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Fédération Européenne des
Industries et Associations
Pharmaceutiques

New Safe Medicines Faster

Proposals for research topics, methodologies, techniques
and other means of promoting the drug development
process to the benefit of European citizens

Report from Workshop held on March 15-16, 2000, Hotel Le Plaza, Brussels

European Federation for Pharmaceutical Sciences - EUFEPS
European Federation of Pharmaceutical Industries and Associations - EFPIA
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Preface

European science and technology and the competitiveness of European industry are in places significantly influenced by the European Union's research, technology and development (RTD) framework programme. Member states widely absorb the signals emanating from Brussels regarding science and technology, incorporating them in their own national research policy.

In recent years, the European Federation for Pharmaceutical Sciences (EUFEPS) has recognised an imbalance within Europe's pharmaceutical sector. Fragmented research by academic institutions does not match up to the needs of large pharmaceutical industry, while the implementation of new methodologies, processes and techniques is hampered by the strict demands placed on the drug development process by regulatory authorities.

The EUFEPS foresees a dedicated effort to reverse the current situation in the forthcoming EU RTD framework programme. To get the process started, in 1999 we published a paper promoting a key action entitled "New safe medicines faster" for the 6th EU RTD framework programme¹. The paper was enthusiastically received by scientists, industrialists and regulators engaged in pharmaceutical science, including the European Federation of Pharmaceutical Industries and Associations (EFPIA), European Federation of Biotechnology (EFB), Danish Medicines Agency, the schools of pharmacy in Uppsala, Amsterdam, Leiden, London, Paris, Copenhagen and Saarland, the industrial associations LIF (DK) and Farmindustria (IT), and the COST B15 EU group.

The next step in promoting this initiative and procuring information regarding the current bottlenecks in drug development and research was to establish an organising committee, consisting of representatives from EUFEPS, EFPIA and the Danish Medicines Agency. Their first task was then to organise a workshop to elucidate ways of improving the speed and efficiency of drug development. The workshop gained support from the Quality of Life theme of the 5th EU RTD framework programme.

This report represents a compilation of the bottom-up input received from the workshop, held March 15-16, 2000 at Le Plaza, Brussels, without filling any of the gaps that became visible during the editing process. We are indebted to the lecturers, rapporteurs and participants for their contribution to the workshop. Without them, this report could not have been produced. Our thanks also go to those who received and supplemented the written text.

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¹ "New Safe Medicines Faster", EUFEPS' proposal for a key action within the European Union's 6th Framework programme, pp.1-14, edition of August 10, 1999, available from the EUFEPS secretariat, P.O. Box 1136, SE-111 81 Stockholm, Sweden; email hans.linden@eufeps.org; fax +46 8 4113217, telephone +46 8 7235086
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Appendixes are available as separate documents on the EUFEPS Website at <http://www.eufeps.org>

1. Executive summary

A targeted effort to speed up the development of safe, new medicines is sorely needed in Europe. Stronger links between industry, academia and regulatory authorities, more efficient use of modern technology, new methods of drug exploration and targeted training are all vital elements of a streamlining process that cries out to be set in motion. Without it, the European pharmaceutical industry is in imminent danger of losing important ground on global markets – a situation detrimental both to European economies and the patients seeking relief from illness and disease.

Despite being the fifth strongest industry in Europe, the pharmaceutical industry is severely hampered by an approach to drug development and approval that is ill-equipped to exploit the huge opportunities presented by modern drug discovery. Growing demands regarding safety, efficacy and quality documentation consume vast amounts of research and development expenditure. But, at the same time, the average number of years spent on getting a new drug through development and onto the market appears to be on the increase, returning to around 12 years after a brief drop to 10 just a few years ago.

In 1999, the European Federation for Pharmaceutical Sciences (EUFEPS) took the initiative to get the ball of change rolling. A key action entitled “New safe medicines faster” was proposed for the EU’s forthcoming 6th RTD framework programme.

The key action has three main objectives:

- to seek new technology capable of more effective selection of potential drug candidates for innovative medicines while accommodating safety demands
- to use such technology to increase the capacity of and speed up the pharmaceutical development process and eliminate bottlenecks
- to cultivate a pan-European interdisciplinary network that bridges the gap between industry, academia and regulatory authorities

From March 15 to 16, 2000, this proposal was supported by the European Federation of Pharmaceutical Industries and Associations (EFPIA) and by the Danish Medicines Agency. It was followed up by an EU supported workshop to identify bottlenecks and speed limitations in the post-discovery phases of drug development and map out a strategy to reduce them. More than 100 representatives from the pharmaceutical industry, academic institutions and regulatory authorities participated in the workshop, producing a description of the research and technology required to bring safe new medicines more rapidly onto the market.

Among the main views expressed was the need for a holistic approach to drug development and research, pulling together all disciplines and specialists from industry and academia and encouraging an earlier involvement by regulatory authorities to alleviate the lengthy procedures necessary in drug approval. Attention was also drawn to the lack of new predictive methods which would allow more efficient decision-

making and earlier clinical trials. Workshop participants further recommended that centres of expertise be established to provide scientists with multidisciplinary training in modern technology.

The diversity of the entire drug development process is too great to be covered by a single workshop. But, as the results obtained from the workshop's seven sessions suggest, an EU-supported effort by industry, academia and regulatory authorities may be the most appropriate means of setting new European standards – bringing new medicines onto the market faster and in a more cost-effective way and establishing Europe's pharmaceutical industry as the best and most competitive in the world.

2. Drug development as a key action

New scientific knowledge and technology are widely exploited in the search for new safe medicines. The biotech boom in particular has been largely stimulated by the pharmaceutical prospects of their implementation. During the complex process of producing more and better drugs, the involvement of nearly all natural science disciplines and many advanced techniques clearly underlines the importance of an interdisciplinary, holistic strategy if optimum results are to be obtained.

Traditionally the entire drug development process has been divided into three largely separate phases: discovery, exploratory development and clinical development. It is these phases that need to be brought together to form a smooth, seamless procedure, ensuring all knowledge and data are maintained and put to maximum use throughout.

