In silico Clinical Trials: A New Dawn in Biomedical Research?

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ABSTRACT

Nowadays, scientific knowledge seems to be increasingly generated using technological methods, but also governed by technological demands and conducted by new technical ways of learning. In this paper I will analyze an effective example of this new trend in biomedical research: the Avicenna project and its "roadmap for clinical trials". My aim is to understand what philosophical issues it arises and whether and to what extent this document provides effective responses and solutions to make its innovative challenges a concrete reality.

keywords: in silico clinical trials, embodied subjectivity, scientific knowledge.

1. Introduction

Nowadays, we are witnessing a rapid evolution of the organization and funding of scientific research. To explore nature beyond what is known, to acquire new knowledge, and to drive innovation, the adoption and development of new technologies seems to be a key factor. Furthermore, with the rapid changes in today's society, companies need innovative technology to respond dynamically to new challenges and so to stay competitive and grow. But, if such an environment seems to be very fertile in generating new and unexpected developments, acting as a motor of ideas, it is also astonishing because it is transforming the way we do science. The chain 'research-technology-innovation' is reversing its trend into 'technology-research-innovation': not only scientific knowledge seems to be more and more generated by using

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technological methods; it also seems governed by technological demands and conducted by new technical ways of learning.

IT are considered as crucial to the development of science, as they enable to progress faster, to 'think big' and above all to decrease costs. So, changing the way by which experiments are performed, information technologies promise to work beyond human capabilities transferring a huge amount of data to electronic digital systems. According to computer scientist Paolo Zanella, "the message is that Big Data involving billions of physics events require automatic processing. Human intervention has to be minimal. All that can be done automatically is left to computers that are an essential part of the analysis chain" (Zanella, 2014, p. 164). In this reading, bioinformatics will shape the future of the life sciences and digitization will become the key factor of biomedical research. The penetration of information technology in healthcare is a pervasive reality through medical informatics, bioinformatics and computer-aided medicine. This opens up an exciting perspective with new possibilities for knowledge and information, making it possible to share not only conclusions, but also raw data. Furthermore, it promises more fully integrated approaches to the patient, enabling more personalized, predictive and integrative healthcare and accelerating the development of new diagnostics, devices and therapies. But, we need to develop a new approach which makes possible the integration of data collected at divergent space and time scales in order to analyze organisms as integrated systems. In this paper I will analyze the Avicenna project, especially focusing on its Roadmap, as a possible and already real response to this new trend. In section two I will illustrate the Virtual Physiological Human project that preceded Avicenna. Then in section three I will consider the Avicenna project, highlighting some philosophical problems. After an analysis of the Avicenna roadmap in section four, I will consider in section five whether and how does this document deal with these problems.

To identify and locate all available studies and documents, the following online sites were searched for information: http://www.vph-institute.org/, http://avicenna-isct.org/ and http://avicenna-isct.org/avicenna-alliance/.

2. The VPH Project

In 2005 a group of researchers proposed the creation of the "Virtual Physiological Human" (VPH) defined as "a framework of methods and

technologies that once established will enable the collaborative investigation of the human body as a single complex system" (Viceconti, Henney, Morley-Fletcher, 2016, p. 88). This project was sponsored by the European Commission. As a first step, the project was concluded with the elaboration of a research and technological development roadmap through a consensus process across a community: *Seeding the EuroPhysiome: A Roadmap to the Virtual Physiological Human.* Through quantitative information about the biology, physiology and pathology of a patient at different scales of space and time generated by using imaging and sensing technologies, this document, published in 2007, aimed to design multiscale computer models containing all the knowledge available on a specific disease, in order to make patient-specific predictions for diagnosis, prognosis and treatment planning.

Although the VPH project is not yet entirely realised, VPH technologies already have practical and clinical applications. So, in 2011 a not-for-profit organisation, called the VPH Institute, was created to represent the emerging community of practice. One of the first steps of the activity of this institute was the publication of a position paper showing three further lines of development for the Virtual Physiological Human project based on the concepts of "Digital Patient", a decision-support system for personalised medicine to the medical professional, of "Personal Health Forecasting", patient-specific models constantly updated by personal health systems and providing decision-support systems for self-management to the patients/citizens, and of "*In silico* Clinical trials", defined as the use of patient-specific models to generate simulated populations on which new biomedical products can be safely tested. The innovation of this approach with reference to statistics is powerful. Indeed, it is said that:

> the distinction between conventional statistical models and individual-based population models is foundational: in the first case we assume there is an 'average' behaviour for the population, and that the deviation from this average is due to uncertainty and measurement noise. In the second we acknowledge that each individual is different, and define population patterns as summation of individual behaviours (Viceconti, Henney, Morley-Fletcher, 2016, p.80).

