

7.4 Appendix 4: Backgrounder

New Safe Medicines Faster: A new concept for drug development

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Executive summary

Society needs more better and safe medicines but despite increasing cost of drug development productivity is falling in terms of new medicines being marketed. Time for drug development has remained fairly unchanged during the 1990'ies even though companies have worked hard to streamline processes. It seems that we have reached the limit for the traditional drug development process. It is proposed to rethink the involved processes taking into account the recent advances within genome research, pharmacogenetics, metabonomics, in-silico modelling and other new technologies and further to align the regulatory process to cope with this. The aim is to pave the way for future individualised medication based on far more specific diagnostic systems than those used today for the benefit of patients, doctors, society and industry.

Why New Safe Medicines Faster?

The EUFEPS initiative which resulted in the proposal for New Safe Medicines Faster in 2000 has had an impact on the formulation of the EU research strategies. The European Council decision of 30-Sep-2002 on "adopting a specific programme for research, technological development and demonstration:

'Integrating and strengthening the European Research Area' (2002-2006)", (2002/834/EC) reads in the section on Research priorities under Advanced genomics and its applications for health:

"Research will focus on: rational and accelerated development of new, safer, more effective drugs including pharmacogenomics approaches; development of new diagnostics; development of new in vitro tests to replace animal experimentation; development and testing of new preventive and therapeutic tools, such as somatic gene and cell therapies (in particular stem cell therapies, for example those on neurological and neuromuscular disorders) and immunotherapies; innovative research in post-genomics, which has high potential for application."

All stakeholders involved are interested in accelerated development of new, safe, more effective drugs:

Patients and physicians: Faster access to more effective and better targeted drugs with less side effects

Society: New medicines that will result in better prevention and treatment of diseases to decrease health cost, days lost through sickness, and to improve quality of life

Regulatory agencies: Faster more reliable and less resource demanding review of applications for marketing approval

Companies: Speed to market to get a longer period of exclusivity before patent expiry and to get a positive cash flow the sooner the better

R&D output is declining despite heavy investment

Despite a steady increase in the global R&D expenditure over the past 10 years as well as projected increases, figure 1, the global output from the pharmaceutical industry in terms of new medicines based on new compounds is declining, figure 2⁷.

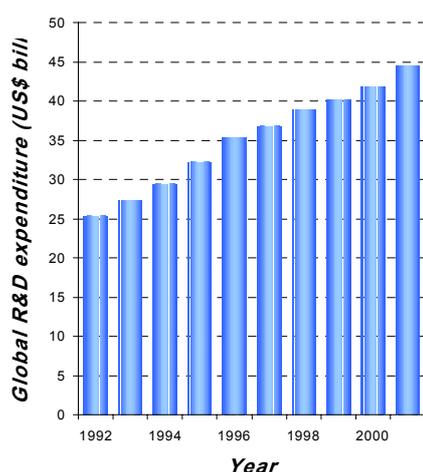


Fig.1 Global R&D investment 1992 to 2001

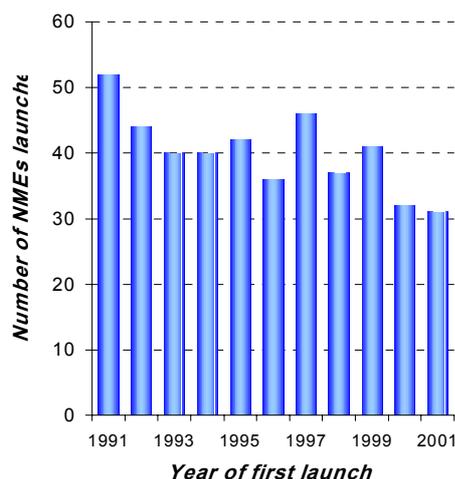


Fig.2. Number of New Molecular Entities first launched onto the world market

Traditionally companies have been strongly relying on few high-selling products; blockbusters⁸. Blockbusters alone contributed almost half of the total revenues of companies such as Pfizer, AstraZeneca, Eli Lilly and Schering-Plough⁹. With the declining number of launches of new medicines combined with high number of drugs losing patent protection, the pharmaceutical industry is now moving towards a portfolio approach, selling a wide number of smaller drugs to maintain growth¹⁰.