Discovery relates to the research topics linked to the identification of a drug target – where a medicine should work – and preparing the target for screening active leads taken from compounds kept in large libraries. Following selection, the drug candidate is subject to additional functional testing, its chemical structure is elucidated, and it is optimised in terms of potency and efficacy. Exploratory development then characterises the candidate's metabolic behaviour. A production procedure and formulation are developed, and further animal testing is performed.

When the drug has passed these tests to the satisfaction of the investigator and regulatory authorities, it is ready for the clinical phase when it is tested in man – first in healthy volunteers and, later, in a group of patients affected by the disease in question, the results being compared with conventional or placebo treatment. Multi-centre trials involving large groups of patients complete the clinical trials. Finally, all the results are evaluated by both the manufacturer and regulatory authorities in terms of quality, safety and efficacy. Only then is the medicine ready for commercial production and sale.

In both the earlier and present EU RTD programmes, support for the research connected with the discovery phase has been highly fruitful. The phases that follow this part, though, have been somewhat neglected and, for this reason, it was decided to make them the focus of the “New safe medicines faster” workshop. Genomics, proteomics, metabolomics and modern chemistry and research technologies have made the later phases of drug development an important focus area as many more drug candidates than previously will be generated in the years ahead. Here, technological and methodological breakthroughs are a particular need to stem the tide of development bottlenecks.

Although equally important to the process, the clinical phase did not undergo the same thorough analysis at the workshop as exploratory development. A separate workshop focusing on the clinical phase would, then, be appropriate.

The process-oriented research used in drug development makes it a well-suited subject for a key action in the 6th EU RTD framework programme, incorporating:

- well-defined deliverables to society
- interfaces to many scientific areas
- bottlenecks that need to be addressed
- a need for pan-European collaboration
- potential for job generation
- room for start-up companies and small and medium-sized enterprises (SMEs)
- links to topics of former programmes

2.1 The academic perspective

Effective pharmaceutical research will, in the years ahead, require the formation of numerous research groups consisting of experts from many fields – chemistry, physics, biology and medical and engineering sciences among them. Only in this way will it be possible to solve the complicated multidisciplinary problems that face drug development. In light of the close link between high quality research and education, this means there is a need for advanced training of pre-graduate and PhD students.

Unique research related to the development of effective medicines is conducted by scientists working within pharmaceutical schools and other related faculties throughout Europe. In some areas of emerging importance, these scientists represent world-leading groups. Most of these schools and faculties, though, are of limited size in terms of active research scientists and often not fully integrated into a broader academic environment of use to pharmaceutical development. The ULLA consortium, consisting of schools of pharmacy in Uppsala, London, Leiden, Amsterdam, Copenhagen and Paris, is a rare example of inter-school collaboration, much more of which is to be desired.

Due to these factors, the opportunities to conduct advanced research and training in pharmaceutical sciences are limited. One of the ideas of the key action is to stimulate the formation of consortia and centres at which advanced education and training can take place at PhD level, incorporating both specialist components and a holistic view of drug development. These education centres should be based on input from academia, industry and regulatory authorities.

2.2 The industrial perspective

Faster and more effective drug development is the only way to tackle the serious threats the European pharmaceutical industry will face in the years ahead. This view was strongly expressed by workshop lecturers concerned that the rising cost of research and development is not matched by a corresponding increase in the number of new products launched (see appendix 1).

Total pharmaceutical research and development expenditure grows by \$3 billion a year. In the UK, such expenditure has increased by up to 12% a year since 1994. At the same time, calculations show that, for the healthy growth of large pharmaceutical companies with an annual turnover of \$5-10 billion, 3-6

products should be launched a year. The current annual average is less than 0.5 new products, the mean time to launch having recently returned to around 12 years after briefly declining to 10.

The reason for this is that the chance of a lead molecule becoming a commercial medicine is less than 2%, while the success rate for candidates that reach the exploratory development phase is just 10%. Although the genomic revolution has generated more leads which could improve this success rate, the techniques currently available for rapidly selecting the most promising candidates are inadequate, for which reason valuable leads may be lost. An improvement of the entire research and development process is, thus, essential to keep expenditure down and avoid further costly expansions in development capacity.

The many mergers among pharmaceutical companies reflect this situation but have not removed limitations to drug development. As a result, the past reluctance of companies to co-operate has been replaced by the realisation that more interaction and collaboration with the public sector is necessary in order to implement new faster drug development technologies.

2.3 The regulatory perspective

Increased interaction between regulatory authorities, academia and industry, right from the initial planning phase through to the market launch of a new drug, would without doubt stimulate the introduction of new techniques and methods designed to make drug development smoother and faster.

Co-operation of this kind would give regulatory bodies the role of ensuring no development pathways are detrimental to drug safety and efficacy. All the requirements for pre-clinical studies should, then, have been agreed before clinical trials commence. This would mean involving regulatory authorities in joint projects with industry and academia to develop new in-vitro test systems and settling future requirements for pre-clinical and toxicological tests.

The next steps in drug development, such as the first series of clinical tests, test procedures and the duration of the test period, represent other areas of significant concern to the authorities. The complexity of producing biopharmaceuticals, too, requires a more proactive regulatory role. By joining in working groups with academia and industry, the authorities could contribute to the development of new methods designed to ensure effective, safe drugs. As a result, new pharmacovigilance approaches could become part of the marketing authorisation procedure. Commitments to conduct follow-up studies instead of completed investigations, such as those already performed on drug treatments for HIV infections, would thus secure faster access to the market.

2.4 The role of the EU

EU funding would undoubtedly be an effective means of stimulating the necessary interaction between academia, industry and regulatory authorities – giving industry better access to new, accepted

development techniques, fuelling academic research and encouraging authorities to play a more active role throughout drug development processes.

At the present time, pharmaceutical companies have no tradition for sharing research results obtained from the public sector or through academic collaboration with industrial partners. A reluctant attitude to the implementation of new methodologies and technical solutions in exploratory and clinical development is also evident within industry, as the regulatory authorities only respond to such initiatives after the investment has been made. These impediments clearly slow down the introduction of faster, more efficient procedures.