The Discipulus action, coordinated by Vanessa Diaz, has already produced a research roadmap on the 'Digital Patient' and the PSH Consortium made a number of reports that partially address the Personal Health Forecasting concept. The Avicenna Community of Practice aims to develop models

parameterised for each patient, that is providing a fully mechanistic, quantitative models capable to predict accurately for each individual member of the cohort so that these predictions are comparable to the measurements for that individual.

3. The Avicenna Project

Funded by the European Commission as part of the Seventh Framework Program for Research and Technological Development (FP7) under the Information Communication Technologies Programme, the 'Avicenna project: a strategy for *in silico* clinical trials' began in October 2013 and was closed in September 2015. The project was conducted by a consortium co-ordinated by the University of Sheffield and included three partners: VPH Institute, Lynkeus srl and Obsidian Biomedical Consulting Ltd. The consortium was tasked with three objectives: creating a roadmap addressing the steps needed for the introduction of *in silico* clinical trials (ISCT), establishing a partnership between the biomedical industry and European research organisations, with the aim of developing the technology, methods, protocols and standards required for *in silico* clinical trials to become a reality, and identifying technologies and determining early examples of *in silico* clinical trials.

The Roadmap has been published on ResearchGate in January 2016 and shows that the use of ISCT is already a reality in industrial practice, but to only a limited degree. So, it suggests investment in *in silico* strategy as one of the most important strategic priorities in biomedical and technological research in order to make it simpler, cheaper, faster, safer, minimising activities such as animal and human experimentation. In this reading, the Roadmap suggests that the European Commission and other international and national funding agencies support *in silico* clinical trial approaches, because they could have a huge socio-economic impact. Furthermore, the Roadmap aims to create a community of deep-thinkers and key stakeholders involved in a consensus process that could identify the scientific, technological and methodological barriers impeding the widespread adoption of *in silico* clinical trials, and to support a pre-competitive alliance among them to overcome any such obstacles. The 'Avicenna Alliance' is an association of industry and research organisations who have a commercial or research interest to promote *in silico* medicine. By working with members and policy makers, this alliance will

operate to create a favourable political environment for the emerging *in silico* market to flourish.

Adopting an *in silico* approach in clinical trails seems to be particularly advantageous, especially considering the strong ethical or social impact it could have. Indeed, it promises improving clinical experimentations lowering costs and animal models, avoiding harmful effects and risks for patients, allowing to treat orphan diseases, refining prediction of long term or rare effects. ISCT seem an exciting perspective and opportunity to overcome our cognitive limitations to store, analyse and represent the complexity of biological and physiological processes happening in the human body, proposing at the same time a fruitful cooperation across disciplines.

Nevertheless, this dawn brings with it many important questions. The Avicenna project is based on the problematic notion of '*in silico* Patient': an embedded predictive model capturing the feature of individual patients, that is representing the inter-subject variability in anatomy, physiology, life style and severity of pathology. Certainly, this concept entails a reflection on model's credibility, but, even more, on 'living' human body. What is the real ISCT perspective on this topic? How does the notion of 'patient specific model' deal with the problems of human bodily identity and its subjectivity?

Furthermore, the aim of providing 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, could involve a wider reflection on whether the living response to a drug or device is mechanical or not.

The roadmap is constructed upon the assumption that in pharmaceutical R&D diseases and disorders can be broken into underlying biological processes that can be defined in terms of their constituent or targets. This premise appears certainly possible and, maybe, rightful, but, from a predictive point of view, it seems to need a deeper reflection establishing what is a 'disease' in a living system and what does that mean.

What views on the task and practical purpose of the medical science does the new concept of Predictive Medicine entail? What theoretical framework?