With a development time of 8 to 11 years and cost up to EURO 800 Mill¹¹ medicines R&D is facing a major challenge in developing new

⁷ Van den Haak MA, Vounatsos FJG, McAuslane JAN. (2002) International pharmaceutical R&D Expenditure and Sales 2001. Pharmaceutical Investment and Output Survey 2001: Data report 1. CMR International Report, CMR02-171RA

⁸ Blockbusters: Products selling more than USD 1 billion per year

⁹ Anonymous (Apr-2002), DataMonitor, Lackluster blockbusters, a cause for concern. <http://www.inpharm.com/intelligence/datamonitor040402.html>

¹⁰ Herper M (2002), Blockbuster Peril: When Big Drugs Go Bust. Forbes.com, <http://www.forbes.com/2002/04/15/0415pharma.html>

¹¹ DiMasi JA, Tufts Center for the study of drug development Press release 30-Nov-2001, <http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=6>

medicines without relying on blockbusters to pay for the less successful medicines and for attrition.

The current cost of drug development and the need for marketing muscles to regain the investment is a major obstacle for SME to enter into the late phases of drug development.

Time for drug development unchanged

Time to market for new medicines has not changed much over the past 10 years¹², despite vast investments in the industry for business process reengineering, outsourcing and other initiatives to optimise the drug development process. Thus the traditional drug development process has not changed much over the past 20 to 30 years, figure 3.

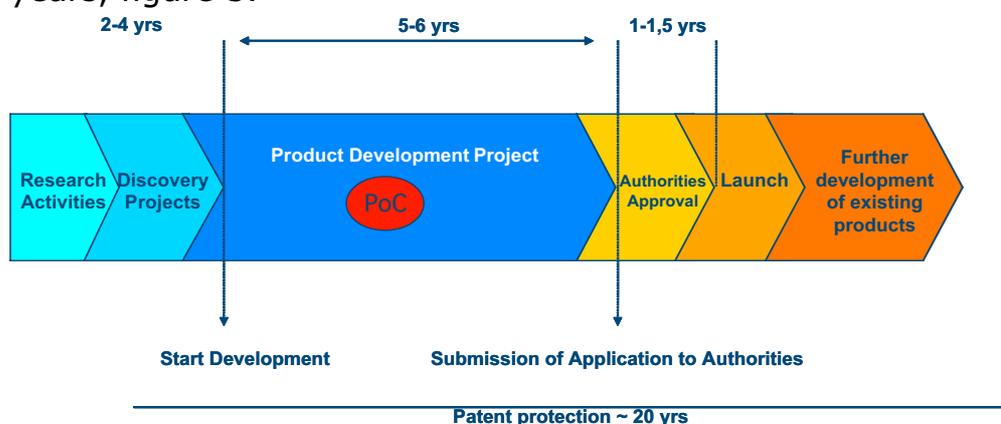


Figure 3. Timeline for drug development

Research and discovery has become more effective due to new technologies such as High Throughput Screening, Computational Chemistry, Combinatorial and automated chemistry which have enabled screening of compound libraries for potential effect at a rate per day that is far greater than the No. of compounds a pharmaceutical chemist can screen manually during a whole lifetime. But both the time to explore the properties of the compounds in terms of efficacy and safety in the pre-clinical and the clinical phase of development has remained largely unchanged.

Also the process of developing a large scale production process is time and resource consuming, especially for biotech compounds

The regulatory process has been streamlined

The regulatory bodies showed good progress in reducing approval times in the first half of the 1990ies, but since then approval time has been rather constant. Figure. 4¹³ shows approval times from submission to approval for the EU centralised procedure.