With EU support, this situation within industry could be radically changed. Academic researchers would also gain access to funds which can be channelled into the many science and technology areas linked to drug development (see chapter 4). Regulatory authorities, too, would be able to overcome their natural hesitation to get in touch with the industry they are to control. Under the auspices of the EU RTD programme, the authorities would be provided with a neutral platform on which to interact with both industry and academia in the effort to speed up development procedures. This way, the actors can be sure that all new methods and techniques fulfil safety requirements from the outset.

A research-based solution is the only way forward for Europe's pharmaceutical industry, providing the fastest and most cost-effective route to safe new medicines for patients everywhere.

3. Organisation of the workshop

All workshop participants attended by invitation, the aim being to gain the broadest view of the pharmaceutical industry's needs by covering as many European companies as possible. A total of 115 took part, comprising 75 representatives from 36 pharmaceutical companies and contract research organisations (CROs), 24 academics from 20 universities and schools of pharmacy and five regulators from four European agencies (see appendix 2). The female ratio was 15%. A number of European Commission officials and civil servants were also in attendance. Clinical pharmacology was unfortunately under-represented.

For practical reasons, seven forums for discussion were created. The drug development process itself was divided into four sessions, with the fifth session taking a look at the overall process, the sixth at the use of information technology and the seventh the creation of commercial products from new biotech molecules. The sessions were given the following headings:

- How to select candidate drugs faster (the discovery and selection phase)
- How to bring candidate drugs faster into humans (aspects of exploratory development)
- How to bring candidate drugs faster into full-scale production (up-scaling and analytical chemistry)
- How to bring drugs faster to regulatory acceptance (regulatory demands and clinical trials)
- How to reshape the drug development process from the beginning
- How to utilise IT in speeding up the drug development process
- How to turn new biotech molecules into deliverable products (special aspects of biotech products)

Distinguished lecturers were invited to chair each of the seven workshop sessions (see appendix 1) and rapporteurs nominated from the organising committee. Session participants were then asked to engage themselves in active discussion about the main aspects of faster drug development: new strategy, research and innovation, new techniques, methodologies and processes, strengthened academic research and training and flexible regulatory authorities. The outcome of the sessions was then reported to the participants as a whole followed by a general discussion. At the end of the workshop, the organisers put forward the conclusions and recommendations.

4. The workshop sessions

This chapter reports the outcome of the seven workshop sessions. The editors have merely organised the input received, adding explanatory text where this was deemed necessary.

4.1 How to select candidate drugs faster

This session dealt with the early phase of drug development up to drug candidate selection. The obvious connection to drug discovery is evident in the focus on target identification and validation as well as early and efficient profiling of potential drug candidates with validated tests. Research and procedures connected to the discovery aspect of drug development have attracted most attention over the past decade. In the EU RTD programmes, this can be seen in the biotechnology research initiatives which have included the genome, proteome and metabolome triad.

4.1.1 Bottlenecks

A smooth and seamless transition from drug discovery to the exploratory development phase is essential to avoid losing a wealth of information in the process. At this early stage, the demands of regulatory authorities play a minor role. Critical issues concerning training and education were not touched upon during the session.

4.1.2 Research and technology aspects

Areas of potential interest and focus for future research collaborations include the discovery aspects of target identification, selection and prioritisation; cellular and animal models; screening and prediction tools; and the upgrading and development of technology and methods.

i) Discovery aspects

The following disciplines and research areas were selected as being the most important for generating targets to be acted upon by new medicines.

- Functional genomics and functional gene analysis
- Target prioritisation in relation to a pathophysiological understanding of diseases
- Disease models both *in vivo* and *in vitro*
- Cell biology, knowledge of cell architecture (functional understanding) and cell protein trafficking
- Population genetics, especially human polymorphism
- Toxicogenomics
- Computational tools, e.g. for bioinformatics.

ii) Cellular and animal models

Reliable models for the understanding of disease processes are a particular need, as are models for predicting the efficacy and safety of potential drug molecules. Research activities include:

- *In vitro/in vivo* models
- Early *in vivo* pharmacology modelling
- "Humanised" predictive cell-based models
- Validated predictive models, including transgenic animals, for safety, pharmacokinetics/toxicokinetics and efficacy assessment
- Validated biomarkers (end-point markers) to reduce the time required to observe and document the effect of drug candidates
- Automation/miniaturisation of various tests, facilitating analyses and increasing the throughput and speed of the selection process.

iii) Screening and prediction tools

These tools remain in their infancy and require further research to improve their versatility and precision.

They include:

- Molecular modelling to select drug candidates for further testing in screens of various kinds, including multi-receptor high throughput methods
- Methods for predicting the pharmacokinetic, metabolic and toxicological properties of drug candidates
- Physicochemical simulations regarding the absorption, bioavailability and transport of drug compounds
- Tools to improve the quality of lead selection, both of small and biotech molecules
- Computational tools in laboratory test measurements and regarding data systematisation
- Cheminformatics, including the handling of more diverse compound libraries
- Overall improved management of data informatics.

iv) Upgrading and development of technology and methods

The diversity of the drug selection process provides numerous opportunities for innovation and the generation of start-up companies. To ensure the most beneficial opportunities are pursued, it is important to focus on the existing needs of the drug development process. The following includes some examples of focus areas:

- Biobank technology (gene and pre-clinical public data banks)
- Gene and protein microarrays
- Improved immunoassays
- Proteomics and related tools
- Phenotyping analysis of patients, e.g. for identifying slow and fast drug metabolisers

- Non-invasive imaging techniques (position emission tomography, magnetic resonance imaging, nuclear magnetic resonance)
- Innovative and improved scaling techniques that enable predictions between animal species, e.g. from rat/mouse/dog/monkey to man
- Bioinformatics – computer hard and software
- High throughput technologies, including chip technology and robotics
- Lead optimisation - high performance molecular modelling and computational chemistry software
- High throughput chemistry – medium-scale production of chemical compounds to increase the supply of test compounds
- High speed and accurate *in situ* analytical methods, "new" analytical probes, direct analysis in cell biophases.

