possibly undertaken alongside, or as part of an existing clinical trial. The predictive accuracy of these models can then be tested against the observations produced by the parallel clinical trial. Once this process is repeated for a sufficiently large number of patients, we will have a library of virtual patients, which can be used to test other in silico treatments, either for a different product or a refinement of the existing one. These simulations can first be used to develop a new product, and then to complement and refine the real clinical trial for such new product.

We can now provide a definition of in silico clinical trials as follows:

The use of individualised computer simulation in the development or regulatory evaluation of a medical intervention. A subdomain of 'In Silico Medicine', the discipline that encompasses the use of such individualised computer simulations in all aspects of the prevention, diagnosis, prognostic assessment and treatment of disease.
2. **Objectives**

2.a. **Engineering a new Industry**

Where we explain what *in silico* clinical trials are, where they can be used in the development cycle of new biomedical products, and how a whole new industrial sector can be formed around them at the intersection of biomedical industry, virtual prototyping industry, consulting/services industry, and the regulatory framework.

In 2007 a group of experts published “Seeding the EuroPhysiome: A Roadmap to the Virtual Physiological Human”. In this booklet a scenario was drafted where imaging and sensing technologies were used to generate quantitative information about the biology, physiology and pathology of a given patient at different scales of space and time. This information was then used as the input for multiscale computer models encapsulating all the knowledge available for a given disease process, in order to produce patient-specific predictions to be used for diagnosis, prognosis, and treatment planning.

In the following years dozens of consortia around the world developed a whole set of new technologies and methods, largely inspired by that original research roadmap. While the vision of the Virtual Physiological Human (VPH) is not entirely realised yet, VPH technologies are being assessed clinically in a number of practical applications, and preliminary results suggest important improvements over the current standards of care.

In some of these projects it was necessary to simulate the treatment in addition to the pathophysiology in order to predict how a patient would respond to a particular treatment option. In the RT3S project the deployment and the fatigue cycling of a peripheral vascular stenting was modelled; the VPHOP project included a model of the effect of bisphosphonates on the metabolism of bone tissue. Some other projects went even further, for example the PreDICT project developed VPH models to assess the cardio-toxicity of new drugs.

All these research activities suggested a new scenario where VPH models could be used not to enhance the clinical management of patients affected by particularly difficult pathologies, but rather to design and assess biomedical products of any kind. In 2011 the VPH Institute introduced the term *in silico* clinical trials (ISCT) to indicate this activity.

The birth of a service industry around ISCT is vital for the rapid and widespread adoption of this new approach. Thus, this roadmap will chart the ISCT territory not from a purely cultural point of view, but rather trying to capture the barriers and the challenges that we need to overcome for this new industrial sector to thrive, engaging the help of a number of industry experts.

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1. [http://www.rt3s.eu](http://www.rt3s.eu)
2. [http://www.vphop.eu](http://www.vphop.eu)

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This project has received funding from the European Union’s Seventh Framework Programme for research, technological development and demonstration under grant agreement no. 611819.
2. Mark the territory: the stakeholders

Where we describe who are the current stakeholders in the development cycle of a biomedical product, and where we identify the new stakeholders that the addition of an in silico component would require.

In this roadmap we will use the term “biomedical product” generically to indicate a product that is intended for the improvement of human health, but recognising that this generic term hides an extremely varied and complex list of components. Still a crude taxonomy is needed: there are medicinal drugs, which achieve their purposes through chemical reactions, and medical devices that fulfil their objectives through any other physical means, and there is a deep industrial difference between the two: they are regulated differently, manufactured differently, and distributed differently. Of course there is a small group of disparate products that combines both chemical and physical means, and we will refer to these are hybrid products.

A second taxonomy relates to the business model adopted by the producers. Large companies operate in mature and stable market segments, and because of the relatively high access barriers, they tend to oligopoly practices. Small companies usually operate in niche markets and/or develop innovative products; these are generally more flexible and faster to adapt to changes in the market, including radical innovations such as ISCT. In spite of their differences, all companies are driven by profit. However, there is an emerging third sector where the development and assessment of a biomedical product is primarily driven by not-for-profit entities such as charities, patients’ organisations, etc.

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4 An oligopoly is a market form in which a market or industry is dominated by a small number of sellers (oligopolists).
Another group is that of the Providers, which includes the traditional providers for product development and assessment services (CROs, Consultants, Research Hospitals), and ISCT providers (hardware, software, data banks, ISCT services).

There are then the Payers: depending on the national model these can be insurance companies, or health providers. In many countries an essential role is played by assessment agencies, such as NICE in UK, that advise the payers on the cost-benefit ratio for new products.

Next are the Regulators: the FDA in the USA, EMA in Europe, but also national agencies like MHRA, standardisation bodies such as ISO, and of course the research ethical committees that monitor the ethics of clinical trials.

Last but not least are the Consumers, represented by patients’ organisations, and by charities.

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**Table 1**

In all these stakeholder groups we will separate representative experts into “technical” and “executive” functions, or “both”. Technical stakeholders are the people in that organisation that would be the end users/providers of ISCT, and thus can inform this roadmap from a technical point of view. Executive stakeholders are those who can take strategic decisions such as joining an alliance; investing in R&D, etc. They are the targets of bespoke “Value Propositions” that we will assemble with the technical stakeholders, who know the internal key performance indicators that are important in their respective organisations. Stakeholders carrying the “Both” labels are typically those in small organisations where the same person covers both roles. In this case the technical discussion and the value proposition happens at the same time.

2.c. Identify the ‘issues’

Where we describe the “issues for”, i.e. the issues with the current development process that require and justify the introduction of ISCT, and the “issues for not”, the barriers that have prevented until now the use of ISCT.

The territory that we plan to chart in Avicenna is complex; but the time is right. As one of the experts we interviewed said: “I don’t understand why, perhaps because of the 2008 crisis, but we have experienced less interest for *in silico* from pharma compared to medical devices. Things are evolving recently”.

During the first Alignment Optimisation cycle the panel of experts we interviewed made a number of statements that were categorised as “Underlying Assumptions/Current State”. These statements were collected and submitted to the experts using the SchellingPoint web-based technology; on a number of them the vast majority of our experts agreed (for each statement the level of alignment among experts is provided):

2.c.i. **Issues with current clinical trials**

- Device CT failures occur most in the last 10% of the pipeline where 90% of the activity needed to get the device out to market takes place.
- Many device CT studies involve a low number of patients, leading to low quality without a broad benefit to the device industry (alignment 93%).
- Microfluidics and nanotechnology are hugely disruptive and will result in consequences for existing CT businesses (alignment 93%).
- With more and more EHR in countries, the innovation will become accessing health outcomes data (alignment 100%).
- Pharma cannot afford the increasing cost of failure and must advance ISCT (alignment 97%).

2.c.ii. Current adoption and expected benefits for ISCT
- There are examples of successful ISCT (alignment 88%).
- The application of ISCT is minimal within the pharma industry (alignment 93%).
- There are ISCT used in pharmacokinetics/pharmacodynamics (PKPD), paediatrics, and for multi-trials in elderly, that show model-specific aspects of the trial (alignment 100%).
- Attempts are being made to replace some organ functions in silico using biomimetics (example: artificial pancreas) (alignment 95%).
- Combinatorial chemistry of in silico-designed molecules has enhanced discovery (alignment 100%).
- Computer based models are being used to study the influence of pharmacogenomics (alignment 100%).
- Good examples of the potential of ISCT have been prototyped by Entelos, but not successfully implemented from a commercial point of view (alignment 89%).
- Pharmacology models do exist for understanding chemical interaction modelling; quantitative systems pharmacology is an area that has enjoyed some adoption (alignment 100%).
- There are few examples of models that can predict drug absorption, distribution, metabolism, excretion and toxicology (ADMET) (alignment 96%).
- We can begin to advance ISCT with the science and modelling capabilities we have now - modelling capabilities are not what is holding up progress (alignment 92%).
- We have not yet exploited the models and simulations that already exist (alignment 97%).
- Over-sophistication of models is not the reason today's ISCT methods suffer low adoption (alignment 86%).
- There is great interest in ISCT in pharma (alignment 81%).
- ISCT will help us understand host-device response up to 80% (alignment 84%).
- There will be greater openness to ISCT methods in areas with high research activity (alignment 100%).

2.c.iii. Limits and challenges for ISCT
- ISCT will never replace entirely clinical trials, but only reduce and refine them (alignment 100%).
- A poor example of using ISCT is where groups are focused on specific areas but do not include that in the CT workflow (alignment 96%).
- An excellent example of ISCT is what is being done in the virtual Physiological Human / Physiome, but there is still a lot to do before it gets close to what's going on in the body (alignment 96%).
- For ISCT to ultimately work, we will need to create the Systems Dynamics model of the human body (alignment 90%).
- Modelling animal to human - there have been whole companies established to do this - but with no material results (alignment 91%).
- Problems that have been encountered in mapping reality with modelling outcomes in process design can be useful to develop ISCT (alignment 100%).
- The validation of models is far from sufficient now (alignment 100%).
- A culture of trust and openness is required to make ISCT successful (alignment 100%).
- ISCT is hugely multidisciplinary and cannot be delivered by small groups working in a lab (alignment 95%).
- Resistance to ISCT will exist from basic R&D to regulators until we can show that it has a remote chance of succeeding (alignment 94%).

So from this corpus of statements that most of the experts consulted agreed with, and from the opinions that emerged during the First Avicenna Event, held in Rome on March 21st, 2014, we can formulate a first tentative list of drivers and barriers for the adoption of ISCT:

2.c.iv. Issues favouring:

1) The vast adoption of Electronic Health Records and the emergence of new technologies such as microfluidics and nanotechnology are disruptive of the current way we run clinical trials;
2) Drugs: there is a general perception that the current clinical trials model is not sustainable and need to be revised to make it more effective in detecting early in the process potential issues, and less expensive, so as to make innovation more affordable;
3) Drugs: avoid expensive clinical trials when the assessment has already been done, but an unnecessary repetition is required (i.e. new indication);
4) Drugs: reinforce the pre-clinical assessment of efficacy, so as to avoid drugs that fail in phase II;
5) Drugs: supplement phase II trials so as to explore safety and efficacy in the more infrequent phenotypes that usually appear only in phase III;
6) Devices: for some classes of devices the current clinical assessment procedures are not entirely effective, so when failures are intercepted by post-marketing surveillance the company must withdraw the product and face significant litigation costs;
7) Devices: reinforce the design by accounting for patient and surgeon variability, effects of lifestyle differences, comorbidities, etc. so as to avoid post-marketing recalls;
8) Devices: there is a need to better understand the host-device response earlier in the assessment process;
9) Hybrid: reinforce the regulatory pathway for products that are extremely difficult to regulate;
10) All: reduce the cost of assessment for simpler assessment problems like re-labelling (i.e. for paediatric use) reducing the number of orphan diseases.
11) Early examples of ISCT use are promising, including trials for special groups (paediatrics, elders, etc.), in pharmacokinetics/pharmacodynamics and more in general in the prediction of drug absorption, distribution, metabolism, excretion and toxicology, artificial pancreas, in silico design of new molecules tested with combinatorial chemistry, effects of pharmacogenomics, the work of Entelos on diabetes and rheumatoid arthritis, quantitative systems pharmacology;

2.c.v. Issues against:

1) ISCT is being developed mostly through accidental findings during research projects not targeting ISCT; the lack of a coordinated research and technological development roadmap prevents the sector from being consolidated, as the definition of needs and the challenges is fragmented.
2) The adoption of ISCT requires the active participation of a number of different stakeholders from industry, regulatory agencies, patients’ organisations, etc. This requires a balanced, pre-
competitive setting where these discussions can be conducted with the risk of any unwanted bias.