4. The Roadmap Document

The Avicenna consortium developed its main document in four steps: the formation of the community of practice, the search for consensus of the experts

of this community, the consolitation of all the inputs in a final draft version of the roadmap, and, at last, the public validation of the roadmap with all stakeholders and its presentation for discussion in the last meeting. Regarding the formation of the community, after a long process of mapping the territory, stakeholder identification, contacts establishment, awareness building and definition of different contribution methods and levels of engagement, the experts list included 525 experts coming from USA, UK, Italy, France, Germany, Belgium, Spain, Netherlands and Switzerland. The aim of this first step was that all key stakeholders were well represented. Five events were organised to develop the Avicenna roadmap using a consensus building process called Alignment Optimisation Process (AO), a method for crowd-sourcing knowledge. 30-50 handpicked experts attended the first four events. They provided essential issues about the introduction of *in silico* clinical trials. At the first event, 45 world's experts from across academia, industry, healthcare and regulatory agencies met in Rome in March 2014 to establish a common vocabulary to be used for ISCT process, setting up a skeleton roadmap and identifying the topics to be discussed in future meetings. The second meeting took place in Rome in June 2014 and brought together around 50 industrial research experts from the medical device and pharma industries with the aim to recognize the conceptual holes of the outline roadmap that had resulted from event one, developing understanding of the research/commercial relationships with industrial organisations and prioritising the topics to be discussed in the next Avicenna event. Meeting three was held in Lyon in October 2014 and was attended by 50 experts from industry, regulatory affairs and patient representative organisations, with experience or interest in the R&D process and in development and assessment of biomedical products. The goals of this event was to identify the research challenges related to the use of modelling and simulation technologies in the development of pharmaceutical products and medical devices and defining a research agenda that is driven by the needs of producers, regulators, medical professionals and patients. The fourth meeting took place in Brussels in February 2015 and aimed to categorize the research, technological and developmental challenges that will be faced by ISCT. Event five was held in Barcelona and was a widely open and public event that brought together around 100 experts to review the final draft of the roadmap and to discuss some topics concerning model credibility, reduction, refinement and partial replacement of clinical trials, the physiological envelope, individual-based

population models and socioeconomic aspects, such as policy and governance frameworks for data sharing. All information and inputs gathered during the alignment process and during each meeting had been collected and embodied in the draft of the roadmap. So, the result was a 'changing' document, consolidated into a final version in August 2015, and drafted to describe the way by which *in silico* technologies of computer simulation will be introduced into clinical trials, overcoming the legal, financial, organisational and technical barriers, and to create a large consensus among a broad range of stakeholders.

This Roadmap is divided into eleven independent chapters, "each a stand-alone document" (Viceconti, Henney, Morley-Fletcher, 2016, p. 6) with its own purpose. An initial reading guide encourages each category of stakeholder to read only those chapter relevant to them. However, we can recognize two main discourses in the Roadmap. The first one, which includes chapter II, X and XI, shows especially the Avicenna project and the roadmap development process. Instead the second part, which includes I, III, IV, V, VI, VII, VIII, IX chapters, explains the *in silico* technology and its introduction into clinical trials.

A general overview on the development and assessment process of a new biomedical product opens chapter 1. It shows that any biomedical product before being distributed must undergo a development and assessment process, in order to lower its potential harmful effects. This process is carried out in a pre-clinical evaluation phase, in which a product can be tested on a laboratory bench or in a mechanical testing frame, in vitro (looking at how a small culture of cells responds to the product), ex vivo (on tissues or organs extracted from a body), or in vivo (using animal models), and in a clinical one, in which the product is tested on humans. Typically, the testing in humans is done in 4 phases. In a first step, the product is tested on a small group of patients or healthy volunteers, in order to evaluate if it can be used safely. Then, the product is tested on a larger group of patients in order to estimate its effectiveness. In the third phase, the product is distributed to a much larger group of persons, such as in hospitals, in order to evaluate its efficacy on clinical outcomes. Finally, after marketing approval, the product remains under surveillance for serious adverse events.

This chapter stresses the need to introduce *in silico* technologies in clinical trials in order to reduce, refine, partially replace and complement them. Indeed, due to the huge complexity of human diseases, the inevitable differences between individuals and the variability in how a treatment is

administered, a product could perform very well during preclinical phase, but it could fail if tested on humans in clinical trial. Furthermore, the current paradigm of a clinical trial tests only if a product is unsafe or ineffective, but rarely enables us to understand the motivation of this failure or suggests how to improve the product. Consequently, if a product fails during clinical trials, it is simply abandoned, even late in the process, with huge loss of investments. Clearly, this system decreases innovation and at the same time increases the costs of development, with the resulting shrinking of research on rare diseases.