4.1.3 Interface areas

New research areas are expected to be based on feedback from studies in exploratory drug development and clinical phases. Other requirements are more animal research in general, including ethical considerations, and broad genetic and genomic studies, including environmental exposure, population genetics and ethics.

Special research initiatives and other efforts will be enabled by virtual Centres of Excellence established by scientists in academia, regulatory agencies and pharmaceutical industries in co-operation, sharing knowledge and costs.

4.1.4 Deliverables

- Smooth and seamless transition from drug discovery to exploratory drug development
- Improved target selection procedures, reducing the risk of failures after drug identification
- Innovative, more reliable and efficient and faster techniques for assessing drug efficacy and safety
- Improved, efficient and predictive techniques, methods or tools, ensuring potential drug candidates have optimal pharmaceutical, biopharmaceutical and pharmacokinetic properties for further downstream development
- High quality predictions of *in vitro/in vivo* (animal) results to proceed smoothly into humans.

4.2 How to bring candidate drugs faster into humans

The second session covered that part of the drug development process normally described as exploratory development. It is here the selected drug candidate is evaluated in more detail in relation to absorption, distribution, metabolism and excretion (ADME), safety/tolerability and relationships between pharmacokinetics (PK) and pharmacodynamics (PD). A test formulation is also produced.

At present, attrition rates are too high: 27% for phase I and 51% for phase II. This means too many drug candidates reach clinical development only to be withdrawn later. Although statistics obtained from the Tufts Centre for Study of Drug Development show that the clinical development times for new chemical entities (NCE) dropped some 18% from 1993-95, more recent information indicates an increase. Thus the need remains to reshape and optimise the drug development process to make it more efficient.

4.2.1 Bottlenecks

The four most important issues in connection with research and development were identified as being:

- Lack of predictive models:
Research regarding modelling is needed both from a theoretical and practical point of view
- Inefficient use of pre-clinical data:
Data produced during the characterisation of drug candidates for general information and regulatory purposes is not exploited further downstream
- Inefficient target identification and validation:
The target for which the lead or drug candidate has been selected often represents the first choice. Further characterisation and validation is needed at the same time as the pre-clinical testing of the drug candidate.
- Improvement paradigm:
More candidates should be tried earlier on man with the purpose of giving feedback to discovery rather than testing fewer, better characterised candidates on patients.

With regard to education and training, the introduction and expansion of pharmacometrics (modelling and simulation) were identified as urgent needs. The encouragement of conversion training between disciplines, for example within informatics, was also considered important along with more training in subjects such as clinical pharmacology to improve scientists' understanding of the entire drug development process.

The regulatory process must evolve in parallel with technological advances. This calls for research activities within European regulatory agencies, including the European Agency for the Evaluation of Medicinal Products (EMA). Regulations based on scientific evidence are also sparse.

4.2.2 Research and technology aspects

In order to test drugs in man at an earlier stage of the development process, the candidate selection procedure needs to be optimised. Micro or homeopathic doses used in association with imaging technologies, such as Position Emission Tomography (PET) and Magnetic Resonance Imaging (MRI), to monitor the destiny of the drugs deserve further consideration.

Predictive and validated models are required for toxicological studies, especially for toxicogenomics and transgenic animals involved in the genetic expression of human genes. More research in new disease models is needed to develop animal models of major human diseases for which we do not yet have an effective cure. The identification of proper biomarkers or surrogate end-points in these animal models is equally important.

Microdialysis research should be promoted as a technique to monitor the destiny of drugs and measure pharmacological responses to them in order to improve continuity, objectivity, sensitivity, repeatability and validity. For this, input should be gathered from industry and academic and governmental institutions.

Research into gene pattern expressions of the target cells and organs for different drug classes is also needed, utilising bioinformatics and functional genomics to interpret the DNA sequences identified.

Mathematical tools of use to the exploratory phase include: artificial intelligence such as fuzzy logic, genetic algorithms and artificial networks for mathematical modelling and computer simulation; non-parametric and physiologically-based pharmacokinetic (PK) models; mechanistically-based pharmacodynamic (PD) models and integrated PK/PD models for different kinds of pharmacodynamic data. Mathematical input would further contribute to the prediction methods used during the progression from chemistry data to toxicology to man, clinical trial simulation and design, and the establishment of public databases.

4.2.3 Interface areas

Support from governments and regulatory agencies is considered important for relevant animal studies and from governments and the EU for the use of genomics data, including ethical issues. The same goes for statistical methods of standardised toxicological and safety studies, embryogenesis and methods to correlate toxicity outcome and genomic information. Good manufacturing practices (GMP) should be implemented early in the discovery phase.

Access to and sharing data in the public domain is viewed as another area of importance. Public databases should be created for pre-clinical and genomic data as well as *in vivo* toxicity data. This may require that the quality problem is addressed, for example in relation to old data. The workshop representative from the large pharmaceutical company AstraZeneca was positive to this, providing such databases are developed in a stepwise fashion. *In vitro* screen methodologies between companies and academic institutes, too, should be shared. In relation to this, the COST B15 EU Programme (Modelling &

Simulation in Drug Development) should be incorporated in the key action.

4.2.4 Deliverables

- High quality predictions via modelling and simulation for a fast track from *in vitro* and animal studies to man
- More reliable, efficient and faster techniques for refining the assessment of drug efficacy and safety
- Extended use of *in vitro* tests in pharmacology and toxicology testing, reducing the use of animals
- Pan-European access to cell lines suitable for *in vitro* toxicology testing
- Improved non-invasive testing methods, e.g. imaging technologies for use in both animals and humans
- Improved pharmaceutical products based on better formulation principles and more precise characterisation and production methods.

4.3 How to bring candidate drugs faster into full-scale production

After a drug candidate has been identified and its validity as a concept estimated to be satisfactory, the drug formulation and production procedures have to be decided and, via technology transfer and up-scaling, carried through to full-scale commercial production. This part of the development phase has, until now, been somewhat neglected, but holds great opportunity to shorten the development time, cut costs and improve the quality and reliability of the products.

