

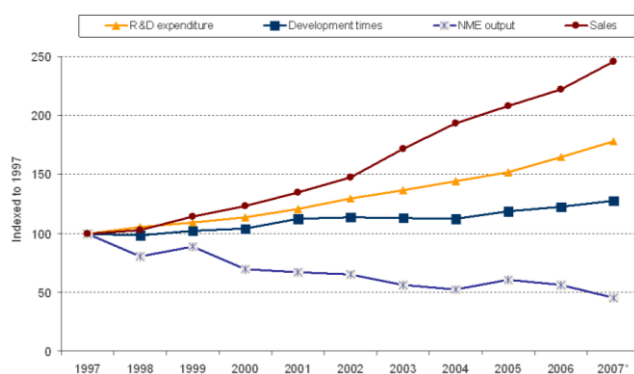
April 28<sup>th</sup> 2010, Leiden, The Netherlands

## The sustainability of the current drug development process: barriers and new orientations

**LEIDEN - The Dutch Top Institute Pharma 'Escher Project' assembled 80 renowned international delegates with various pharmaceutical healthcare perspectives to identify barriers to drug innovation on April 28<sup>th</sup> 2010. This unique gathering of stakeholders from the academic, industrial, patient and regulatory world led to a 'shopping list' of new avenues to energize the drug development process and to improve therapeutic options for patients.**

During the last decade the climate for innovative pharmaceutical development has deteriorated. It has become increasingly difficult for pharmaceutical companies to bring efficacious, safe and affordable medicines to the market. Besides the declining number of drug registrations, showing evidence for added therapeutic value of new medicinal products has become a mounting challenge. A few 'first-in-class' compounds have made it through the wilderness of regulation requirements and economic bad weather, but where is the next generation?. Is the era of pharmaceutical bloom coming to an end? Have drugs become an unaffordable luxury or are the scientific wells dried up? At the same time, the pharmaceutical market is expanding with many patients waiting for (better) treatments. Then, what are the barriers that arrest drug innovation today?

The WHO Priority Medicines Report of 2004<sup>1</sup> investigating ways in which pharmaceutical research and innovation could best address health needs and emerging threats, already indicated 'gaps' of untreated diseases and flagged R&D problems on the economic and regulatory level. Other authors, including Rawlins and Eichler, have doubted whether the current R&D process is sustainable and still the best way to cope with the future.<sup>2,3</sup>



\* The development time data point for 2007 includes data from 2006 and 2007 only

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In the ancient Museum Naturalis, Prof. Dr. Hubert Leufkens (UU / CBG-MEB / Escher project) and Prof. Dr. Daan Crommelin (UU / TI Pharma) invited the speakers and audience to reflect on the impediments of pharmaceutical development today, with the aim to identify alternative strategies for more efficient delivery of new drugs to patients.

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Prof. Dr. Jacob de Vlieg (MSD / Radboud UMC, Nijmegen) says that increased regulatory requirements are one of the reasons for lack of output and increased R&D cost. Much larger studies are necessary to ascertain safety and efficacy. "This has led to double the amounts of patients per study as compared to 10 years ago", De Vlieg states. Pharmaceutical enterprise has become more difficult and risky due to high costs and scientific challenges, since the easiest diseases have been tackled and the new genomics targets have not been validated sufficiently.

"Only half of all clinical Phase III studies are successful today", affirms Dr. Hans-Georg Eichler (EMA, London)<sup>4</sup> "and of all market authorization applications (MAA) in 2009 40% failed"<sup>5</sup>. "Safety requirements are driven to such a high level that I wonder whether aspirine or diclofenac would get a license today", Eichler doubts. 'It is surprising that pharmaceutical innovation declines when there still is a strong need for innovative drugs with the ageing of the population, emerging diseases, emerging markets and an abundance of potentially druggable targets.'

Convention delegates divided into four working groups investigating barriers to drug innovation and formulated a 'shopping list' of solutions from four different perspectives (society at large including patients, the academia, the industry and regulatory authorities). The groups reported with plenary presentations under chairmanship of Prof. Dr. Douwe Breimer (RU Leiden).