3) To be effective in a number of diseases ISCT must predict better the systemic responses; but more research is necessary to unravel systemic processes using Virtual Physiological Human strategies, systems dynamics models and the lessons learnt form process design;

4) The use of in silico methods to translate from animal models to humans is promising in principle, but requires a lot more of research and technological development before it can be effectively used;

5) The adoption of ISCT requires a significant investment in validation studies to identify those approaches that work reliably, conducted publicly and openly, will help to establish some trust among stakeholders around those;

6) The development of ISCT is a grand science, because of its extreme interdisciplinarity that can be tackled only in very large research institutes; we need to support the formation of such large institutes, but also explore Virtual Organisation approaches where small groups can join forces and work together to tackle complex problems.

2.d. This roadmap

Where we explain what the roadmap should include, why, and which effect we expect to achieve with such a collective effort.

This research roadmap consists of four sections: Objectives, Philosophy, Roadmap, and Recommendations. In the Objectives section we define the scope of the roadmap and the stakeholders involved in the process of drafting and subsequently implementing it; under Philosophy we discuss how ISCT can impact the various phases of development of a biomedical product and how ISCT can serve the evaluation and the validation of such a product. This discussion shall in turn highlight the scientific and technological challenges that need to be addressed for the successful adoption of ISCT and that will be described in detail in the Roadmap section. These challenges shall be presented from the perspective of all stakeholders that will translate the research results into products and services for ISCT, i.e. the producers, the regulators, and the providers. Suggestions on how to effectively implement this roadmap from each stakeholder’s point of view are provided in the Recommendations sections.

2.e. Establishing a pre-competitive alliance

Where we explore the possibility of a process through which the group of stakeholders formed around the Avicenna support action might decide the nature scope and implementation of a pre-competitive alliance on ISCT.

The type of research and technological development that the roadmap describes cannot be achieved in a single type of setting. The more fundamental methodological and scientific challenges must be tackled primarily in academic settings, or in private research labs. On the other hand more technological aspects such as standardisation or interoperability are typically tackled at the industrial level; while de facto standards might emerge, the definition and the adoption of such standards is much quicker and effective when industry can formulate pre-competitive agreements. But there is a third zone, in between research and technological development, that involves delicate issues such as evaluation of reliability, limits of validity, best practices, etc. where academics, industrial and clinical researchers, standardisation and regulatory experts, developers of ISCT solutions and services, CROs and research hospitals need to work together to define a set of reliable, effective, and sustainable practices for the use, assessment, and interpretation of ISCT.

In parallel to the development of the roadmap, the Avicenna consortium will explore whether there is a need for a permanent structure to permit all stakeholders to continue consensus and co-design processes beyond the end of the Avicenna project and, if there is, to define what form, support and mode of operation such an alliance could assume.
3. Philosophy

3.a. Pharma and devices: development pipelines

The industry research and development pipelines for medical devices and pharmaceuticals, including the regulatory processes that oversee them, appear to be very articulated through different disciplines, but have the same essential components:

1) identification of a clinical need,
2) design of a tool to meet that need,
3) assessment of the risk associated with the tool,
4) identification of the efficacy of that tool in answering the need, and
5) clinical assessment of the tool in the medical marketplace.

In the Pharmaceutical industry, the design phase is known as Discovery (blue), the assessments of risk, efficacy, and clinical utility are called Development (green), and launch and post-market analysis is referred to as Business Development (red).

In the Device industry, the phases are Design (blue), Pre-clinical (risk) assessment (orange), Clinical assessment for efficacy (green), and post-market analysis, called Business Development (red). Besides differences in the naming conventions, medical devices have specific preclinical risk assessments of the possible modes of failure of the device.

Development schemes are summarized below. The life cycles have cosmetic differences, but share the same basic set of milestones. We assume that the previous generation of innovation sets the stage for new products.

Figure 2 Development schemes of pharmaceuticals and medical devices.

3.b. Modernising the development of medical devices

Where we list the main shortcomings of current product development & assessment approach, how ISCT could improve such process, and what would be the metrics of success.

The complexity of the regulatory process for medical devices is in part due to the significant fragmentation over the global market. Essentially each country has its own set of rules, procedures, etc. For example, while USA and Europe agree in dividing risk in three classes, many Asian countries use four. A full review is beyond the scope of this roadmap. To get a taste of the regional differences
the interested reader may use this three parts article that covers Europe\textsuperscript{5}, USA\textsuperscript{6}, and the rest of the world\textsuperscript{7}.

In contrast, the internal development process of a new medical device is quite similar across companies and families of products, and can be roughly divided in three stages:

- Design
- Pre-clinical assessment
- Clinical assessment & business development

It is convenient to discuss the modernisation of the process separately for these three stages.

3.b.i. Design

When the development of a medical device starts from a clearly identified clinical need, in most cases such need is formulated as a change/improvement over an existing device, and the innovation is incremental. Less frequently the device is designed from scratch, stating from a previously unmet clinical need.

In the first case the manufacturer will claim some similarity with existing, clinically tested devices, and will pursue a Premarketing Notification (PMN) process; in the second the manufacturer must obtain a Premarketing Authorisation (PMA). The differences between PMN and PMA, and the criteria when one or the other must be used, vary considerably between countries. But the general principle is that if the new design is “similar enough” to one already widely used in clinics a simple notification (PMN) is required before the first in-man procedure. Otherwise, before the device can be tested in humans, a full set of pre-clinical studies must be conducted to ensure that the device is safe, at least with respect to the known failure modes for that type of device, (PMA). Which one of these two cases applies will make a considerable difference on what are bottlenecks in the current design procedures.

Design changes driven by commercial needs tend to be very conservative, and minimally innovative. The two most common scenarios are product diversification (add something that makes our product special), or patent circumvention. In these cases, the primary problem is regulatory: from the producer point of view in most of these cases the similarity principle applies (no additional controls are needed because a similar product is already on the market without any adverse reports). But the regulators are concerned with those situations where apparently minor changes in the design trigger entirely new failure modes, ultimately resulting in serious clinical complications.

When improvements in existing designs emerge from clinical needs, they are usually triggered by issues with usability (i.e. surgical issue reports for implantable devices), or by complications (i.e. clinical case reports). The two major difficulties in this case are: the confirmation of anecdotal reports, i.e. their translation in a specific functional requirement that can be addressed with a design change; and confidence that the solution of a minor problem does not trigger unpredicted failure modes, creating a much bigger problem. Then, the tension with the regulator around when the similarity principle applies is always present.

Regardless of the motivation, when designs emerge as a minor modification of an existing one, and the manufacturer is planning to pursue a PMN, the major challenge is to ensure that the changes introduced to the pre-existing design do not considerably change its risk profile, without repeating the whole pre-clinical experimental evaluation.

Using ISCT it would be possible to compare the old and new design with respect to all failure modes relevant for that family of devices, revise the design if major risks appear, pursue the PNM when the differences are minimal, and conduct some experimental tests only when the ISCT evaluation indicates small but not negligible differences. Of course such processes must

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\textsuperscript{5} \url{http://www.mddionline.com/article/engineer-takes-medical-device-regulatory-process-part-i}

\textsuperscript{6} \url{http://www.mddionline.com/article/engineer-takes-medical-device-regulatory-process-part-ii}

\textsuperscript{7} \url{http://www.mddionline.com/article/engineer-takes-medical-device-regulatory-process-part-iii}
be designed in close collaboration with the regulators, so that when properly applied they would most likely produce the PNM.

The metrics of success for ISCT in such case would be:

a) % of cases where the manufacturer requests a PNM, and the regulator agrees (i.e. does not imposes a PMA)

b) % of cases where an additional design revision is not required later on in the development process (i.e. for complications made evident in early clinical trials).

The most complex scenario, however, is when a device is designed from scratch. The first challenge is the capture of the clinical need, in a reproducible and quantifiable form. Once it is clear what problem needs to be solved, the design cycle can start. Traditionally engineering design is divided into design for assembly, for function, for manufacturing, and for cost:

- **Assembly**: for a medical device this means deployability/implantability and anatomical compatibility;
- **Function**: this is how the device physically interacts with the host organism, both with respect to the intended function (i.e. pump blood, provide skeletal articulation), and with respect to the secondary unavoidable interactions (i.e. while the heart deforms during cardiac cycle, the artificial valve is moved around);
- **Manufacturing**: for a medical device this means first and foremost the choice of the materials, with all biocompatibility/bioactivity aspects involved. But materials must be manufacturable, and their physical and chemical properties are frequently also function of the manufacturing process. So the selection of the material together with the manufacturing process is essential.
- **Cost**: medical devices are high unit value products, so the issue of cost is less pressing than in other engineering sectors. But in some areas, where innovation stagnates, buyers tend to buy on price rather than on features, and producers end up competing on the selling price (and thus on the production costs). Another aspect is the indirect costs; some design choices might make sterilisation or packaging much more expensive. Similarly, some designs require that a set of specialised instruments is made available in every hospital where the device will be implanted, with all inventory costs associated.

The most challenging aspects of this design process are those involving the proper representation of the patient anatomy, physiology, and biology, as well as of the deployment process (i.e. surgical procedure). For example, if we refer to devices that are expected to fit the patient anatomy quite closely (i.e. a hip replacement, or a cardiac valve), too frequently the design is made targeting one generic anatomy; later on during the pre-clinical assessment such design usually result to be inadequate, and multiple design revisions are required. **ISCT could enable the designer to perform “virtual deployment” of the new design rapidly into hundreds of simulated patients’ anatomes, immediately highlighting whether some design features need revision.**

If the ISCT-supported design of conceptually new devices is properly codified and regulated, the evidence it produces should be usable as part of the PMA process, thus drastically simplifying the pre-marketing authorisation.