4.3.1 Bottlenecks

i) Research and development

The low availability of active substances is due to the choice of cost-effective routes of synthesis, scale-up problems and excessive "validation". In the pharmaceutical development phase, more possibilities are required to work with smaller amounts of material in small-scale predictive studies. In other words, new methodology is needed to work with a tiny amount of substance and gain results transferable to a larger scale.

Another problem is that key ingredients, such as excipients with their auxiliary function, are not always available with the right quality, hampering new approaches in drug delivery. If traditional excipients have to be replaced by new versions, they will require expensive safety testing and toxicity studies. New methods are also required to characterise the relevant properties of excipients. Such functionality-related testing has been taken up by pharmacopoeias but needs to be accepted by users and producers.

Excessive and time-consuming end process testing is used to document or characterise the production process in terms of product quality. Process analytical chemistry, leading to parametric release, may represent a solution but, like other alternatives, must be discussed with the regulatory authorities.

ii) Education and training

Process analytical chemistry is not identified as a strategic research discipline within the EU and lags behind other initiatives in the US. This has resulted in a lack of experienced process analytical chemists. Training is, therefore, needed and a pan-European concept would be the method of choice. The thin and uneven distribution of expertise in applied mathematics, such as multivariate analysis and experimental design (chemometrics), means additional training is required here, too. The same goes for applied spectroscopy, which is used to take measurements in laboratory and process environments.

Differing skills among researchers employed in research and development and manufacturing also impede the transfer of technology. These deliverer/recipient problems call for holistic training courses.

iii) Regulatory problems

The introduction of new technologies for control and advanced in-process testing is hampered by the absence of a common scientific platform for industry, academia and regulators. Common projects involving all three partners would facilitate integration.

When an application for approval is sent to the authorities, the integrated process from formulation to manufacture is not considered as the documentation is presented step-by-step, and this causes delays in the assessment. To remedy this, integrated processes should be developed and documented with regulatory authorities. Smoother validation techniques would also alleviate the heavy workload involved in repeating the documentation process when changes have to be made.

4.3.2 Research and technology aspects

A series of manufacturing areas require further research and the development of new and better techniques.

- Predictive methods are required for up-scaling. This includes process system engineering for the quantitative prediction of chemical processes.
- Real-time quantitative measurements of properties at molecular level, i.e. of physicochemical, functional properties as well as an indication of interactions, are needed during manufacturing. Measurements taken in the production of pharmaceutical dosage forms should go from being indirect to direct. By combining measurements of indirect process parameters, such as temperature, pressure or flow, with selective measurements of molecular properties, it becomes possible to follow changes in the reaction processes in much more detail.
- Pan-European process analytical chemistry initiatives should be supported and developed, consolidating national efforts conducted at different levels and increasing their scientific critical mass.
- Sensors devoted to the phenomena taking place in pharmaceutical process environments should be developed. This particularly concerns information-rich sensors, such as those tailor-made for quantitative molecular information and based on process system engineering research.
- Applied spectroscopy should be further developed to support pharmaceutical processes, along with mathematical tools for the exploitation of real-time direct measurements. In this way, it should be possible to move from pure empirical modelling to a combination of empirical modelling with fundamental physical models.
- More toolboxes for the simulation and modelling of chemical processes would provide much-needed quantitative models for predictive up-scaling.
- Sameness testing and its acceptance should be facilitated through an interaction between industry and regulatory authorities. Instead of single parameters, then, the regulatory guidelines should involve the entire information package, preferably using non-invasive tools.
- Technology for reliable quantitative measurements of sameness with a specified quality should be prioritised. Current positive experiences with non-invasive techniques, like Near Infrared and Raman Spectrometry, should be extended to other fields.
- The development of characterisation methods for relevant polymer excipients, also known as functionality-related testing, should strengthen the material sciences. In this, cross-disciplinary approaches should be used, involving for example physical chemistry, material sciences and analytical chemistry for an optimum outcome.

- The field of crystallisation and polymorphic control is becoming more and more important and represents a natural part of the development phase. Early studies with relevant techniques are necessary, and new approaches have to be developed.
- Recycling and energy-saving aspects of the production process and closed processes for hazardous chemicals need to be considered, along with continuous processes as an alternative to present batch production. For the continuous processes, different quality control aspects have to be developed with the authorities involved. The application of information system technology combined with advanced measurement technologies, too, need to be implemented for the steering and monitoring of processes (see also 4.3.3).
- High throughput analysis instrumentation and automation are required. The approach used in the discovery phase should also be utilised in the development process after adapting to the different situation represented by the dosage forms.

4.3.3 Interface areas

The research and technology aspects can only be solved by a collective effort that covers many disciplines and technologies. These include:

- The pharmaceutical sciences (material science, physical chemistry, analytical chemistry, formulation design, pharmaceutical technology, biotechnology)
- Scale-up, i.e. from milligrams to a few grams. How can sufficient material of appropriate quality be obtained for early formulation and toxicity studies? This is a problem involving more than 100 substances.
- Process analytical chemistry (sensor technology, non-invasive spectrometry, chemometrics, process interfacing, pharmaceutical technology, process system engineering and control technology)
- Process system engineering (measurement technology, including process analytical chemistry, chemical engineering, pharmaceutical engineering, fermentation technology, process modelling, process control technology and multivariate statistics)
- Process validation (strategy to apply, for example, chemometrics at an early phase of process development and, thus, prevent unnecessary validation programmes)
- Formulation technology design for strengthening the multidisciplinary concept and developing generic tools for industrial pharmaceutical applications.
- Application of information system technology in the steering and monitoring of processes. Instruments and software need to be developed to consolidate all the measurement data generated (cheminformatics). Tools are required for data reduction. Improvements are needed in the logistics area and the design of production lines.

EU collaboration should be established by creating cross-functional research programmes involving scientists from academia and industry and regulators. A common scientific platform for these three

interested parties would ease the introduction of new technologies, including the generation of ideas, tests of technological concepts and evaluation of new technology on a realistic scale. Resources could also be pooled for expensive equipment and educational needs and to enable virtual Centres of Excellence to make special research efforts.