By developing reliable computer models of the treatment and its deployment together with reliable computer models of the patient, it would be possible to administer a virtual therapy to a virtual patient observing through a computer simulation how the biomedical product performs, without inducing adverse effects that might be potentially dangerous. Thus, ISCT, defined as "the use of individualised computer simulation in the development or regulatory evaluation of a medicinal product, medical device or medical intervention" (Viceconti, Henney, Morley-Fletcher, 2016, p. 12) promises: reducing the size and the duration of clinical trials through a better design and implementing a smaller clinical trial population by adding simulated patients that might fill gaps in the individual variability seen in real patients; refining clinical trials through better detailed information on potential outcomes, understanding how a product interacts with the patient anatomy and physiology, and a greater explanatory power in interpreting any adverse effects, predicting long-term and rare effects that clinical trials are unlikely to reveal; complementing clinical trials by the ability to test the product increasing experimental variables, such as in cases of co-morbidity; partially replacing clinical trials when ISCT can generate scientific robust evidence. This last point shows clearly that the Avicenna project has become more ambitious over time. Indeed in the second-last version of this document at the same point it was said that *in silico* clinical trials could help by "partially replacing clinical trials in those situations where they are not an absolute regulatory necessity, but only a legal requirement". Interestingly, in the last passage of this 'layperson's introduction' it is said that the introduction of *in silico* strategies in trials supports a change in the meaning and concept of medicine, because it emphasizes especially its predictive ability.

The third chapter, after an overview on the current process of developing and assessing new products in the biomedical industry, shows the industrial need for the introduction of *in silico* technologies in clinical trials because of

the crisis that pharma industry is facing, mainly due to the growth of attrition rates, to the increase of costs and lack of innovation. The current industrial practice does not employ *in silico* clinical trials throughout the product life cycle and even when modelling and simulation are used, physiology and individual variability are not taken into account. Indeed, pharmacokinetics-pharmacodynamics models are exclusively statistical and predictive of average properties for population, but not accurate for individual patients. They are entirely based on induction, so they cannot be used to investigate infrequent situations, even slightly different from the one they were collected on. Instead, ISCT technologies, introducing the concept of patient-specific model and capturing as much biological and physiological knowledge as possible, could provide predictive and explanatory powers, reduce the costs of assessment for problems such as pre-labelling, allow a treatment of orphan diseases, reduce animal experimentation and speed up the process of understanding how a device performs. The barriers to the introduction of ISCT would be overcome above all by the creation of a pre-competitive setting where a number of different stakeholders from industry, regulatory agencies, patients' organisations can effectively collaborate and work together to tackle complex problems and the need, to be effective in a number of diseases, of more research to unravel systemic responses and processes using VPH and systems dynamics models.

So, chapter IV focuses on the barriers, challenges but also opportunities of the factors preventing the penetration of *in silico* technologies into biomedical industry from a social and economic point of view. After a general overview about the difficulty for industry to embrace ISCT, especially due to the lack of training of most experts in this sector, this new approach is defined, from a cultural point of view, as a disruptive one. Indeed, *in silico* clinical trials are a huge multidisciplinary practice and require a close collaboration between scientific disciplines, a stable partnership between academia and industry, and the facilitation of data sharing over country borders. To face these difficulties, a key point has been identified in training. This is an important factor to understand modelling and simulation in biomedical disciplines, to validate and interpret emerging results and understanding how to apply ISCT approaches to support risk assessment. In this regard, another important issue to deal with will be the development of a standardised process of model validation in order to improve models credibility.

From an economic point of view, this chapter emphasizes the need to introduce ISCT in biomedical industry to cope with the steady growth of pharmaceutical expenditure, the inadequacy levels of care and to rebalance the global pharma market, now fully cantered in the US. In particular, it is stressed that the lack of innovation, the extensive recourse to patent strategies, which aimed at excluding competitors and, consequently, at decreasing innovative efforts, the delay of generic entry and the dominance of a small group of big firms are the current characteristic features of the European pharmaceutical market. So, the adoption of ISCT in biomedical industry seems to require mainly contextual changes, such as the entrance of a number of new entities in the market and the change of the present business models. In this regard, it is said: "ISCT can represent a fundamental element in making this 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 for medicine can become the trigger for the transformation of the entire healthcare system and biomedical industry as an overarching aim of the EU" (p. 37).