In this case the metrics of success are quite similar to the ones before:

a) % reduction of the time/costs to receive the necessary PMA, when compared to average time for devices of the same classes without using ISCT.

b) % of cases where an additional design revision is not required later on in the development process (i.e. for complications made evident in early clinical trials).
3.b.ii. Pre-clinical assessment

With the term pre-clinical assessment we indicate every activity aimed at assessing the safety and the efficacy of medical devices that do not involve human clinical trials. Depending on the type of device and on the failure mode being investigated, pre-clinical assessment might be a device-only experimental test, an ex vivo test where the device interacts with some animal or human cadaveric tissues, an in vitro test where the device or part of it interact with cells and tissues cultures, or an in vivo test, where an adapted version of the device is implanted in an experimental animal.

Once the candidate design is finalised and internally approved, the pre-clinical assessment process starts. One effective approach to pre-clinical assessment is to use the risk analysis as guidance. Most regulatory processes require as part of the dossier a full risk analysis, based on risk management methods such as Failure Mode and Effects Analysis (FMEA); for example CE marking requires a risk management procedure complying to EN ISO 14971:2012. Here we use FMEA as guiding example: but the essential concepts would change very little if other risk management methods, such as Failure Mode, Effects and Criticality Analysis are used instead.

FMEA requires the manufacturer to list all known failure modes for that class of devices, and for each of them to provide an estimate of probability that such failure occurs in the device under examination while applied according to the intended use, and of the severity of the effects in case such failure occurs. This produces the following two extreme scenarios:

1) Best case: known clinical failure modes
   a. The clinical failure mode is associated with engineering failure modes
      i. A technical standard is available to test the risk for such failure
      ii. The severity of the effects of the failure is known

2) Worst case: unknown clinical failure modes
   a. Clinical failure mode when observed cannot be reduced to known engineering failure modes
      i. No technical standard exists to test such risk
      ii. No clinical experience is available to estimate the severity of the effects if such failure occurs.

Every real-world case falls in between these two extremes.

When the device under examination involves mostly risk of failure modes close to the best-case scenario, the current methods are usually adequate. In these cases the use of ISCT is rarely necessary. However, even when most elements of the risk analysis are well known, if the pre-clinical assessment highlights an unacceptable risk, and a design revision becomes necessary, some experts report benefits of using ISCT to shorten the trial-and-error cycle (revise design, make prototype, repeat experimental testing on new prototype).

But it is where only limited a priori knowledge is available that ISCT could show the biggest benefits. First, a word of caution: If the device fails producing a clinical failure mode that is completely original and nothing similar has ever been observed before, it is only with the in-human clinical trials that this failure mode will become evident. Computer Modelling & Simulation helps to organise all the knowledge available, even when it is fragmentary and incomplete; but cannot help when no knowledge at all is available.

More realistically, when:

1) The design is at risk for a clinical failure that can be produced by multiple engineering failure modes;

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2) The risk for an engineering failure mode to occur does not depend only on the design, but also on the patient, his/her lifestyle, and the way the device has been deployed;

3) The severity of the effects that such failure could produce is hard to estimate.

ISCT could play an important role in refining, streamlining, and reducing the cost of the pre-clinical assessment.

Once the design is approved, its deployment needs to be optimised. This activity varies considerably depending on the type of device. For implantable devices this involves the definition of the surgical procedure, and the related instrumentation.

It is not unusual that the optimisation of the deployment imposes also some changes to the design of the device itself. Again, the manufacturer usually assumes that these changes are insignificant with respect to the safety and performance of the device, and thus no additional laboratory testing is required. But in practice this separation is a thin line, and rarely the regulator accepts lab tests done on a design even if only marginally different form the final one.

Deployment optimisation frequently involves a lot or cadaver testing. Specific aspect of the deployment might be explored on dissected organs in the company labs, but full surgical procedures are usually tested performing the operation of an intact cadaver, to be performed at morgues specifically organised to conduct experimental surgery studies. The costs and the logistic complications involved in these experimental surgery sessions are considerable, calling on the availability of a highly specialised surgeon, all of which are located at the experimental surgery facility where the cadavers are. The optimisation process is largely trial-and-error: it is not unusual that one of such experimental surgery sessions is interrupted after 5 minutes because a major problem with the device or the instrumentation emerges. The session is then stopped, a design revision is done, new prototypes manufactured, and a new session must be organised.

In such cases, when the development plan is already delayed and marketing is pressing the technical team, it is easy to end up cutting corners and to not fully optimise the deployment. However, this would most likely result in modifications needing to be made to the devices and/or the instrumentation later on when the first in man studies are running, with all the complexity and costs that this involves, also from a regulatory point of view.

In conclusion, ISCT can play an important role in almost every step of the pre-clinical assessment, both for moderately or radically innovative products. Where innovation is moderate, ISCT can reduce the number of trial-and-error cycles required to optimise the product or its deployment. For radically innovative products it could drastically reduce the return on investment threshold below which the development of the product would not be cost-effective; reducing the cost, the time to market, and the associated risks, ISCT can dramatically reduce the barriers to innovation, especially for SMEs.

The metrics of success for ISCT in the pre-clinical assessment of medical devices would be:

a) % reduction of the time/costs to receive the necessary PMA, when compared to average time for devices of the same classes with out using ISCT.

b) % of cases where an additional design revision is not required later on in the development process (i.e. for complications made evident in early clinical trials).

3.b.iii. Clinical assessment

In the previous section it was made clear that in no case ISCT could completely replace the clinical assessment, when the product requires it. Thus, the question here is rather to explore how ISCT can be used to supplement and support the clinical assessment.

But this is a very complex territory, primarily because the clinical assessment of medical devices is a much more heterogeneous and much less organised activity than in pharmaceuticals. This is due to historical, but also operational reasons. In general well-controlled clinical trials are difficult to design for medical devices because:
- Device performance is not independent from the patient or the surgeon: frequently the clinical outcome of a medical device is dominated by the conditions of the patient, his/her lifestyle, and the quality of surgical procedure used to deploy the device.

- Comparative trial design is limited: in some cases there are no other similar devices on the market, so the design would be required to compare patient with intervention to those without it, which in most cases is unethical. Also the performance of most devices is not independent from the deployment (i.e. surgical technique) and the surgical teams have significant experience with the old device, but not with the new one. All these problems exist also with pharma products, but it is more common in devices.

- Single or double blind studies are impossible: the surgeon cannot be blinded to the type of device implanted, and no placebo exists (sham operations are almost never ethical). It is not unusual that the first clinical trial for a device is accomplished by the consultant who contributed to the design, so the level of investigator bias is much higher than usual.

To use a parallel with animal experimentation, ISCT could be used in relation to the clinical trials of new medical devices to reduce, refine, and partially replace them.

In many device clinical trials the end point that can confirm the outcome of the device is difficult to measure, it is affected by a large variability, or it requires an observational study to run for a long time. In all these cases, the use of patient-specific models as part of the clinical trial could allow a reduction of the cohort size and/or the duration of the trial, by replacing the outcome with surrogate outcome that requires easier measures in combination with some modelling; a drastic reduction of the inter-subject variability and/or of the reproducibility of the outcome measurement; the provision of a model-based surrogate outcome that is evident much earlier than the standard one, thus reducing the duration of the clinical trial. In all these ways, Patient Specific Modelling (PSM) can help to reduce clinical trials in size and duration.

PSM can also drastically improve our ability to quantify the most complex outcomes (i.e. functional outcomes, which typically are poorly captured by unreliable questionnaires), and also capture side effects with a much broader observational angle than normal trials can provide. Thus, the use of ISCT could refine clinical trials of medical devices, making them more effective, and reducing the risk of complications emerging only after full marketing.

Last, while ISCT will never fully replace clinical trials, there are special cases, typically where replications are necessary for regulatory purposes but the outcome is quite obvious from previous data, where a clever combination of ISCT and conventional clinical experimentation could partially remove the need for such clinical trials. Of course this would have to happen within a very robust regulatory framework, such as the one that MDIC, ASME and FDA are developing in the USA.

3.c. Modernising the development of pharmaceuticals

Where we list the main shortcomings of current product development & assessment approach, how ISCT could improve such process, and what would be the metrics of success.

Pharmaceutical R&D is built upon the concept that diseases and disorders can be broken into underlying biological processes that can be defined in terms of their constituent elements or targets. By developing therapies that interact with these target elements, pharma target interventions to alter the biological process in question, assuming this will intervene in the disease process with the ultimate aim of delivering therapeutic benefit to the patient.

The industry has largely been built on an approach composed of a variety of *in vitro* and *in vivo* screens, studying the interaction of therapeutic targets with medicinal or biological therapeutic entities. With the development of highly detailed molecular and cellular technologies, especially post-genome, the approaches have adopted an increasingly reductionist focus. As outlined in Figure 2 above, the pharma R&D pipeline is typically broken down into three broad phases: “Discovery”, “Pre-Clinical” and “(Clinical) Development”.

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3.c.i. The status quo

Discovery scientists typically begin Target Identification in areas of high unmet medical need by using information on disease epidemiology, pathways, mechanisms and potential targets culled from the literature in the public domain. These data are used to frame hypotheses about how intervention with a drug might alter the course of disease and, importantly, to build the case why they are starting points for the development of a successful and commercially viable product. This case be built from experimental studies in a variety of cellular and, possibly animal models designed to confirm, or partially validate the connection between the target and the biological process, sufficient to build confidence in the rationale.

Prioritised molecular targets are subjected to the first of a number of screening strategies to identify potential therapeutic entities. For small molecules, this involves the use of high throughput screening of a library of compounds, often numbered in the millions, to identify active compounds that have an element of selectivity for the target and are potentially “druggable”, i.e. structures that from a medicinal chemistry perspective have properties that would be required for a successful drug, and that are readily modifiable. The process is different in the case of biological therapeutics (e.g. antibodies). In recent years, the ability to screen virtual chemical structures in computers has enabled the expansion of the “chemical space” that is otherwise available only through the use of physical compound libraries, increasing the potential for novel starting points for chemical synthesis. This process culminates in Hit Identification; that is, a series of many structures that represent potential chemical starting points for more detailed study alongside the biology being investigated.

The Lead Identification phase turns these initial structural “hits” into potential “leads”. In vitro cellular assays are used to assess how structural changes to the chemical starting points influence the target. An iterative make-test cycle creates a much smaller number of compounds, typically represented by a range of different chemical “series”, that the assays have shown interact with the target in such a way as to demonstrate the potential to become an effective treatment.

Chemical leads then undergo a major focus on further refinement. Lead Optimisation focuses on the prioritised compounds to optimise them in terms of absorption, duration of action, and delivery to the target in vivo. As before, these studies involve similar make-test cycles between chemical modifications and biological assays, this time including studies in animal models designed to investigate the physical and toxicological properties of the molecules. This is with a view to building confidence that the compounds have the potential to eventually undergo Principle and Concept testing in humans. Usually this will result in no more than two or three compounds emerging as potential drug candidates. These detailed investigations become even more focused on these two or three compounds during the Pre-nomination phase, to scrutinise them in terms of safety, the method/route of administration and bioavailability in vivo. Another important consideration at this point is the ease with which synthesis of the compound can be scaled up for routine manufacture ease, as well as the cost of goods associated with that, either or both of which could be hurdles to further progression of promising molecules. At the end of this phase, a dossier supporting the profile of a single compound as a Candidate Drug is submitted for transition into the Development process. One or two back-up molecules that are similar to the preferred candidate, but for whatever reason are ranked below it, normally support a Candidate Drug nomination, ready to be called upon in the event that it fails.