4.3.4 Deliverables

Investments in research, technologies, collaboration, training and education would result in:

- Faster processes and products with an improved and more consistent quality. This would benefit all parties (producer, regulator, retailer, consumer and taxpayer).
- A considerable reduction in the overall time needed for developing drug substances and drug products, whether biotechnological or conventional therapeutics
- Process models based on information gathered from quantitative measurements of material properties at the molecular level
- A seamless development process and, most importantly, improved scale-up and technology transfer via predictive process models
- A considerable reduction in traditional quality control costs following the introduction of parametric release, i.e. by measuring product quality during instead of at the end of the process
- Continuous information from process analytical chemistry with product quality measurements during processing – considerably superior to the end-of-process quality control used today.
- A better understanding of the advantages of new technologies due to joint programmes involving regulatory authorities, the pharmaceutical industry and academia. This will remove hurdles within companies and hesitation among regulators.
- New improved methods for producing active pharmaceutical ingredients and solid dosage forms.
- Cleaner and greener reactions and processes through safer and more energy-saving processes.

4.4 How to bring drugs faster to regulatory acceptance

The opinions of industry and authorities will always differ regarding matters of importance to the authorisation procedure for human medicine. Companies usually prioritise speed, though never at the expense of safety and efficacy, while the regulatory authorities put public health interests in relation to efficacy and safety first.

This workshop session dealt with how to improve the efficiency of the authorisation procedure. Aspects concerning the provision of the necessary data before drugs can be used in humans and market acceptance were not discussed. This clinical part of the drug development process would benefit from a separate workshop.

4.4.1 Bottlenecks

The following regulatory issues were considered important in relation to research and development and training and education:

- Industry-regulation interface
It is extremely important that the needs and demands regarding a specific development plan for a new drug are discussed by industry and regulatory authorities as early as possible. Continuous discussion during the whole research and development period will also cut the time to market.
- Clinical development
An initial dialogue between the developer and authorities will reduce the clinical development time.
- Pharmacovigilance
Risk groups should be discussed from the beginning of the clinical planning phase to ensure all potential patients are included in the safety programme, facilitating the authorisation process.
- Quality of the review process
The procedures followed by regulators and industrial experts should be fully transparent. Evaluation projects should be conducted to compare the procedures and decisions of agencies in Europe, the USA and Canada.
- Improvement of IT support
All submissions should be sent electronically in safe systems like the newly-developed EUDRASAFE.
- Joint assessor courses
The courses already initiated between authorities and industry should be extended to include academic partners as well. Examples are the pre-clinical “assessor” courses held in Portugal and Denmark in 1998 and 1999 respectively.

4.4.2 Research and technology aspects

The following initiatives involving industry and regulatory authorities were proposed:

- Assessment of the quality of applications submitted through the central procedure (CP) and the mutual recognition procedure (MR). The aim is to obtain more identical procedures in terms of quality and time to approval.
- Assessment of reasons for major public health objections from single member states in the mutual recognition procedure and submission withdrawals. Misuse of the phrase “major public health concern” in the summary of product characteristics is not acceptable.
- Comparative assessment of EU advice procedures and those in the US with input from both industry and academia. Both positive and negative aspects should be covered.
- Acceptance criteria should be determined to initiate clinical trials of new biotech/gene products in man and identify surrogate end-points in major therapeutic areas.
- Current and future problems should be solved regarding the translation of regulatory matters as new member states join the EU. Joint projects involving industry, academy and authority are required to limit the amount of double and triple information sent to different authorities. The usefulness of IT in this area is clear. Pilot projects between industry and the US authorities are already running. Ways to shorten the process of obtaining adverse event information in summaries of product characteristics and patient product information could be other subjects of important joint projects.
- Inter-authority quality assessment projects with academia would raise the quality of the review process. What do the quality assessment of reviews and mutual recognition and central procedures have in common during their development? The need for joint projects involving all three interested parties was put forward. Cross-authority analyses of review outcome are already running within the EU. In the future, these should also include US and European analyses of projects to assess the quality of marketing authorisation applications.

4.4.3 Interface areas

i) Research

European regulatory IT initiatives were considered significant and necessary for improving the regulatory process. The general view was that the EUDRAWATCH and EUDRANET programmes should be expanded. These relatively new systems should be used as correspondence tools for both industry and authorities all over Europe. Many agencies and companies have not yet joined the systems, suggesting that forced commitment, possibly in project form, could be initiated.

The authorities should introduce electronic communications wherever possible. In the future, all written contact should be in the form of electronic mails and electronic documentation forwarded in secure mail systems such as EUDRANET. Technology allowing the secure electronic exchange of information between industry and authorities should be implemented. To ensure smooth communications, software applications should be harmonised, removing incompatibilities.

ii) Networking, training and infrastructures

A pan-European network and forum for discussing acceptance criteria should be established to initiate

clinical trials with new biotech or gene products in man. These initiatives are well supported by the proposed changes to the new EU e-directive concerning clinical trials.

Another pan-European forum for discussing acceptance criteria of surrogate end-points in major therapeutic areas is also required. This very important task should top the list of joint projects involving industry, academia and authorities. The training and education of assessors within quality, safety and efficacy should be established at a European level.

A central EU adverse event database regarding feasibility and development aspects and an EU Centre of Excellence in pharmaco-epidemiology are both great needs. Such European centres should be organised in such a way that the necessary information can be simply obtained from national agencies and industry.

4.4.4 Deliverables

The establishment of an early dialogue between regulatory authorities, academia and industry regarding the implementation of new methodologies and techniques would mean more new safe medicines could be brought faster to the market.

4.5 How to reshape the drug development process from the beginning

Scientific advances, competition and commercial considerations have created a need to accelerate discovery and the development of new and better medicines. Due to the fundamental change that has taken place in drug discovery and development, pharmaceutical companies are now developing, assessing and introducing new advanced technologies to optimise the drug development process. Key issues here include training and education and the crucial interface between regulatory authorities and industry.