¹² Platts LAM, Ellis CE, Whittaker JY. (2002) Performance Metrics in Global Pharmaceutical R&D. CMR International Report, CMR01-166R

¹³ Van den Haak MA, Schulthorpe PD, McAuslane JAN. (2002). New Active Substance Activities: Submission, Authorisation and Marketing. Pharmaceutical Investment and Output Survey 2001: Data report 3. CMR International Report, CMR02-171RC

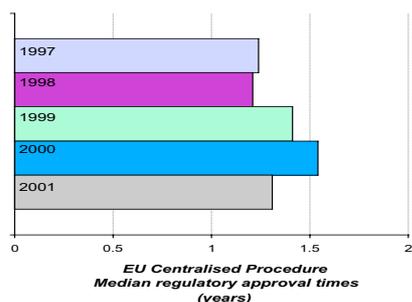


Figure 4. Regulatory approval times (1997-2001)

In conclusion, we have reached a limit for the speed of the traditional drug development process.

Therefore it is time to rethink the involved processes.

George Milne, PhD executive vice-president, Pfizer says in an essay about the next generation medicine: "Testing directly against human cells has two important benefits: There is likely to be less attrition later on in the development process thereby saving years of work and millions of dollars. There should also be a reduced incidence of side effects because of more specificity in identifying receptor subtypes"¹⁴.

Initiatives have been taken by the FDA to create a more transparent drug development process by developing special guidelines for brand-new technology, such as gene therapy, bioengineered tissue or drug-and-device combinations so companies can design the right studies from the beginning. This is to ensure a higher 1st time approval rate. Currently the FDA rejects half of all novel drug applications and 93 percent of cost-saving generic drugs on the first try¹⁵

But this initiative is only patchwork. It is necessary to start from scratch and rethink all the processes taking into consideration the recent advances within genome research, pharmacogenetics¹⁶, metabonomics¹⁷, in-silico modelling and other new technologies together with the future individualised medication based on far more specific diagnostic systems than those used today.

The traditional way of thinking is that one person has one particular disease that needs one particular treatment. This has proven wrong for many chronic diseases. A good example is type 2 diabetes which

¹⁴ George Milne, PhD executive vice-president, Pfizer Global Research & Development in World Pharmaceutical frontiers 2002/2003

¹⁵ <http://www.washingtonpost.com/wp-dyn/articles/A3318-2003Jan30.html>

¹⁶ The goal of pharmacogenetics is to identify "genetic fingerprints" that may predict a patient's response to pharmaceutical treatment. The use of pharmacogenetics replaces the trial-and-error strategy, which governs much of our clinical decision-making regarding treatment allocation in current medical practice, with individually tailored therapy.

¹⁷ Metabonomics is a systems approach for studying in vivo metabolic profiles, which promises to provide information on drug toxicity, disease processes and gene function at several stages in the discovery and-development process.

is not just a disease where the patient cannot utilise insulin. The disease also affects other systems such as the blood lipids and the blood pressure. Therefore individualised multipharmacological therapy is needed. Basically the person's genome and lifestyle will determine which organs are affected to which extent and which specific dose level is needed of which medicine to provide the optimal treatment.

Identification of which patients responds to which medicine before start of treatment will minimise the need for patients in clinical trials and lower the number of non-responders and thereby provide a faster proof-of-concept and answer the question: Does the new drug work?

Furthermore this will also minimise the number of patients to experience unacceptable side effects. If this could reduce or eliminate the need for phase 3 trials, society at large would benefit.

Despite the enormous amount of information generated by the technological developments, translation into improved health care is only materialising slowly. A fresh and innovative reassessment of drug development and approval may create new break-through opportunities to

Develop new safe medicines faster

Minimise the cost of drug development

Provide better prevention, treatment and cure

Provide a better, more individualised treatment

Create the basis for a more efficient health care system

We suggest funding a pilot project to generate an ambitious proposal on how to generate a leap forward in drug development and approval with the aim of streamlining and shortening the development and approval time without compromising efficacy, safety and quality. The idea is illustrated in figure 5.