The hand-over between Discovery and Development typically takes place during a Pre-clinical Development phase. Here, pivotal toxicity studies are undertaken, alongside safety pharmacological and other investigations to compile the necessary regulatory dossier for submission to the relevant authorities to allow the first administration of the compound in human subjects (First Time in Man) as an Investigational New Drug (IND), in preparation for Principle Testing.

Phase I clinical studies are conducted in healthy volunteers, or patients, and are usually non-therapeutic, intended to study the safety and tolerability of the candidate drug in humans as opposed to animal models, as well as its pharmacodynamic and pharmacokinetic properties, using single and multiple ascending doses. Phase II studies follow on from these, and are designed to test Proof of Principle in a limited number of patients. This provides evidence that an intended pharmacological effect results in an expected change in a biomarker in a dose range, without any unwanted effects. Studies are also designed to test dose-response relationships and efficacy to help select suitable doses for subsequent Phase III studies.
Concept Testing is the phase during which demonstrable evidence of clinical efficacy and safety emerges in studies conducted on the target patient group: Proof of Concept. This provides the clinical confirmation that an investigational product has the desired effect in patients with the disease of interest through placebo-controlled studies, or dose-response studies against a validated surrogate variable or clinical outcome variable. The studies will also establish the dose range that can be used for subsequent confirmatory studies. This phase and the subsequent Development for Launch is where various Phase IIIa and IIIb studies are conducted to add further details confirming safety and efficacy, dosage, formulation and other studies all conducted in relevant patients to complete the dossier required for regulatory approval. Following the successful launch of the new drug, additional Phase IV studies will be conducted as part of the approach to support product maintenance and life cycle management, including long-term effects and health economic aspects.

A representation of the typical duration for each phase in the pipeline is shown in Figure 3.

Figure 3 Duration of phases in the Pharmaceutical R&D Pipeline

The latest estimates of the cost to bring a successful new medicine from project start to delivery to the market is close to $2 bn, with less than 1 in every 10 projects entering in development succeeding, having seen the failure of many hundreds of projects as they progressed through the Discovery phase. The approach has been to adopt an "increased number of shots on goal" as a route to cope with the attrition in the pipeline, the consequence of which is the need to finance many failures to have a chance of delivering a successful outcome. If failure comes early, the cost is relatively low, but once in development, the cost of project failure escalates the later it happens.

An alternative approach is to improve the odds by refining our ability to predict outcomes at each point in the value chain.

3.c.ii. Applications in Discovery

<TO BE DONE>

3.c.iii. Applications in Preclinical
3.c.iv. Applications in Development

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3.d. In silico clinical trials: Current Practice

Where we describe real-world case studies where in silico methods are used in developing and assessing biomedical products with some difficulties, and what are the lessons to be learnt.

The outcome of the various opinion surveys and syndicate discussions as part of this research programme has identified some core statements describing the “current state”:

- The ability of pre-clinical testing to predict efficacy and safety in the clinical phase is insufficient.
- All drug projects include modelling as part of PKPD studies.
- Those labs that are multidisciplinary will gain from the introduction of ISCT compared to those labs that are not.
- An excellent example of ISCT is what is being done in the Virtual Physiome, but there is still a lot to do before it gets close to what’s going on in the body.
- Good examples of the potential of ISCT have been prototyped by Entelos, but not successfully implemented.
- A number of companies have been established to do modelling animal to human, but with no material results.
- There are few examples of models that can predict drug absorption, distribution, metabolism, excretion and toxicology (ADMET).
- We can begin to advance ISCT with the science and modelling capabilities we have now - modelling capabilities are not what is holding up progress.
- We have not yet exploited the models and simulations that already exist.
- The validation of models is far from sufficient now.
- Modelling and simulation approaches are clearly being used within biomedical research so demonstrating their scientific feasibility. However, a lack of convincing evidence exists regarding where they can be optimally used now.

3.e. Uptake of ‘alien’ technology

Where we describe what are the changes in term of culture, human resources, retraining, and infrastructures without which the introduction of ISCT would be resisted.

Taking the views collected during our opinion surveys and the syndicate discussions at the events, there is agreement over the value of ISCT, either for devices or medicines, in that it is regarded as a disruptive technology that will improve the R&D process for both, and ultimately improve the current healthcare “information marketplace”. Following from this, perhaps logically, it is considered that life science companies first adopting ISCT approaches could make the greatest progress in the marketplace, and also open up new markets based on ISCT. In this context it is believed that those laboratories that have a multidisciplinary ethic and practice will most likely gain from the introduction of ISCT compared with those that do not have such an approach, and educational institutions that do not
include training in this area as part of the curriculum might lose some of their competitiveness in the future.

Some specific points were identified in the surveys conducted within the project that relate to the introduction of an alien or new technology, and that will need to be taken into account in the development of the final roadmap:

- ISCT is hugely multidisciplinary and cannot be delivered by small groups working in a lab.
- Resistance to ISCT will exist from basic R&D through to regulators until we can show that it has a remote chance of succeeding.
- A recognizable and respected group of people from academia and industry should be visibly dedicated to ISCT predictive science.
- IT companies need to be fully engaged in ISCT to deliver the advanced technologies that are needed.
- Regulators should have a group focusing on in silico approaches (Post-survey note: we are aware that they do and they are active in exploring this area, but its existence is clearly not widely known).
- The advancement of ISCT will require new levels of close collaboration between scientific disciplines.
- Organisations need to be satisfied that ISCT is not being used for purposes that could be deemed unethical.
- Academia/industry partnerships need to be enhanced.
- European co-operation schemes should promote the sharing of assessment results, from proof of concept, to efficacy results, alongside with toxicity.
- We will need to gain access to Electronic Medical Records and prescribing practice.
- ISCT needs an interactive modelling database operating between academia and profit organizations to be used for prospective and retrospective studies.
- Big data issues will need to be addressed in a similar way to that proposed in the Digital Patient roadmap.
- We need to identify how to share ISCT data fluently.
- Proprietary data needs to be shared appropriately.
- There should be ISCT 'Cloud' resources that facilitate data sharing across R&D "silos".
- ISCT should allow sharing of public databases over country borders.
- We need to build research data repositories that can be easily shared and accessed.

Finally, training was identified as a key element for successful implementation. This was seen not only for understanding modelling and simulation in biomedical disciplines, which are typically unaccustomed to these concepts, but also as the need to effectively interpret emerging results and understand how to apply ISCT approaches to support risk assessment. The possible need to provide appropriate training packages for clinicians was also emphasised.

3.f. In silico clinical trials: Best practice

Where we describe real-world case studies where in silico methods are already successfully used in developing and assessing biomedical products.

While the idea of ISCT is radically innovative, there are some examples of its early adoption, some of which can be considered success stories; these use cases represent the best practice so far in this domain. Below, we listed a few of them, which emerged during the Avicenna consensus process.
Without claiming to be exhaustive, we believe these use cases can give a tangible representation of what ISCT can mean

3.f.i. **Stryker Corp: in silico pre-clinical assessment of Proximal Epiphyseal Hip Replacement - Marco Viceconti, University of Sheffield**

Stryker Corp designed an innovative mini-invasive total hip replacement called Proximal Epiphyseal Replacement (PER). The geometry of the femoral component was designed to reduce the risk of bone avascular necrosis in the residual epiphyseal portion. The conceptual design was a modular head and a short curved stem. However, experimental tests on cadaver bones highlighted a weakening of the host bone implanted with the initial conceptual design of the PER, increasing considerably the chances of a post-operative femoral bone fracture [1] even more significantly to what observed for current mini-invasive hip devices. An in silico model of the implant-bone interaction was developed, and used to revise the prototype design by optimizing the bone-implant load transfer mechanism while keeping the risk of implant loosening and prosthesis fracture low. Extreme anatomies and surgical misplacements were studied. The revised design strengthened the femoral neck of the implanted femur by an average 10% over the intact contralateral femur while reducing the relative risk associated to loosening from 45% to 60% [2]. The model was then used to generate a virtual population where the patients’ anatomy, their bone quality, and surgical procedure were varied using a stochastic scheme, and the risk associated to each failure mode was obtained [3]. This confirmed over a whole population the good performance of the new design that was further corroborated by experimental tests performed using the newly developed prototypes.


In 2013, GE Healthcare announced the U.S. Food and Drug Administration (FDA) approval of Vizamyl™, a radioactive diagnostic agent for Positron Emission Tomography (PET) imaging [1]. The cost of developing biomedical imaging agents can be very high. The process includes identifying a biomarker target that is specific to a disease and expressed at levels sufficient for detection. A molecule must then be developed with specific binding affinity to the biomarker target. This molecule must also exhibit good delivery and clearance pharmacokinetics over the imaging time frame. Furthermore, the binding molecule must include a detectable marker that provides a measurable signal well above the noise level of the imaging modality and at a dose that can be safely administered in humans. John Graf and his colleagues at GE Global Research have used physiological-based pharmacokinetic modelling (PBPK) in combination with physics-based image simulators to assess feasibility of molecular imaging using PET in oncology, neurology, and cardiology [2-4]. The in-silico models and calculations they have generated have been used to assess the feasibility of imaging during the early research and preclinical stages. “We have learned that this model-driven approach focuses the project team on the clinical problem from a system perspective. In silico calculations can promote asking the right questions and making early decisions based on quantitative calculations rather than on speculative, and sometimes wishful thinking”. But the early detection of potential issues with a product is not always necessarily good news. Dr Graf comments: “unfortunately, many of proposed imaging targets and agents have flaws. It is not always easy for the computational biologist to be the bearer of bad news or to stop a project with strong support or too much momentum and investment. I wonder: does a company need to have a computational mind set in its leadership for an in silico paradigm shift to really take hold?”.


Scientific barriers, including how to employ Phase 2 trial results within the context of the clinical trial population. More specifically, they have been working continuously with selective entities which are not likely to meet that threshold. While many challenges still remain, their perspective is that the most difficult challenges to widespread adoption of in silico trial applications are rooted in the cultural state of the industry. [http://www.immunetics.com].