4.5.1 Bottlenecks

Research into the drug development process continues to be insufficient. Opportunities to, for example, perform overlapping phases of clinical development and combine multiple objectives and efforts in a given trial remain relatively unexplored. More databases, benchmarking and modelling tools for better decision-making processes are a necessity, along with new technologies and research areas. Fields such as genomics, proteomics, automation, miniaturisation and bioinformatics with their tremendous potential still have to be integrated and used appropriately throughout the drug development process.

High throughput procedures that use small quantities of material to determine key parameters for predicting the efficacy and safety profile of a product are often lacking in the clinical candidate selection process. The generation, capture, analysis and mining of data have to be more closely monitored and the proof of concept process streamlined through the development of better prediction models within *in silico* biology.

Optimisation of the drug development process requires technical and scientific expertise in many areas. In some disciplines, such as bioinformatics and applied mathematics, there is a lack of well-trained experts. Due to the multidisciplinary nature of drug development, knowledge covering a range of disciplines is required. This highlights the need for a European syllabus for holistic drug development.

Regulatory requirements often do not reflect the latest scientific developments. The interaction between regulatory authorities, academia and industry is generally insufficient concerning the adaptation of existing or establishment of new guidelines for drug development.

4.5.2 Research and technology aspects

i) Without lowering scientific and medical standards, it is necessary to intensify process research in order to accelerate drug development. This involves:

- The implementation of chemometrics and presence of high quality material in the right quantities
- Developing IT-supported information data management and decision-making processes, including clinical data storage, retrieval and analysis tools and the integration of pre-clinical and clinical data
- Introducing structure-based predictive systems based on complex mathematical modelling and analysis of data sets and simulation techniques, e.g. for drug formulation and manufacture

- Integration of existing and new structure-pharmacokinetic relationships in a network of models supported by a growing volume of experimental data generated by high throughput screening
- Genotyping, pharmacokinetics, pharmacodynamics and phenotyping to be introduced as integral parts of novel drug discovery and development
- Mathematical modelling to connect disease with individual variance and biochemical symptoms and disease progression.

ii) Clinical candidate selection requires new predictive methods for better and earlier decision making. Efforts are needed to reduce the cycle time from drug discovery to application of the first dose in man. These include:

- High throughput predictive toxicology, absorption, distribution, metabolism and excretion (ADME) screens and other cell assay predictors to study large numbers of compounds available in small quantities. This requires the implementation of nano-technology.
- The development of new technologies based on human tissues, cells and membranes (*in vitro*), new transgenic animals and new models of gene expression (*in vivo*) to facilitate scaling up prior to use in man
- Increased efforts in the field of innovative delivery systems
- Better computational methods are necessary to determine the impact of physicochemical properties on structure-function relationships
- *In silico* simulation and modelling with high predictability will be of increasing importance (e-ADME, e-toxicology)
- The establishment of an optimised early drug supply chain to ensure the prediction of biopharmaceutical and formulation properties. Large scale chromatography and rapid scale up, parallel and automated production all of which would provide a timely drug supply for clinical studies.

iii) Proof of concept clinical trials are used for "go/no go" decisions and are, therefore, of critical importance to the entire development programme. These require:

- New concepts for clinical trial design and evaluation including statistical analyses
- Mathematical modelling for a better understanding of diseases and simulation techniques for elucidating biological and pharmacological issues
- Whole animal, mechanism-based modelling to forecast human pharmacokinetics – the pharmacodynamic relationship is essential
- The development of cell assay systems in anticipation of down-stream development issues
- Panels of biomedical markers and surrogate end-points and their disease correlation
- Stronger early and multi-centre clinical concept evaluation, including regulatory definitions of the minimum requirements for entry into man
- The development of pharmacogenetic profiling techniques for genome-based trial subject selection.

4.5.3 Interface areas

The interfaces between the various phases of the R&D process have to be eliminated and a seamless discovery-development process established. IT will play a major role here. Interfaces between different techniques and disciplines, too, need to be overcome by forming interdisciplinary project teams and providing training and education that combine a number of disciplines.

In today's drug development environment, networking is essential at various levels, relating to co-operation within a given company, among small, medium and large players in industry and between industry, academic institutions and/or regulatory authorities. The legal, fiscal, managerial and organisational foundations for such co-operation networks need to be improved in order to benefit from the synergistic effects created. Centralised databases and database networks based on a variety of topics (e.g. antibiotic resistance and orphan diseases) should be developed at a European level.

An official forum for interaction between regulators, academia and industry would be conducive to reshaping and optimising the drug development process, particularly in the light of new therapeutic approaches and emerging technologies.

Training possibilities would increase if an inventory was established with a detailed description of all the available education programmes and training courses related to the pharmaceutical and biomedical sciences involved in drug discovery and development. Action should be taken to fill gaps and strengthen weak areas and training and education in holistic oriented drug development made available.

New product types, techniques and therapeutic approaches sometimes fail to gain social acceptance. More efforts are required to inform and educate the public adequately. This calls in particular for the training and education of ethical committees.

4.5.4 Deliverables

Under the leadership of the EU RTD programme and with the appropriate support and incentives, drug research and development could take a big step forward. An improved, science-based, decision-making process, helping to avoid study delays and bottlenecks, would provide patients with faster access to better medicines.

More research and interaction between industry, academia and regulatory would result in the development of predictive models, including *in silico* methods, and the establishment of a common database. Tested and approved pre-clinical methodology for clinical candidate selection would also emerge, along with modern, pragmatic and science-based regulatory guidelines.

Validated and predictive biomarkers and surrogate end-points will result from a better understanding of biochemical pathways and their correlation to disease progression. More processes based on small-scale experiments would contribute further to the optimisation of the supply chain.

The establishment of Centres of Excellence would ensure better training and education in cutting edge technologies and holistic drug development methodologies – promoting the entire drug development process.

4.6 How to utilise IT in speeding up the drug development process

This session covered the importance and expected impact of information technology in the creation of a more effective drug development process.