Indeed, the penetration of ISCT could help to redefine the patent system, which seems to be the root problem of the current biomedical industry. Furthermore, it could ease the adoption of "two-part pricing", which was considered a solution to the crisis, one for *in silico* biomedical R&D and another for the resulting products. In this sense, ISCT innovation would become a public good, removing the manufacturing of medicines and devices from the monopoly of few companies, in order to ensure maximum competition among generic producers, low prices and high levels of efficiency. A lot of positive effects are mentioned together with such strictly economic and strategic aspects: *ad personam* medical treatments, avoiding the waste of medicines or cases of over-treatment or under-treatment, both due to problematic packaging formats; a greater transparency of information, based on the ISCT nature of wholly digitised process; an effective response to Anderson's insight "the biggest money is in the smallest sales" as the key factor of the future trend in economy cures based on customised algorithms tackling the individual disease conditions; the capacity of delivering drugs for orphan diseases. Barriers to adopting this new ISCT approach concern privacy, management of big data, the need to protect individuals from harmful usage of their personal data, the danger of the use of these data for eugenic radical manipulations and the risk that these frontiers could remain available only to a

limited portion of the population creating unbalance and possible persistent states of conflict.

Chapter V and VI follow the same structure. They describe possible uses for ISCT technologies respectively in the development of medical devices and pharmaceuticals. In the design stage the claim to develop a medical device starts from a clinical need and leads to improve or change an existing device. Here, using ISCT seems helpful in comparing the old and new design with respect to all failure modes relevant to these devices, in revising the design if major risk appears, in pursuing the pre-marketing notification when the differences are minimal and in conducting some experimental tests only when the evaluation after an *in silico* trial indicates small but not negligible differences. Instead, when a conceptually new device is designed from scratch to meet a previous unmet clinical need, the ISCT technology, allowing for the proper representation of the patient anatomy, physiology and biology, and for the virtual deployment into hundreds of simulated patients, could immediately highlight what features of the device need to be improved. In this sense, it could reduce the percentage of the time and costs needed to receive the pre-marketing notification and to overcome complications evident in early stage of a clinical trial. Currently, designs are frequently found to be inadequate at the pre-clinical assessment stage, because they are targeted to fit one generic anatomy. In the pre-clinical assessment stage the importance of using ISCT in refining, streamlining, reducing the costs and estimating the severity of the effects that a failure could produce, is especially evident when a clinical failure mode cannot be accounted for by known engineering failure modes, because it could be produced by multiple modes, and it could depend not only on the design but also on the patient and the way the device has been deployed. Furthermore, the adoption of *in silico* technology seems to be particular important both for moderately innovative products, reducing the number of trial-and-error cycle, and for radically innovative one, cutting down the return on investment threshold, the costs, the time to market, the associated risks and the barriers to innovation. Despite the advantageous uses of this technology, it is also said that an ISCT can only support and supplement a clinical trial, never completely replace it, because computer modelling and simulation only help to organise all the knowledge available, even when it is fragmentary or incomplete. In the clinical assessment step, patient specific modelling can reduce clinical trials in size and time, because it allows replacing the outcome

with a surrogate one more easily measurable, decreasing the inter-subject variability of the sample and the reproducibility of the outcome, predicting a model-based surrogate outcome that can be obtained much earlier than the standard one. Furthermore, patient specific modelling can quantify most complex outcomes and capture side effects with a much broader observational angle, so it can refine clinical trials of medical devices, reducing the risk of complications emerging only after the marketing stage. Chapter V also contains a description of the current use of Patient Specific Modelling in the medical device industry, providing examples, 'success stories', of its early adoption and a list of examples of possible future uses, highlighting related key issues.

Chapter six starts with a general overview of pharmaceutical products assessment, emphasizing that less than one in every ten projects enters into development succeeding because many hundreds of projects fail at the discovery phase. Then the chapter underlines the need for the introduction of 'dry' computational methods to guide next experiments with data derived from 'wet' experimental high-throughput screening methods in pharma industry, to refine the ability to predict negative outcomes at each point in the value chain in order to prevent harmful effects, to minimise animal experimentation, to speed up the process and to reduce the costs. Then, as the previous chapter, chapter six describes the current state and some examples of ISCT early adoption into pharma industry.