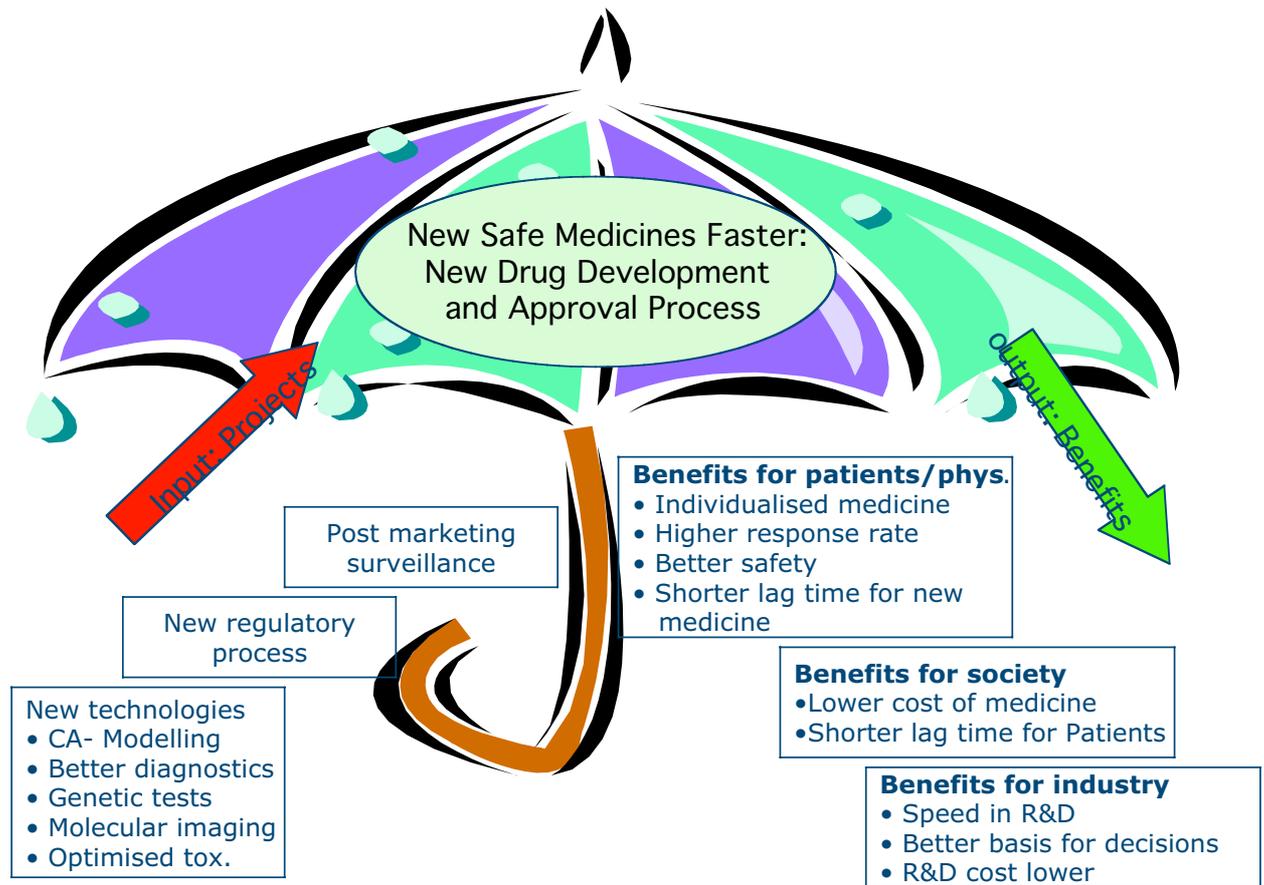


Figure 5. New Safe Medicines Faster provide an umbrella for a number of projects to support provision of benefits for patients, doctors, society and industry.

Such a proposal should be based on open-minded discussions between stakeholders representing universities, hospitals, regulatory authorities, and the pharmaceutical industry including small and medium enterprises.