in silico Clinical Trials - Bringing the Digital Revolution to the Biomedical Industry

The European Commission is broadening its investment in *in silico* medicine by funding the development of a 'roadmap' describing the route by which *in silico* techniques of computer simulation will be introduced into clinical trials, the studies that are routinely conducted to establish the safety and efficacy of new medical interventions. The roadmap initiative, Avicenna, is designed to cultivate consensus amongst a broad range of stakeholders who will come together to agree a research and technological development strategy; as the initiative's organisers, we are inviting participation from all with an interest in this goal, in order to assemble the best possible far-sighted and comprehensive roadmap.

Why *in silico*? - The term *in silico* medicine indicates the use of computer simulation in the design of new biomedical products, and in the assessment of their safety, accuracy, and efficacy. *In silico* clinical trials will be faster, cheaper and safer than traditional clinical trials: by simulating the effects of biomedical products on large numbers of "virtual patients" trials will not only be improved, but the door will be opened to *in silico* drug and device development, the key step initially identified by the EC as being required to support increased competitiveness for European industry.

- Computerisation already contributes to many aspects of the drug discovery and development process, especially by identifying promising compounds for further exploration. Chemo-informatics, virtual screening, algorithmic protein structure modelling, cellular drug transport simulation tools, and critical assessment of automated structure determination are all in routine use. Through the better understanding and improved modelling of proteins/drug interactions, molecular binding, drug absorption, distribution, metabolisation and excretion, researchers will be able to identify and test drugs for new uses, as well as determine whether natural compounds have potential as candidates for new drug development.
- For many device designers their working methods have long involved the use of computer-aided techniques and, increasingly, anatomically-informed individualisation has contributed to the understanding and refinement of the product development process. Now *in silico* clinical trials offer the possibility of shortening and cost-reducing the time-to-market, by extending the computational involvement through to the regulatory phase of the process.

We are proud to have been selected as facilitators for the challenging process of drafting the roadmap for the introduction of *in silico* clinical trials. Around a shared vision, Avicenna will develop and promote this roadmap, and work to overcome the legal, financial, organisational and technical barriers that could slow the adoption of computer simulation in this domain.

Why Avicenna? - Avicenna, a Persian physician and philosopher (980-1037), in his Canon of Medicine, first gave a formal structure to the process of evaluating the effect of a treatment on a disease. Since then, the fundamental nature of clinical trials has changed surprisingly little. Today, a new biomedical product is still developed and tested with an empirical approach that fundamentally relies only on knowledge resulting from direct observation. 1,000 years ago Avicenna was the father of modern medicine and it is now appropriate to use his name again as we begin the medical revolution brought about by computerisation and in silico techniques.

The fact that biomedical products are heavily regulated reinforces a conservative attitude in this industrial sector. As a result, the cost associated with the development and assessment of new products has been constantly increasing, and the effective rate of innovation has been decreasing. In other industrial sectors, such as aerospace and nuclear power, where similar trends were observed, the optimum approach to keeping the cost and complexity of safe product development at bay has been computer simulation, usually referred to as Virtual Product Development (VPD), The adoption of VPD in the development and assessment of biomedical products has, however, so far been frustratingly slow. Avicenna aims to engage deep-thinkers and key stakeholders in a consensus process that will identify the primary scientific, technological, and methodological barriers that hinder the widespread adoption of *in silico* clinical trials, and promote a pre-competitive alliance amongst them to overcome any such obstacles.

Avicenna and the Innovative Medicines Initiative (IMI) - The Innovative Medicines Initiative is playing an effective and significant role in the biopharmaceutical sector and Avicenna will pursue the highest possible level of collaboration and integration with them, putting our results in their hands. Collaboration and engagement with stakeholders from all sides is at the foundation of Avicenna's approach. Our focus is technology-driven and highly specialised, and the results of our work will be put at the service of the sector.

Partially funded by the European Commission under the Information Communication Technologies Programme (Contract Number 611819)

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Who are the Stakeholders?
There are three identifiable communities of practice that should be engaged in this process:

1) *Biomedical sector* a. Biomedical industries i. Biopharmaceutical industries (already organised in Europe around IMI) ii. Medical devices industries iii. Health technology industry iv. Diagnostics industry	b. Biomedical Research Organisations c. Research Hospitals d. Contract Research Organisation e. Regulatory Affairs Organisations f. Patients Organisations g. Healthcare Provision Organisations
2) *Virtual Product Development* a. Hardware manufacturers b. Software manufacturers	c. Consulting firms d. Computational Science & Engineering research organisations
3) *In silico* Clinical Trials a. Tools and services for *in silico* clinical trials b. Data providers c. *In silico* medicine research community i. Bioinformatics ii. Systems Biology	iii. Computational Physiology iv. Health informatics v. Personal Health Systems vi. Computer Aided Medicine vii. Virtual Physiological Human

Different Stakeholders - Different Motivations
The different stakeholders have diverse viewpoints and motivations, but they all have crucial contributions to make to the Avicenna process and roadmap:

- Biomedical industry experts: Get what you need to improve the rate of innovation, the time to market, and cost to market. Influence the research and technological development agenda at the European level toward the needs of a vital industrial sector.
- Biomedical researchers: Complement your wet-bench methods; manage the complexity; reduce and refine animal experimentation.
- Clinical trials experts: Obtain better estimates of safety and efficacy from pre-clinical assessment; obtain outcome indicators earlier and more cheaply; reduce risk profile for patients.
- Regulatory experts: Support a better rate of innovation with lower risk; ensure regulatory aspects are central in the development of *in silico* clinical trials methods and technologies.
- Patient representatives: Find better and faster innovation, more personalised products, better treatments for rare diseases, lower risk in clinical trials.
- Healthcare providers: Develop more products, better products, cheaper products; better evidence of efficacy and safety.
- Virtual Product Development experts: Find a new, fast-growth, high-return market for VPD products and services.

How You Can Contribute - Over the 18-month period to mid-2015 we are organising a series of events to develop the Avicenna roadmap using a consensus building process called Alignment Optimisation, and we will be inviting experts in various relevant domains to help us by participating in discussion.

During the Alignment Optimisation process, Experts will be asked to:

a) Participate in Alignment Cycles (have a look at http://www.schellingpoint.com/). The development of the consensus among experts will be achieved through a formal method that involves each expert in answering a set of questions through an on-line interface. Typically every alignment cycle requires no more than 40 minutes of expert time.

b) Attend meetings: during Avicenna we plan to organise a number of physical meetings, in easy-to-reach locations. Each meeting will last one or two days. Experts from not-for-profit organisations will be offered financial support to cover travel and accommodation costs. During the action we expect to hold up to five such meetings, although not every expert will be asked to attend every meeting.

The Last Word
Avicenna provides a chance for experts to broaden their horizons, and develop a collegial vision driven by the real needs of the industry - and of society at large - strong enough to impose a research funding allocation that is truly innovative, and that will give rise to a significantly positive socio-economic impact.

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