*From the perspective of the society at large, including patient organizations, one of the main perceived problems is the lack of transparency and independency of clinical trials as these are organized and funded by the profiteers. More public funding of clinical research, especially public ownership of Phase IV data with wide availability of data, including mandatory reporting of failures, is recommended. They further argue to intensify the involvement of patients at all stages of clinical trials by assessing their medical needs and using their input to establish more meaningful benefit-risk ratios for drug treatment. "After all, the patients are the experts of the disease", stated Prof. Dr. Richard Laing of the WHO. They feel that 'nothing should be developed for us without us', he continued. On the question of Dr. André Broekmans (MSD) whether the current initiative to disclose clinical data was sufficient, Prof. Laing answered that indeed this train was moving towards more openness to the public domain. This workgroup questioned whether treatment options could be improved by arrival of innovative drugs or just by better use of existing products...*

*The working group examining the pharmaceutical industry perspective led by Dr. Rui Santos Ivo (Apifarma, Portugal) agreed about extending the participation of patients in decision making and development. They advised to extend the patent life in order to maintain the profit driven innovation through good science. For the latter they suggest enhancing public-private partnership (PPP) especially for target validation, Proof of Concept and development. The audience added that PPPs ought to have a risk-sharing model where both gains and risks are being shared.*

To optimize preclinical development De Vlieg argued to integrate experimental data on all levels and combine data from various targets as input for rational drug design. "Dialogue between disciplines and knowledge management are essential", he concludes. "Information technologies can lead to new pathways by distinguishing patterns that are invisible by the human eye". De Vlieg said that animal models of disease are not predictive enough of therapeutic effects in humans and should be replaced by mechanistic animal models. For optimizing clinical development companies can now use 'virtual patients' in 'whom' biological processes and drug effects can be simulated.

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Using clinical studies as examples, Prof. Dr. Dick de Zeeuw (UMC Groningen) pointed out that when drugs are developed and regarded only as single-parameter effectors, unexpected positive or negative effects occur on overall health benefit. "When focussing on just a single endpoint, possible detrimental effects of the drug on other targets may be overlooked", emphasized De Zeeuw. He proposes to use a combined set of relevant clinical markers to evaluate a drug at the registration level.

Towards the regulatory authorities the industry working group pledged for more transparency of the regulatory process, and to apply guidelines as 'principle based' rather than 'rules based'. They welcome early and informed scientific dialogue with regulatory bodies to get feedback on their data and studies, thereby optimizing the 'learning phase' of drug development. Eichler (EMA, London) showed in his lecture that companies that seek scientific advice of regulation authorities during the development process are more successful in the MAA procedure. He advised that industry should not 'skip the learning phase' for economic, management or other reasons. The high failure rate at phase III and MAA indicates that the earlier clinical phases did not successfully weed out most problematic compounds. "I am convinced that a substantial fraction of new active substances that are unsuccessful during phase III or MAA would have fared better with a different development plan", Eichler proclaims. This could have been prevented by better study designs.

Prof Dr. Donald Light (Stanford, UMDNJ, US) showed striking results discarding the view that EU pharmaceutical development (*what is it anyway?*) was losing ground to the US. Despite less funding, EU companies had in fact a higher output in NCEs. More funding of the R&D process apparently does not necessarily lead to more or better results. Light stresses the need for good international data on structural, pharmacological, pharmacokinetic and clinical gains. "Most new drugs offer few if any advantages. Costs of health care systems are very high. Patients are not winning." Light advises to reduce companies' risks and costs in return for focusing on clinically superior drugs for societal priorities.

*From the academia point of view* the number one priority is academic freedom, stated Prof. Dr. Jan Raaijmakers (UU, UIPS). These stakeholders want to preserve the in-depth scientific knowledge and expertise as a fountain of innovation. Their ultimate goal is achieving a stable, high-level of research in an open, intellectual atmosphere where 'sharing' (and not silos) is the key. They see specially trained clinical scientists as the centre of drug development.

*The regulatory angle* was presented by Sir Dr. Alasdair Breckenridge (MHRA, London). He emphasizes that regulatory authorities should change their attitude from 'gatekeepers' towards a more advisory role. They can help to develop drugs by sharing information, assist in constructing statistically sound trial designs, help to assess benefit-risk ratios and allow conditional approval of drugs under active surveillance. This group recommended an exploration on where regulation could be reduced. "We would like to redirect responsibilities to the industry and reduce bureaucracy where possible", said Breckenridge. Another advice is to re-assess the requirements for preclinical research, for instance dropping unnecessary, expensive toxicology experiments.