3.f.iii. Immunetrics: an ISCT company - Steve Chang, Immunetrics

Immunetrics is an in silico modelling company that builds predictive computer models based on the biological response to disease and intervention. With the expertise of biologists, mathematicians, and software engineers, Immunetrics employs their own powerful suite of modelling tools to predict clinical outcomes of therapeutic interventions in acute and chronic inflammatory diseases and autoimmunity at both individual patient and trial population scales. For over a decade, Immunetrics has been engaged in the endeavour of more than 20 in silico trial applications for large pharmaceutical companies across several different disease states. More specifically, they have been working continuously with select large Pharma for the past 8 years using bio-simulation to assist in actual trial designs that have been implemented. One of their most recent successes involved the FDA waiving the requirement of a second trial for one of their clients based on the simulation outcome in combination with statistical results. Building on years of experience, Immunetrics has worked out example solutions to a large number of technological and scientific barriers, including how to employ Phase 2 trial results within simulation models to predict whether the efficacy observed would translate successfully into Phase 3 trials, how best to power Phase 3 trials for a greater likelihood of success, and predict pre-trial novel entities which are not likely to meet that threshold. While many challenges still remain, their perspective is that the most difficult challenges to widespread adoption of in silico trial applications are rooted in the cultural state of the industry. [http://www.immunetics.com].

3.f.iv. Entelos’ in silico model predicted 2010 revision of NICE guidelines - A success story for in silico drug trials

In 2007, in silico studies done by Entelos, a leader in predictive biosimulation for pharmaceutical and consumer product R&D, predicted that Rituximab would be superior to anti-TNF in preventing bone erosion in patients with severe (but not moderate) disease. This recommendation was later confirmed by clinical research. This modelling insight predated a revision to the NICE guidelines for the use of Rituximab by several years. In 2010 NICE issued guidelines recommending that rituximab, adalimumab, etanercept, infliximab and (in certain circumstances) abatacept, be used as possible treatments for rheumatoid arthritis after treatment with a tumour necrosis factor (TNF) inhibitor has failed. Further, Rituximab (MabThera) in combination with methotrexate, was recommended as an option for the treatment of adults with severe active rheumatoid arthritis that has responded inadequately to other disease-modifying anti-rheumatic drugs (DMARDs), including treatment with at least one TNF inhibitor, or who are intolerant of other DMARDs. These guidelines are aligned with and were supported by insights derived from predictions of the Entelos model, made in 2007. The Entelos biosimulations showed that rituximab induces sustained benefits in joint structure; e.g., a decrease in the rate of cartilage degradation and bone erosion persists for months after cessation of treatment, even after joint inflammation returns. The success of Entelos’ in silico predictions suggests broad application in more efficient drug development and wide implications for the future of clinical trials.

http://www.nice.org.uk/guidance/ta195/resources/nice-recommends-treatments-for-rheumatoid-arthritis
http://www.entelos.com/


The physiologically-based pharmacokinetic-pharmacodynamic (PBPK/PD) modelling and software tool (BioDMET version 2) is available to the scientific community from the Amazon Cloud at http://pdsl.research.ge.com/. BioDMET was developed under a 4-year Defense Threat Reduction Agency (DTRA) contract to aid in the rational design of antibiotic and antiviral drugs [1,2]. The tool provides an end-user with the capability to rapidly setup a pathogen-infected host, calculate the bio-
distribution of an administered antimicrobial drug, and simulate the in vivo effect of the drug on the pathogen growth rate based on mathematical pharmacodynamic equations. BioDMET's PK/PD capability was demonstrated by testing the tool's ability to predict the in vivo pathogen load in a Staphylococcus aureus thigh infection mouse model across several classes of antibiotics. Under the DTRA contract, we also conducted extensive testing on BioDMET's pharmacokinetic predictions using a database of over 15,000 time-concentration measurements on small molecules, antibodies, peptides, and oligonucleotides compounds. This curated database derived from over 300 published scientific studies, represent 248 compounds and covers multiple species (human, monkey, rat, mouse, guinea pig), multiple tissues, and administration methods. The results of this testing was to reveal both the strengths and limitations of our tool in raw prediction accuracy. But the real challenge, comments John Graf “is to decide for each problem what good is good enough? In other words, what level of predictive accuracy is required for each problem? And how this relates to the confidence in in silico methods by the stakeholders?”.


3.3.vi. Computational models help to identify mechanism underlying IRESSA® sensitivity

It had been reported that gefitinib (IRESSA®)-responsive tumours in non-small cell lung cancer carried mutations in the EGF receptor ErbB1, and it had previously been observed that internalisation-deficient ErbB1 receptors are strong drivers of oncogenesis. Using a computational model of the ErbB1 trafficking and signalling network, Hendriks et al. [1] showed that a deficiency in receptor internalisation was sufficient to explain the observed signalling phenotype of these gefitinib-responsive ErbB1 mutants in lung cancer cell lines. The hypothesis generated by the mathematical modelling was supported by experimental studies that confirmed gefitinib-sensitive cell lines, with and without ErbB1, mutations exhibit markedly slower internalisation rates than gefitinib-insensitive cell lines. Additionally, the computational model demonstrated that reduced ErbB1 internalisation rates were mechanistically linked to upregulated AKT signalling. Experiments confirmed that impaired internalisation of ErbB1 was associated with increased AKT activity, which can be blocked by gefitinib. The combined experimental and computational approaches led to the conclusion that gefitinib sensitivity is a marker of a reliance on AKT signalling for cell survival that may be brought about by impaired ErbB1 receptor internalisation.


3.3.vii. Predictive biosimulation cuts time, cost and number of subjects in phase I

In a paper from Entelos Inc., describing the application of modelling and simulation during pharmaceutical clinical development phase, various case studies were presented from its use in translational medicine studies from animals to man, to optimisation of clinical trial protocols [1]. In this latter section, they highlight a study with Johnson & Johnson R&D on a first-in-class therapy for type-2 diabetes, with a novel mode of action that had yet to be tested in human subjects. The Entelos teams used their proprietary computer models for metabolism to simulate a typical phase I protocol, using all the relevant compound information to simulate oral glucose tolerance in healthy subjects following single ascending doses of the novel compound. Based on the outcome of the model predictions and in discussions with the clinical teams, a modified Phase I trial design was proposed and run, where four dosing arms were eliminated from the original protocol, substantially reducing the number of subjects recruited and cutting the duration of the trial from 14 to 8 weeks, with a consequent cost saving to the company. Additional information from these studies contributed to optimising PK/PD profiles for the backup compounds and identified biomarkers appropriate for use in subsequent phase II trials.

3.g. Acceptance of simulation

Where we describe how we can develop an informed trust in ISCT in the various stakeholders: executives of biomedical industries, product developers, clinical research organisations, research hospitals, medical professionals, patients, regulators, healthcare providers, healthcare payers, etc.

ISCT rely on computational modelling methods for the simulation of biological, physiological, and physical processes happening in the human body. Building trust in ISCT requires:

1. the development of standardized processes for code verification – are the equations being solved correctly? – i.e. to demonstrate that the implementation of the computational modelling and simulation methods, including the analysis and post-processing tools, is correct. Code verification must critically assess the suitability (accuracy and validity) of the code with regard to all features of relevance within the context of use, including, e.g., the modelling of material interfaces or boundary conditions. It is based on a comparison between computed results and known solutions.

2. the development of standardized processes for model validation – are the correct equations being solved? – i.e., to ascertain whether the model reliably reproduces the crucial behavior and quantities of interest within the intended context of use. Model validation is based on a comparison between simulation results and experimental data capturing critical behaviour with high fidelity. Model validation is only possible for a portion of the reality of interest for which experimental data can be gathered and extrapolation is necessary to go beyond this limited domain. Extrapolation remains reliable as long as the model remains credible for the context of use.

3. the generation of reference approaches on experimental and computational uncertainty assessment, which is necessary for evaluating the quality of the validation and ascertaining that the validated range adequately covers the context of use.

4. the adoption of a standardized documentation and reviewing procedure for verification and validation documents and for uncertainty assessments

5. the adoption by the R&D community, including executives of biomedical industries, product developers, and clinical research organizations, of official verification and validation standards that have been reviewed and accepted by the regulators and the health care providers

6. the availability of realistic and illustrative verification benchmark examples that medical professionals and patients can understand

7. the availability of verified simulation platforms that are designed for life science applications and have been validated for specific applications.

3.h. Socio-economic issues

Where we describe other issues related to ISCT, including the ethical imperative/patient safety issues driving in-silico medicine, the benefits (and potential costs) for individuals, society, industry, exploitation issues, policy and regulatory issues, etc.

3.h.i. A broken model?

Though scientific breakthroughs in the biomedical sector are clearing the way for revolutionary applications, the image that some observers project of the state of health of the pharmaceutical industry is highly critical. Let’s take Eric Topol9 for one.

Sure – he says – the pharmaceutical sector is the biggest component of the life science industry, which includes biotechnology, medical devices, and diagnostics. Still, “if there was ever an industry in peril, this is it. It faces a triple whammy—research and development costs have increased from $15

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billion in 1995 to $85 billion in 2010; the number of new prescription medications (known as new molecular entities) approved per year by the food and Drug Administration (FDA) has fallen from fifty-six in 1996 to about twenty in each of the past few years (including twenty-one in 2010); and the ‘patent cliff’ of lost revenue as a result of branded drugs going generic is $267 billion through 2016, with $52 billion in 2011 alone. […] The pharmaceutical industry, once considered the ultimate blue chip and extraordinarily profitable, has gone from a blockbuster to a busted model. […] In the fifteen-year period from 1995 to 2010, the approximate expenditure for a newly approved drug for the overall industry went from $250 million to over $4 billion, a sixteen-fold increase. […] Rather than innovate, at least in the short term, the industry has been going into consolidation […]. Furthermore the big pharmaceutical companies have been buying up large biotechnology companies […]. These companies have also been buying up generic manufacturers, once their dreaded competitors […]. Where is the innovation to develop exciting new drugs and confront the real challenges of public health?¹⁰

If we turn to the Official Sector Inquiry¹¹, published in 2009 by the European Commission (DG Competition), the pharmaceutical sector was shown to be vital to the health of Europe's citizens and medicines to be a major expense, nearing 2% of the EU GDP, and around €500 per year for every man, woman and child, not mentioning Europe's ageing population, with its likely subsequent increase in pharmaceutical costs due to an increased chronic disease burden. The same could be said of medical devices sector, where the European medical technology industry generates annual sales of roughly € 100 billion, invests some € 4 billion per year in R&D and employs around 575,000 highly skilled workers.

Both sectors occupy therefore important positions in the EU economy: pharma on its own accounts for 600,000 jobs and for some 4% of total manufacturing value added. This share is much higher in some Member States, such as Belgium, Denmark, Sweden and Slovenia, reaching between 8.5 and 10% of manufacturing value added. Together, the pharmaceutical and the medical devices sectors account for some 4% of total manufacturing employment in the EU.

As a natural complement to the Sector Inquiry – which had the aim “to examine the reasons for observed delays in the entry of generic medicines to the market and the apparent decline in innovation as measured by the number of new medicines coming to the market”, a subsequent study on the EU market and industry for pharmaceuticals had the objective of providing: “a comprehensive, comparative, and macro-level analysis of the relationships between the economic performance of the pharmaceutical industry in Europe i.e. its potential for investment, economic growth, development, and employment on the one side and external factors, in particular externalities induced by European public/governmental bodies which affect this industry on the other side”.