Chapters VII, VIII, and IX explain the challenges that must be met to ensure a broader introduction of Patient Specific Modelling technologies in clinical trials. Particularly, the seventh shows the issues that can be applied to all types of biomedical products, such as the need for a shared and widely accepted validation and certification framework for *in silico* models, the lack of appropriate and unique policies and governance structures establishing sharing mechanisms for data and models, the absence of adequate grid/cloud computing infrastructures for data storage, modelling and simulation. Regarding horizontal challenges, it has been detected and proposed the need for educational activities, divided between training, targeted to students who have not entered the work market yet, and re-training, targeted to those who are already employed. Furthermore, this chapter points that ISCT research is linked to other topic research of great interest, such us the broader concept of *in silico* medicine, the 3D organ printing and synthetic biology, the organ-on-chip, the opportunity to reduce, refine and partially replace animal models

using directly human models, the systems biology and the opportunity to integrate them to provide context dependent and predictive outputs, the mobile health. However the major horizontal challenges are related to the data and their sensitive and confidential nature, the need for algorithms to process efficiently them, the complex linking of genomic and phenomics data at the organism, organ and tissue scales.

Chapter VIII shows challenges related to medical devices to overcome to a successful diffusion of ISCT. In this reading, the emphasis is on the model credibility, that is the process to ensure that a predictive model is accurate in its predictions, for which it is proposed the need to develop for each type of device and simulation a set of good practice, widely tested and accepted, that could provide guidance on the question of verification and validation. As regards the *in silico* design and pre-clinical assessment for wearable or implantable devices, it is proposed to develop for each type family of devices and for each failure mode a reliable computational predictor of the probability that such failure mode will manifest in a specific design and to run in parallel and in double blind *in silico* and experimental evaluations of new designs. Another important barriers concerns the problem of variability and the need for large, validated and widely available statistical atlases of specific anatomic and anatomo-physical models, that should be considered as models on their own. In this regard, it is proposed that:

> In order to be effective, this process should be performed on hundreds and sometimes thousands of anatomies, which implies a need for automation. We need to develop 'anatomical fitting' tools, fully integrated in the design suites, which automate the process of fitting a new design into hundreds or thousands of digital anatomies, and automatically analyse the anatomical fitting, highlighting cases where the design pose some anatomical fitting issues (Viceconti, Henney, Morley-Fletcher, 2016, p. 72).

Furthermore, other challenges are the need for information and scientific visualisation technologies that allow rapid comparison of multiple simulation cases in meaningful ways and the lack of specialised interactive visualisation technologies that could improve communication with non-technical members. From this point of view, maybe the most problematic issue is being able to quantify for selected populations the range of lifestyle and environmental conditions relevant for a class of medical devices, under which such medical devices must operate when implanted. This point involves obtaining a

collection of sufficient data and the elaboration of the necessary models to reliably estimate the entire range of possible values a physiological parameters relevant to the design of specific families of medical devices can assume in a given subject and the quantification of the deployment and implantation of particular classes of device. Indeed, given the diversity of specialists, it is underlined the need:

> To develop deployment simulators [...] that we can use to estimate the reproducibility of specific procedures across multiple specialists, at different level of training and experience. And of course we need to conduct comparative studies with real deployment procedures to establish sufficient confidence in these simulators (Viceconti, Henney, Morley-Fletcher, 2016, p. 73).

Moreover, in order to improve clinical trials reducing the number of patients involved, refining proceedings and lowering risks of harmful effects, it is underlined the importance of using ISCT for predicting long-term outcomes obtained over unusual populations.

Finally, chapter IX describes the research and technological developmental challenges that need to overcome to introduce ISCT in pharmaceutical industrial sector. In this light, in the first part it is stressed that the traditional and current approaches adopted in pharmaceutical industry have a reductionist focus in industry pipelines, that does not allow to explore in depth failure mechanisms, due to pathways and network interactions at the cell, tissue, organ and integrated physiological levels. Then, some topics are identified in which the adoption of ISCT could enable a serious improvement in discovery, translational-studies and pre-clinical assessment and clinical development stages. Issues are in form of open questions, as a repeated 'why not', highlighting the great opportunity and importance of assuming Patient Specific Modelling. So, in the second part of this chapter, patient variability is identified as a key factor to break down the barriers.

> The distinction between conventional statistical models and individual-based population models is foundational: in the first case we assume there is an 'average' behaviour for the population, and that the deviation from this average is due to uncertainty and measurement noise. In the second we acknowledge that each individual is different, and define population patterns as summation of individual behaviours (Viceconti, Henney, Morley-Fletcher, 2016, p. 80).