Apart from the challenges around marketing approval as such, there are growing concerns about variable patient access and reimbursement. David Hearry from the European AIDS Group mentioned the regulatory problems that occurred when different EU countries tried to gain early access to new

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HIV-medication. "Because there was no harmonization within in EU there were patients who could not have access to this medication. People die because of this", Hearry stressed.

Table 1. Shopping list.

What to get rid of?		Building blocks for 'new orientations'
Society at large, including patients	Dependency of research 'Sitting' on data Mergers may lead to less openness	Transparency of the drug development process Patient involvement at all stages Sharing data, better use of therapeutic outcomes; benefit-risk assessment from patients perspective Phase IV data should be owned by the public Writing our failures
Academia	No patient data and materials sharing Loss of freedom (management chooses focus areas) Distrust of industry Lack of awareness of general context: thinking in silos Withdrawal of government resources	Foundation of good science: this has to be funded Facilitating open structure New benchmarks Clinical scientist (education) as central/integral part of drug development Stable / sustainable public private partnership Patients are an integral part of clinical research Academic peer review New talent
Pharmaceutical industry	Need to target better the medical needs Does the business model neglect the medical need? Too much focus on safety rather than the B/R balance 40% approval failure	More public-private partnership, including in target validation and outsourcing of development PoC to academia Transparency in the regulatory process Guidelines are guidance rather than rules Early access through Conditional Approval Early and informed scientific dialogue Optimize the use of the learning phase More science driven decision taking in industry Need for incentives for 1st in class/ first in disease Keep the patent life, profit driven innovation Patient involvement in decision making and development
Regulatory perspective	Rationalize regulatory requirements and reduce bureaucracy where possible Rationalization of preclinical regulatory requirements	Partnership between stakeholders to share expertise, e.g. biomarker development, disease identification Goals and trial design agreed between drug developers, regulators, HTA agencies Flexibility of trial designs Adaptive clinical trial design Modelling (PK/PD) Formal Benefit Risk Assessment Recognition problems of early approval (Active Surveillance) Regulation follows Science

Ideally, drug discovery is public-private enterprise, said Dr. Jackie Hunter (Proximagen / IMI, UK). 'We're moving into an era of collaborative efforts, although this should not mean that the industry is funding everything', she continued. Hunter: "I think it is important to create incentives for people to work together."

Prof. Dr. Huub Schellekens (UU, MEB) believes patents should be abolished to have a fair competition, as is done with surgical procedures. He further argues to drop a consistent part of the

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450 EMA guidelines of which some are 'contradictory, some are outdated and some are even dangerous'. A statement that led to quite some noise among the delegates.

The meeting breathed a general desire for working closer together for exchange and dialogue with all involved parties. "We are jointly shaping the future of the drug development process", finished Bert Leufkens. Donald Light was very strong in his urge that fundamental changes are necessary to overcome the barriers that arrest drug innovation today. The 'shopping list' containing expert opinions from all involved parties will be used to revive the process of drug innovation for the benefit of patients. The Escher team will further pursue the ideas summarized in the shopping list.

*The TI Pharma is public-private partnership between 23 academic and 46 industrial parties for the benefit of high-quality pharmaceutical research, improvement of the efficiency of the drug development process and education/communication with the outside world. Escher is a project of TI Pharma aimed at bringing stakeholders from public health, industry, regulatory and academia together for dialogue and energizing pharmaceutical R&D by identifying, evaluating and removing regulatory and methodological barriers to drug innovation. Currently, TI Pharma and Escher seek alternatives for animal experiments and large clinical studies.*

For more information on TI Pharma and the Escher Project see <http://www.tipharma.com/>.

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### List of abbreviations

EMA	European Medicines Agency (London)
HTA	Health Technology Assessment
IMI	Innovative Medicines Initiative
MAA	Market Authorization Applications
MEB	Medicines Evaluation Board (Dutch)
MHRA	Medicines and Healthcare products Regulatory Agency
MSD	Merck Sharpe & Dome
NCE	New Chemical Entity
OTC	Over the Counter
PoC	Proof of Concept
PPP	Public-Private Partnership
R&D	Research and Development
TI Pharma	Top Institute Pharma
UIPS	Utrecht Institute of Pharmaceutical Science
UMDNJ	University of Medicine & Dentistry of New Jersey
UU	Utrecht University
WHO	World Health Organization

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