3.ii. Assessing competition

In this context, competition in the pharmaceutical sector has been analysed on two different grounds. On one hand, dynamic or non-price competition among so-called originators, competing in R&D of new drugs; on the other hand, static or price competition between originators and generic companies, which, as soon as the originator product encounters loss of exclusivity, enter the market with a medicine that is equivalent - in terms of efficacy, safety, and quality - to the original, and sell their product at a much lower price than the original, enhancing access to affordable treatments. Originator companies carry out research into new pharmaceuticals, develop them from the laboratory to marketing authorisation and sell them on the market. These companies can range from very large multinationals to SMEs concentrating on certain niche products. Their products are largely patent-protected.

¹⁰ E. Topol, cit., pp. 196-198.
¹¹ A sector inquiry, as per Article 17 of Regulation 1/2003 on the application of the EC Treaty competition rules (Articles 81 and 82), is the tool the European Commission makes use of when there is ground for suspecting a potential systemic problem in a specific industry. Such inquiries are the regular “upstream” approach in any specific case where an antitrust proceeding may or may not follow.
Generic companies active on the European market tend to be significantly smaller than originator companies. The use of generic medicines has been increasing worldwide and is being promoted through government policies worldwide. Generic penetration is more successful in countries that permit (relatively) free pricing of medicines (e.g. Germany, the Netherlands and the UK) than in countries that have more strict pricing regulation (e.g. Austria, Belgium, France, Italy, Portugal, Spain). This is because in these countries, medicine prices are generally higher, thus providing greater incentive to generic medicines companies to enter these markets. In regulated markets, by contrast, price regulation lowers the originator price over the life cycle of medicines, lowering the potential profit margin for a generic medicine company, discouraging their market entry.

According to the European Generic Medicines Association (EGA) generic products sell at a 20-90% price differential to the off-patent brand product, generating €25 billion in drug cost savings each year for the European health care systems.

Table 3

3.h.iii. Europe Pharmaceutical Exports
The EC 2009 sector inquiry found that in Europe there was a comparatively low level of innovation by originators and a slowing down of the entry of generic drugs. However, it was remarked that although the US is a major producer of pharmaceutical products, its exports are relatively limited compared to the EU, which is clearly the largest exporter. Within the EU, Germany, Belgium, the United Kingdom and France are the largest exporters and overall Germany, Belgium and Switzerland and each export more pharmaceuticals than the US. The market shares in world trade confirm the important role of the EU in pharmaceutical trade, accounting for about 70% of world exports and almost 60% of world imports in 2007.

Strikingly, the pharmaceutical sector is the EU high-tech sector, which has experienced by far the highest increase of real business R&D expenditure over the past decade. The sector also shows the second highest increase in real value added among all sectors considered. Furthermore, since the business expenditure on research and development increase was twice as high as the increase in value added, the pharmaceutical sector is the high-tech sector in the EU which recorded the fastest growing R&D-intensity.

There were 4 EU-based pharmaceutical companies in the world’s top 50 R&D companies based on their total R&D investment: Sanofi Aventis (France, place 12), Glaxo Smith Klein (UK, place 20), AstraZeneca (UK, place 23), and Boerhringer Ingelheim (Germany, place 49), and 2 Swiss companies, Roche (Switzerland, place 4) and Novartis (Switzerland, place 10). However, most of the largest R&D pharmaceutical companies had their headquarters in the US.

3.h.iv. Pharmaceutical innovation – less for more

Despite the increase in R&D intensity in the EU, the success rate of innovation seems to have declined. The rising R&D costs, partially explaining the increased R&D intensity, result from the fact that many of the “easy” inventions have already been made making current clinical development more complex; and also that regulatory requirements (e.g. on clinical trials) have become stricter and differ by country, which makes testing more expensive. Regarding the decreasing success rate of innovation, the pharmaceutical industry is currently investing twice as much as it was a decade ago but achieving only some 40% of the previous number of new medicines launches.

R&D outputs have lowered in recent years inter alia due to launch delays and non-approvals. With regard to the low level of innovation, the inquiry ascertained an extensive recourse to "defensive patent strategies" which interfere with the development of competing medicines precisely by focusing on patents, which are aimed at excluding competitors without really pursuing innovative efforts.

The sector inquiry also found that originator companies use a variety of strategies and instruments to maintain revenue streams from their medicines, in particular blockbusters, for as long as possible. These practices delay generic entry and lead to healthcare systems and consumers paying more than they would otherwise have done for medicines. Also some patent settlements in the pharmaceutical sector may prove to be problematic from a competition law perspective, such as settlements that lead to a delay of generic entry in return for a value transfer (e.g. a payment) by the originator company to the generic company.

One increasingly common practice has become the introduction of a generic version of the original drug prior to the loss of exclusivity – expiry of patent or supplementary protection certificate (SPC) –, either through a subsidiary or licensee/supply partner (early entry).

In order to identify which settlements delay generic market entry to the detriment of the European consumer possibly in violation of European competition law, four rounds of monitoring, conducted annually from 2010 to 2013, have followed-up to the initial inquiry.

The blockbuster-model appeared to be under pressure. Despite the huge amount spent on R&D, the big pharmaceutical companies appear to be failing to develop new ‘blockbusters’. Leading pharmaceutical companies have increasingly being making (biotech) acquisitions in order to refill their product pipelines. Acquisitions are often the result of earlier alliances (joint ventures) between big pharmaceutical companies and smaller companies. For a lot of smaller companies, acquisition is the (only) way to bring their product to the market, because they lack funds and market expertise. Selling the company (or product) appeared also as a way to realise previous investments and efforts as cash.
For smaller pharmaceutical firms licensing and cross-marketing alliances with Big Pharma represent their most probable exit strategy for their initial investment.

Integrated Big Pharma companies remain at the top of this chain because of their unchallenged superiority in running clinical trials and regulation issues. However, these firms are increasingly acting as receivers, rather than originators, of new drug candidates (NDCs). Potential NDCs (especially those with early-stage clinical data) come from a variety of sources, but increasingly this niche is being satisfied by “Small Pharma”, corporate organizations that employ from 25 to 500 employees. A role for “micropharma” has also been observed, mainly in combining the academic knowledge with a more business oriented approach.

In conclusion, the European pharmaceutical market can be considered as characterised by the dominance of a relatively small group of big pharmaceutical companies, which represent a significant part of the annual European turnover. Past experience shows, however, that mergers and acquisition have rarely produced significant advances in innovation or research productivity. The relevant question is therefore whether such a relatively concentrated European biopharmaceutical industry will be open to the potentially disruptive competition which could ensue from the spreading of in silico drug development and in silico clinical trials.

3.h.v. ISCT – a new context

A majority of the stakeholders involved in the first 3 Avicenna Events posited that ISCT leads mainly to contextual changes, determining the entrance of a number of new entities in the market, like more specialised CROs, new diagnostic modelling research centres, new apps for personalised medicine, rather than to changes of business models. In this sense they have deemed that at least in the short to medium term ISCT is going to be a sustaining component of the pharmaceutical and biomedical industry, rather than a disruptive one.

This assumption needs to be carefully framed within the current economic phase.

Healthcare should by definition be a non-cyclical area of economic activity, and the increasing need for better treatment should in principle also translate into a steadily growing demand for constantly improved drugs and medical devices.

Paradoxically, however, as we have seen, the pharma sector is struggling with increasing challenges with regard to R&D expenditure, time to market, regulatory barriers, patent expiring of major blockbuster drugs, and reductions in the number of R&D personnel.

According to a GBI research report, despite efforts made by pharmaceutical firms to cut down on costs, R&D expenditure expanded at a Compound Annual Growth Rate (CAGR) of 6% from 2000 to 2011. Conversely, the number of new molecular entities (NME) approved during the same period dropped on average, decreasing at a CAGR of 1%.

If before the recent wave of austerity measures drug companies faced relatively low resistance from European governments when they were setting prices and introducing products, the ongoing EU pressure for budget cuts is affecting also healthcare, showing an increasing willingness of many European governments to exert as much as possible their monopsony buying power in order to reduce the required expenditure for pharmaceuticals and medical devices.

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12 From 1999 to 2008 the market share in turnover of the bigger pharmaceutical firms (> 250 employees) had increased from 78% to 82%, while the other categories had seen a decrease: ECORYS, Competitiveness of the EU Market and Industry for Pharmaceuticals, Final report, Vol. 1, Rotterdam, December 2009, p. 29.
15 A monopsony is a monopoly operating from the side of demand.
Spending on healthcare in Europe has in fact constantly grown more rapidly than the economy, even before the post 2008 downturn. Difficult as it may be to assess directly the impact of technological change on healthcare spending, the promise of personalised medicine to “reverse the ever escalating costs of healthcare – introducing diagnosis to stratify patients and disease, less expensive approaches to drug discovery, preventive medicine and wellness, and exponentially cost-decreasing measurement technologies”\(^\text{16}\).

The European Commission had rightly assumed that new technologies would have “the potential to revolutionise healthcare and health systems and to contribute to their future sustainability”\(^\text{17}\), even though this assumption contrasted with a generalised belief that healthcare expenditure were necessarily increasing faster than incomes and that new technology were a cost driver\(^\text{18}\).

ISCT can represent a fundamental element in making the EC forecast prove true. It may even be said that the necessary conjunction of sustainable healthcare expenditure and universal affordable care provision will only be ensured if in silico medicine can become the trigger for the transformation of the entire healthcare system and biomedical industry as an overarching aim of the EU: “The sustainability of healthcare systems is becoming the number one issue in a number of member states …, [where] some common requirements are emerging, [i.e.] to maximise the yield of biomedical research expenditure; to achieve personalised healthcare for individuals and groups (women, children, etc.); to improve the reliability, repeatability, and the timeliness of medical decisions; to integrate digital health information on a global scale”\(^\text{19}\).

As euro zone countries lower the prices they pay for drugs, the European market is also feeling the effects of cross-referencing by governments, looking to drug prices in other countries to help determine what they accept to pay.

While general financial conditions are highlighting and accelerating the need to demonstrate value for medicines, pharma price reductions in Europe can have a ripple effect, since profits from sales in emerging markets may fall as well, because governments in emerging markets refer to the prices set in Europe to determine their own.

Notwithstanding all this, one may question what impact will ISCT exert in a context where, as we have seen, the pharmaceutical is currently characterised by substantial problems related to a failure of competition, which is linked to the existence of barriers to entry.

3.h.vi. **Barriers to entry**

We know that, like in many other industries, any new entrant into the pharmaceutical sector is faced with various “hurdles” that have been previously erected by already established businesses and by national and European standards and regulations. These include, but are not limited to:

- economies of scale - manufacturing, R&D, marketing, sales
- distribution product differentiation - established products, brands and relationships
- capital requirements and financial resources
- access to distribution channels: preferred arrangements
- regulatory policy: patents, regulatory standards
- switching costs - employee retraining, new equipment, technical assistance

Barriers to entry are particularly high in the pharmaceutical industry. Of course, many of the top firms have manufacturing capabilities that are hard (and extremely costly) to replicate. Also, they have


\(^{18}\) CBO, Technological Change and the Growth of Health Care Spending, January 31, 2008.

extensive patents that guarantee the protection of their products while they defend their brands with large marketing budgets.