From this point of view, an important challenge to overcome is identified in the need to capture knowledge and not just information or data for building

models in order to obtain a causal explanation of an *in silico* observation. Indeed:

> First, data is heavily time and context dependent. Knowledge, which emerges from data after the aggregation of multiple analyses over time – until it becomes a scientific fact, is far more reliable. Second, knowledge-based models are mechanistic in nature, whereas data-driven models risk mistaking correlation for causation (Viceconti, Henney, Morley-Fletcher, 2016, p. 81).

Thus, it is important supporting knowledge-based model designs by carefully crafted standardised methodologies and procedures. Furthermore, three domains have been identified to contribute to the development of a complete and comprehensive systems pharmacology platform, where mechanistic models and mechanistic knowledge is available, in: physics-based and physiology based mechanistic models describing organisms, organ and tissue behaviour, biology-based and chemistry-based phenomenological models describing single cells and intracellular processes and physics-chemistry based models describing molecular processes.

Since this approach involves multiple knowledge and address multiple type of open-ended questions, it is clear that project needs the collaboration between academic, industrial and clinical experts in order to achieve its aim. So, in chapter X it proposed the creation of a pre-competitive alliance, ensuring that all parties are represented and considered as a setting to discuss and define reliable, effective and sustainable practices for the use of ISCT.

> This Association for Predictive Medicine will operate as both a trade association tackling key regulatory and market barriers to solutions, and as a forum for experts to discuss EU policy, its effect on the interests of members and to respond to these developments accordingly. This association would be the interlocutor, between industry, the scientific community, and policy makers in the European Medicines Agency, European Commission, European Council and the European Parliament (Viceconti, Henney, Morley-Fletcher, 2016, p. 86).

5. Open Questions

From a structural point of view, this roadmap appears a very interesting document. Indeed, it shows a proper and unique 'unstructured structure' that allows anyone to read it selectively. Furthermore, it is focused more on the

barriers and the need to introduce ISCT in pharmaceutical domain. So, in many chapters it does not seem contain specifically technical information such as methodological and procedural pathways by which individualised models could be built. For this reason, it could be considered a preliminary document, almost a 'seminal paper' that prepares the consensus to the revolutionary message it contains. Particularly, it focuses on the key concept of reducing the percentage of the time and costs, often leaving in the shadow that ISCT can only support and supplement a clinical trial, but it could never completely replace it. Computer modelling and simulation 'help' only to organise all the data available. But, at the same time, the Roadmap says that:

> While we may not have a complete mechanistic explanation for each step, we acknowledge that when a validated mechanistic theory is available the resulting predictive models are infinitely more accurate, robust, and reliable than any phenomenological alternative. And predictive models must be assessed in the frame of pure physics epistemology, where models make quantitative predictions about one patient, and their predictive accuracy is measured against measurements made on that patient (Viceconti, Henney, Morley-Fletcher, 2016, p. 89).

Thus, what is the real 'revolutionary' and powerful vision proposed by this document regarding scientific and medical knowledge? Can a model generate scientific knowledge and reliable medical outcomes? If yes, how and to what extent?

The Roadmap does not conclusively answer to many problems it arises and many philosophical issues remain open-ended questions.

In this regard, in the roadmap it is stated that the risk for an engineering failure mode to occur does not depend only on the design, but also on the patients, their lifestyle, and the way the device or the medical treatment has been deployed, but no word is spent on the problem of subjectivity and on how to deal with this issue '*in silico*'. Is it sufficient to consider a huge amount of data to predict an individual, particular and maybe 'unique' response to a drug or to a device?

Even if the strategy of Clinical Trials comes as a possible bridge to *ad personam* medical treatments, nevertheless it seems to contain many obscure theoretical issues to overcome in order to create the right horizon and framework upon which we can operationalize its promises. This last one is maybe the biggest challenge to be overcome to transform this visual ideal in an accessible reality.

6. Conclusion

To sum up, after a general overview on the current relationship between scientific research and technology, in this paper I have presented the VPH project as an example of this new trend in science. Particularly, I have analyzed the Avicenna roadmap in order to explain that this new and exciting perspective often conceals a lack of theoretical reflection we have to face with in order to transform this visual ideal with its promises in a tangible and concrete reality.

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