New medicines are often very expensive, and this may cause market access problems as long as they are not inserted in the welfare or insurance reimbursement lists.

Copying with this, innovative approaches have been introduced, based on “performance-based” agreements and “pay-back” schemes.

Beyond the role of economies of scale and scope as well as of sunk costs of investments and reputation effects, incumbent producers usually tend to create artificial barriers to entry by having recourse to brand loyalty, market segmentation, cross-subsidisation and vertical foreclosure conditional schemes, not to mention strategic uses of advertising and marketing.

3.h.vii. Legal barriers and the patent-based IPR system

On top of these elements, there are however also the legal barriers: patents and market authorisation, and related to that, the approval costs.

Traditionally, it was given for granted that the present IP system is the only mechanism that can ensure the continuity of the flow of pharmaceutical innovations in the future. Recent economic literature has however shown growing criticism of pharmaceutical patents. Some have indicated an alternative approach where the economically efficient solution would consist in two-part pricing: a flat charge for access plus a variable charge that depends on level of usage.

In fact, it has been argued, pharma companies have two distinct outcomes but only one instrument for pricing them. They develop new products and they manufacture the actual drugs consumed by individual patients, but they can price only the latter. The patent system is the root problem. It encourages innovation by granting a monopoly and then allowing the owner to set prices for the resulting product. Thus the only way that R&D, including clinical testing, costs can be covered is through high prices for the resulting drugs.

When R&D costs are small, there is no serious problem. But when R&D costs are very large relative to production costs, as is precisely the case for pharmaceuticals, using price for drugs as the only mechanism for rewarding the product developer drives prices upward, and far higher than is economically efficient.

The solution, of introducing two prices, one for the R&D, another for the resulting drugs, would admittedly be “not painless, but neither is the course that public policy is now on.”

3.h.viii. Two distinct prices?

The proposed plan would have two components. First, massive awards would be made to the developers of safe and effective new patented pharmaceuticals. In effect, appropriate public authorities would purchase drug patents; developers of successful new drugs would be rewarded for successful R&D. Second, use of the patents would be freely offered to any firms wishing to produce the pills. This would ensure active competition among generic producers and low prices, as competition forced prices down toward their low marginal production cost.

The two elements of the process, R&D and drugs production, would be separated: “consumers would get low prices, and innovators would get financial awards.”

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22 B. Weisbrod,cit.

23 Ibid.
Could this be an avenue for a faster introduction of ISCT?

3.h.ix. Transparency of information

Another interesting element of analysis is determined by the drive to improve the transparency of information on efficacy and safety of medicines, allowing regulators and users to assess the existence and magnitude of the therapeutic added-value of a new product.

In the past it has been customary that companies would not report all the clinical trials of a given drug, but predominantly only those that would give favourable results for the new product.24

Now, the biopharmaceutical industry is officially committed to sharing with qualified medical and scientific researchers patient-level data, study level data, and clinical study designs and protocols.25

Given the concern that the data requestor could intend to use the company’s patient-level data or other information to help gain approval of a potentially competing medicine, EPFIA has stated that “while companies may enter into agreements to co-develop medical products, these data sharing Principles are not intended to allow free-riding or degradation of incentives for companies to invest in biomedical research.”26

Their chosen approach has been therefore that “in order to maintain incentives for future investment in biomedical research, individual companies may choose at their discretion to withhold from public access to CSRs various business and analytical methods; manufacturing and pre-clinical information or other confidential commercial information; any information not directly related to the conduct of the study or that could jeopardize intellectual property rights; or information that the company has no legal right to share (e.g., due to an existing co-development agreement)”27.

Of course, ISCT can potentially have a huge impact on transparency issues, given its very nature of wholly digitised process.

3.h.x. The long tail

*In silico* technology can also be used to understand more about the study population; particularly to distinguish between potential responders and non-responders to a drug. This information can then be used to reassess the study inclusion and exclusion criteria, identifying, through appropriate simulations, which patients may experience adverse events.

With drugs being targeted to specific populations, one can imagine the importance of in silico modelling increasing and becoming more widely accepted. In fact, the main concern surrounding in the past targeted medicine has been the cost. How can an appropriate return on investment be made when the market is limited?

As the virtual patient model becomes increasingly validated for specific disease areas, can it increasingly replace biomarker-based stratification, tremendously simplifying the approval of drugs for molecularly defined patient subgroups?

The 80/20 mathematical formula, introduced in 1906 by the Italian economist Vilfredo Pareto to describe the unequal distribution of wealth, has long been a recurrent mantra in organization studies. The so-called Pareto’s Principle, or 80/20 Rule, stated that 20 percent of something would normally be responsible for 80 percent of the results.

A few years ago a paper in economics,28 started to revert the traditional 80/20 approach, following the innovative insight of Chris Anderson’s *The Long Tail*, and the concept that, when transaction costs are

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26 Ibid.
27 Ibid.
greatly lowered, “the biggest money is in the smallest sales”\textsuperscript{29}, whereby a series of small niches cumulatively achieve a much larger amount than the traditional focus on selling the preferred 20% of the items.

Internet has dramatically changed business, because it has infinite shelf space. The long tail has been extremely lengthened, and consumer can really find and choose what they want. With the blockbuster industry of music, for instance, about 40% of the market was not seen.

Blockbusters are now Niche Busters. One size doesn’t fit all, and while niches hadn’t been economic in the past, they can better fulfil the market.

3.h.xi. Is the era of blockbuster brands in pharma a thing of the past?

Can the Long Tail insight also be applied to the area of pharma business, and specifically of drug discovery, if the implied transaction and processing costs are considered, and if clinical trials can be focused on specific cohorts of virtual patients for personalised drugs?

We’re seeing signs of life on the long tail in some ways, with futuristic predictions of people receiving drugs specifically targeted to their own DNA (pharmacogenetics). When you can tailor content (drugs) to everyone’s individual needs (DNA), that’s precisely what the long tail’s all about. Additionally, the long tail means all those diseases and ailments suffered from a relatively small number of people or by a large number of people who are being underserviced.

Without a regulatory update, personalized stem cell therapies, gene therapies, and customized drugs risk to be commercial failures, crushed by the huge costs of antiquated regulatory systems.

ISCT can bring about long-tail medicine, i.e. also drugs with enhanced personalised information content, based on customized algorithms tackling the individual disease conditions which can best cured only by personalised treatment.

3.h.xii. Orphan drugs

There are traditional “orphan” diseases, which affect fewer than 200,000 people in the US or in the EU each year. Because of their low prevalence, little direct investment has been made by NIH or industry in research to understand them or to develop new treatments for them.

These developments will reduce risks for patients participating in clinical trials, reduce the likelihood of detrimental effects on specific subpopulations of patients, and reduce the number of clinical trial participants to achieve statistical significance, markedly reducing time and cost of drug development.

The biopharmaceutical industry has long focused on the one size fits all approach, but one size medicines do not fit all patients, and the same is true of the R&D process. The limitations of this approach—on which the industry has relied for many years — have become increasingly clear.

Data sets from a sub-population or from longitudinal clinical data have the potential to expedite the development of targeted therapies in terms of both patient population and disease.

3.i. Ethical issues

\textless TO BE DONE\textgreater

\textsuperscript{29} C. Anderson, \textit{The Long Tail}, 2006
4. The Prerequisites for ISCT

4.a. Digital Repositories

<TO BE DONE>

4.b. Virtual Patients

<TO BE DONE>

4.c. Simulation Platforms

<TO BE DONE>

4.d. Product Prototypes

<TO BE DONE>

4.e. Education and training

4.e.i. Educating clinicians and medical students

<TO BE DONE>

4.e.ii. Providing appropriately trained software and modelling engineers

<TO BE DONE>

4.f. The bigger picture

The focus of the Avicenna roadmap is the use of in silico medicine technologies in the development and assessment of traditional biomedical products, such as pharmaceuticals, medical devices, etc. But how in silico clinical trials relate with the other ideas that represent the future of healthcare?

4.f.i. From In silico Clinical Trials to In silico Medicine
As we started to poll our industrial experts, it became evident that the narrow scope that we gave to this exercise does not reflect the perception of many industrial players. While there is a considerable interest in exploring how in silico technologies can improve the development process of biomedical products, there is an equally large interest in understanding how in silico technologies can become themselves radically innovative products, alone or in combination with other technologies. Some examples that emerged during our consensus process were: patient-specific, simulation-assisted surgical planning; imaging systems with embedded simulation capabilities; patient-specific models to tune complex medical devices such as ventricular assistive devices; devices with embedded in silico technologies, such as implantable drug delivery systems for artificial pancreas applications. So while ISCT is a good starting point, the pre-competitive alliance should target in silico medicine in a broader sense.

4.f.ii. **3D organ printing and synthetic biology**

A number of synthesis technologies, which allow the fabrication of complex systems with very level of control, are being explored in the context of biomedical applications. ISCT is the backbone of these futuristic ideas: if 3D printing can print a heart, ISM can design it.

4.f.iii. **Organ-on-chip**

A number of tissue engineering technologies are now being exploited not with a regenerative medicine perspective but in order to realised in vitro systems that combine the level of control of an in vitro experiment, to a much higher level of “realism”, in relation the interaction between fluids, cells, and tissues. These complex biological devices are being using for example to screen large numbers of candidate compounds in contexts where the mechanisms emerge from the systemic interaction of different cell types, tissues, and transport mechanisms. ISCT models can be validated using organ-on-chip set-ups, as the very high controllability of these experiments ensure a solid validation framework; organ-on-chip results can be then generalised using ISCT models, where the generalisation to a whole organ, and to its interaction with other organs or the whole organisms would become prohibitively complex to model physically.

4.f.iv. **The digital mouse**

ISCT entertain a similar relationship with animal models, and their digital counterparts. Animal models can be used to validate ISCT models; ISCT models can help to reduce, refine and partially replace animal models. In addition, ISCT can be used to better “translate” observations form the animal model to the human target.

4.f.v. **Big data analytics in Healthcare**

A recent paper has identified an interesting potential relationship between big data analytics and VPH models, in spite one would tend to see them somehow opposite in their intent (the first focused on predicting from the data, the other to use knowledge). The need for a continuum range of options from purely phenomenological to purely mechanistic; the need to account for the “physiological envelope”. These and other are relevant points of contact.

4.f.vi. **System biology**

Is systems biology part of in silico medicine? It depends. The very popular single cell, only chemistry, molecular system biology, where very complex pathways are described with limited or absent notion of time and/or space, simply as statistical correlations between the appearance of chemical species inside the cell, is definitely not part of in silico medicine. The other one, which is still described more frequently in vision papers that in research papers, which attempt to provide largely mechanistic quantitative models for complex biochemical and biophysical processes, described over space, time...
and across scales from the molecular scale to the whole organism scale, that systems biology, is another name for in silico medicine.
5. The research and development roadmap

5.a. What to do: R&D needs from a products perspective

Where we identify the RTD priorities for the various types of biomedical products.

In pharmacology research the process of transforming PKPD into mechanistic modelling started with PBPK needs to be extended to a complete “systems pharmacology” where mechanistic models are used where mechanistic knowledge is available.

There is a partition between:
1) physics-based, physiology based, heavily mechanistic models to describe organisms, organ and tissue behaviour;
2) biology-based, chemistry-based heavily phenomenological models to describe single cells or intracellular processes;
3) physics-chemistry based, heavily mechanistic models to describe molecular processes such as docking, protein folding, etc.

Because these partitions also imply a significant cultural and epistemological gap among experts, models that bridge the cell-tissue gap, and the molecule-pathway gaps are the most difficult to address; dedicated funding should target the development of such models by heavily interdisciplinary consortia.

The need for sharing data and models in order to ensure a faster development of the field is a recurring theme. But, considering this has been said and tried many times without much success, we need to explore the roots of the problem, and develop sharing mechanisms based on business models that effectively motivates data producers and data consumers to proceed in this direction.

The definition of the life-style related physiological envelope for a number of aspects (loading spectrum over a joint replacement, alcohol intake during the day for drug) is a grand challenge of ISCT. For those physiological envelopes that are most relevant for the development of biomedical products, we need to conduct systematic data collection campaigns. It is also necessary to establish sensitivity analysis frameworks under which it is possible, case-by-case to decide which of the patient-specific determinants (genotype, phenotype, life style, environmental factors, clinical history, etc.) needs to be taken into account individually or as stochastic envelope of possible values.

The physical behaviour of biological and advanced artificial materials can be modelled accurately at the continuum scale only if appropriate constitutive equations are developed for the most complex materials.

The separation between data-driven and mechanistic models is currently too rigid. There are a number of situations where we need a more flexible approach:
- Estimation of life-style related physiological envelops, which are difficult or impossible to measure directly;
- Clinical data incomplete or inaccurate enough to prevent a valid input for the mechanistic model;
- Run-time re-designs due to unexpected stratifications in the clinical trial cohort, which would require a redesign of the mechanistic model.

In all these cases a combination of data-driven models and physiology-based models would provide a much higher flexibility, and the ability to cope with whatever observational data, and theoretical knowledge.

The validation of ISCT models poses relevant theoretical problems. However, these have been recently framed into specialised publications (Chapter 12 in recent VPH textbook\(^{30}\)) and a

standardisation committee (ASME V&V-40 verification and validation in computational modeling of medical devices) is currently working on some codified guidelines. What is really missing are the benchmark data that can be used at each stage of the process for the most common types of model, and some specific guidelines for aspects such as assessment of reproducibility.

Specific research should be conducted on how ISCT can be helpful in facing the 1st in class vs. best in class conceptual challenge. When a radically new product is proposed, there is no frame of reference to define the possible failure modes, and thus design the appropriate assessment protocol. Can ISCT be used intelligently to reduce the risk that is implied by such radical innovation?

5.b. How to check it: R&D needs from a regulatory perspective
Where we identify the RTD priorities toward reliability.

<TO BE DONE>

5.c. How to do it: R&D needs from a technology providers perspective
Where we identify the RTD priorities in terms of technological development.

We need specialised technologies for knowledge management that automate the annotation of predictive models with all published knowledge that was used to build them, as well as with all that reinforce the credibility of the model. Semantic composition of data and models would help considerably in reducing the complexity of very large problems. However, while the reasoning mechanisms currently available can be quite sophisticated, manual curation remains the true barrier: very little is available for the automated annotation of data and models. Specific technological development should be funded to obtain widely available tools that take existing collections of data and models, semi-automatically annotate them, and expose them so that they can be composed semantically. The usage of standardised model description languages such as CellML or SBML is an organic element of this challenge: for difficult modelling categories like PDE, where the community is struggling to develop such model description languages, higher-level semantic descriptions via standardised ontologies should be explored as an alternative approach to simplify standardisation, interoperability and sharing.

Clinical Decision-Support Systems need to be re-designed to include / wrap predictive models in order to transform a predictor into support for decision making, both in the clinical practice and in the product development pipeline. It is also necessary to explore if and how CDSS can be used also to improve the communication between ISCT specialists and clinical and industrial specialists.

For surgically deployed devices, develop simulation-based design tools better integrated with surgical simulation tools, so as to be able to investigate also the deployment aspects early in the design phase, and to compare better with existing products. More in general, technologies must be developed to provide interactive design, where the simulation is optimised to the point that it can be run in real-time within an interactive session.

Specific regulatory research is required. We need solid criteria to define how an in silico cohort is robustly designed, and how it relates to the real one. Under which conditions a real clinical trial can be reduced in size/duration, refined, or partially replaced with an in silico clinical trial? It is necessary to fund the development of modelling challenges, cases for which all the input data and the true values to be predicted are accurately measured, and all modellers compete to best predict those cases, against measured true values. These challenges could evolve into regulatory tools where before being certified a simulation tool must be scored against some certified challenges. Similarly, we need to fund the development of experimental techniques that allow measuring physiological and biological properties over space, time, and across scale, possibly in relation to specific predictive model that

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31 https://cstools.asme.org/csconnect/CommitteePages.cfm?Committee=100108782
complement/supplement the experiment, in order to produce much more robust evidence for pre-clinical validation.

There are two broad categories of demonstrators that we need to develop: one that targets the development phase (design/discovery, pre-clinical assessment), the other that targets the clinical assessment, and that might see clinicians as end users. These prototypes need to be extensively tested and revised before deployment, to avoid the negative effect of pushing immature technologies into use.

We need to develop proof of concept demonstrators for digital repositories where disease and intervention models could be developed and exposed, and where guided ISCT, designed following best practices and the regulatory requirements, could be developed for a given product and over a set of patient-specific data representing a cohort.

Another proof of concept demonstrator worth to develop is a simulation environment at variable accuracy. These are stacks of multiple models, all solving the same problem but with progressively reduced complexity (and thus progressively reduced accuracy), that are exposed to the user as a single model that can be run very quickly to get a crude estimate, or more slowly to get more accurate predictions.

5.d. Who will do it: education and workforce

Where we identify the training and re-training needs that ISCT involves.

Currently multiple groups with distinct but complementary interests and perspectives perform ISCT work, focusing on specific areas of research or product development. Inefficient integration of these diverse competencies and capabilities limits progress towards the goal of widely accepted and understood ISCT. There is an epistemological divide between physics-based and biology-based disciplines. On one side there are physiologists, bioengineers, computer scientists, applied mathematicians and biochemists; on the other biologists, geneticists, pharmacologists, epidemiologists and statisticians. The first respect deduction from theories, the second induction from data. In the middle, there is a cultural vacuum, which needs to be bridged with events and research funding targeting this interface (which typically manifest at the cell-cell or cell-tissue interaction scales).

A paradigm shift at this point in time can fill this void, revolutionizing the way we train our workforce and what that workforce can accomplish.

Recognizing that all of the interests are complementary, the new workforce must be equipped with tools to broaden their perspectives outside of their speciality to understand better their contribution to the entire process. Moreover, this will enable all of the players to more effectively understand and utilize the contributions of others. To an extent, these tools are specific to an individual's discipline. For example, clinical training should receive a robust injection of quantitative thinking and deductive epistemology. Basic scientists and engineers need to understand biological and clinical relevance. Other tools are common to all groups, such as the need for a much stronger “systems thinking” perspective. Also it is important to find a balance between specialist and interdisciplinary training; the former should focus on deep knowledge the latter on transferable skills.

Most critically, the new worker must have an expanded set of communication skills. There is the need for a layperson narrative of modelling, and of the differences between phenomenological and mechanistic modelling, but there is also a need for specialists trained in multiple disciplines to integrate the process. A common need for all groups is better communication skills for stakeholders, with these groups making efforts to understand work by other groups. Based on their training, members of the workforce have their own vocabulary, which can limit interactions between all of the stakeholders. There is a suggestion to develop a common vocabulary, however this effort is time consuming and should develop organically from improved communication and collaboration between all parties. Improvement in communication should start with the support of the internal evangelists toward the top management. Shared resources should be compiled to make this easier, such as a list of common objections to ISCT and appropriate answers with strong examples, to “de-fear” the investment in ISCT. A portfolio of well-documented success stories is essential in this regard.
5.e. How to say it: Policy & communication

Where we discuss how ISCT should be disseminated.

Both “In Silico Clinical Trials” and “Virtual Physiological Human” terms have been questioned on the ground that they can convey the wrong message. The VPH name in particular has been accused of suggesting the aim to create a model of a whole human body accounting for every single process. This is like accusing physics of trying to build a theory of all manifestations of the reality. It betrays the big cultural gap there is within this emerging community between who work only on observations, using statistics or qualitative deduction, vs. those who approach biomedicine with quantitative measurements and aim to establish mechanistic knowledge. Rather than debate on the names we give to new concepts, we better work on providing rigorous, well thought, well expressed definitions for these terms, and promote interdisciplinary communication. It is also essential to promote a counter-disinformation campaign that aims to picture the VPH like an abstract exercise aimed to model “life” as a whole, rather then targeting specific clinical problems. A recent CASyM (Coordinating Action Systems Medicine) paper\textsuperscript{32} suggests this explicitly; we need to react.

There is a strong signal coming from the industry experts that the partitioning of in silico medicine into VPH = patient-specific modelling for diagnosis and treatment planning and ISCT = patient-specific modelling for product development may create artificial barriers. There is a continuum of cases between where the patient-specific model is the device (all VPH applications), is inside the device (on board simulation software in artificial pancreas, defibrillators, etc.), or is used to design the device. \textbf{We should probably pursue \textit{in silico} medicine as a whole, rather than ISCT specifically.}

Research assessment metrics should not stifle collaborative work among academic institutions around industry-driven large-scale projects. In some systems, such as last UK REF, while “impact” is being more and more recognised as a vital output for academia, the metrics was designed for single centres exploitation, not promoting collaborative approaches.

Consider the creation of “modellathon” events where modelling specialists present in great detail the models they developed to successfully solve given problems, and they do quick and dirty development of new models to try solving difficult new problems posed by industrial experts.

ISCT should be positioned so that i) its success is measured by the improvement in the throughput time (total time from conception to market) while keeping the level of safety at least as good as with the current process and ii) ISCT-developed new products are at least as safe and as effective as those already available.

6. Recommendations

Where we make specific recommendations toward the creation of an alliance, toward the orientation of public research funding toward specific objectives, toward the revision of regulatory processes that are required for an effective adoption of ISCT.

<TO BE DONE>