4.6.1 Bottlenecks

A large and increasing number of activities related to the development of medicines involve the use of advanced IT, such as informatics, modelling and trial design. A series of barriers to more effective use of IT in the development of medicines can, though, be identified:

- Too little understanding of the potential impact of modern IT among scientists working with drug development
- A need for information systems with more user-friendly communication, data handling, data storage, data presentation, etc.
- A need to implement standardised and validated information systems
- Culture change in data handling – from paper to electronic data
- Insufficient consideration of key elements in data handling – the storage, use, share and reuse of data
- Insufficient management in all aspects of IT
- A lack of professionals in the IT field and tough competition with other industrial branches
- A need for more effective and secure systems for data handling with respect to the storage, use, reuse and sharing of data.

4.6.2 Research and technology aspects

Based on these barriers, a series of research and technology aspects can be identified, facilitating progressive and necessary development. These include research in IT relevant to the pharmaceutical sciences, for example experimental design and data treatment, such as the design of experiments, modelling of data, generation of predictive models and calculation of model precision.

The generic principles and models for information management and bioinformatics are important issues. The same goes for cost-benefit analysis in drug development in terms of data generation, utilisation and quality.

New ways of communication with regulatory agencies are needed, such as continuous dialogue and integration or on-line delivery of data. Streamlined systems are also required for electronic communication within health care systems, hospitals and laboratories and among general practitioners.

In silico testing of drug candidates in biological and developmental models raises many intriguing problems for the regulatory authorities with regard to the validity of the results obtained from such simulations. Here, the authorities have to depend on the amount and comprehensiveness of the data on which the results are based. The authorities determine how much data has to be produced before the results are recognised as consistent.

4.6.3 Interface areas

IT is highly relevant to the following elements of the drug development process. The list is not exhaustive.

- Prediction of pharmacokinetic/pharmacodynamic behaviour
- Toxicokinetics
- Pharmacogenetics
- Computer-aided trial design
- Assessing risk associated with specific projects
- Elimination of failed/equivocal studies
- Dose ranging/optimisation early in the development programme – always in relation to key studies of commercial doses and formulation
- Use of all data available to the project teams - toxicology data, known class effects, data from previous trials, competitor experiences
- Automation of trial management process
- Web-based networks for data capture
- Development planning and trial design using real-time data
- Real-time adverse event effects and outcome reporting
- *In silico* trials
- Process analytical chemistry towards parametric release, reducing quality control costs
- Batch release based on information-rich, non-invasive process analytical chemistry methods, also known as chemometrics
- Web-based patient recruitment.

Education in modern information systems and their potential use by researchers, administrators and other personnel involved in the drug development process should be developed. Activities related to this include the formation of a European demonstration centre with super computers and modern information systems and Centres of Excellence for public clinical and toxicity data, which can be shared among clinical scientists. Some representatives from industry further expressed an interest in gradually sharing data with such a centre.

4.6.4 Deliverables

A drug development process incorporating information systems (IS) and information management (IM) would result in better decisions, less expensive knowledge and faster, more efficient drug development due to:

- Fewer but better trials conducted in more focused development programmes
- Faster trial reporting with real time data, attracting faster regulatory review
- Availability of public databases for all types of clinical data
- Fully implemented electronic communication between health care bodies and employees.

4.7 How to turn new biotech molecules into deliverable products

Macromolecular drugs which have been discovered and are possibly being produced by modern biotechnology methods represent some of the special aspects of biotech products. Discovery of such compounds, including peptides and proteins, antisense agents, such as oligonucleotides, and vectors for somatic *in vivo* gene therapy, may be expected to increase over the next few years, with many already awaiting adequate pharmaceutical development. In the future, pharmaceutical biotech products may also comprise genetically modified cells, artificial organs and devices designed and manufactured by modern tissue engineering.

4.7.1 Bottlenecks

i) Research and development

Compared to classic drugs consisting of small organic molecules, macromolecular biopharmaceuticals appear to be much more efficient. Not only do they alleviate symptoms but, in some cases, even cure diseases, such as cancer, or inherited metabolic disorders. They also impose particular demands on the development process, mainly because of their structural complexity, large size and poor metabolic stability. In addition, they are plagued by a very difficult delivery, particularly via the most common and preferred oral route and through the blood-brain barrier to reach the brain and central nervous system. The pathophysiological background required for the design of new biotech molecules, too, is often lacking. These factors were identified as significant bottlenecks in the development of these compounds.

Due to their biochemical structure, biotech compounds impose particular needs and demands on the analytical techniques used for quantification and quality control. A particular emerging problem relevant to proteins may be their glycosylation. Animal models and bioassays relevant to diseases and metabolic disorders are often lacking.

Immunogenic side effects of systemically administered macromolecules deserve particular attention. How can they possibly be overcome or avoided by adequate molecular design? Sufficient quantities of compounds for clinical trials, though, have to be provided by processes that meet the regulations of Good Manufacturing Practices (GMP) – a prohibitive cost for proof of concept. Such process development requires better access to cell banks, as well as adequate fermentation, purification processes and facilities.

ii) Education and training

The development of pharmaceutical biotech products requires adequate education and training of the scientists responsible for such projects. In many respects, traditional pharmaceutical curricula do not provide sufficient background in molecular biotechnology, while specialists trained in molecular biology and biochemistry often lack knowledge and skills relevant to the development of pharmaceutical products.

Facilities and institutions for relevant training in pharmaceutical biotechnology at both an academic and post-academic level are considered vital. These can be organised by multidisciplinary collaboration between the existing Centres of Excellence in various disciplines, for example pharmacy schools and

faculties, molecular biology, biochemistry and bioengineering departments and departments covering fermentation, scaling up and purification. Their activities need to be co-ordinated by the creation of virtual and international centres, securing the necessary critical mass and fulfilling education and training goals.

iii) Regulatory problems

Like most traditional pharmaceutical scientists, the regulators responsible for registering pharmaceutical products have a fair understanding of how to handle small organic molecules, but lack experience in handling the larger biotech molecules. This calls for a constructive dialogue between scientists, developers and regulators. In this, the regulatory authorities and their personnel must interact with both academic institutions and industrial companies to develop constructive partnerships.

Other specific problems identified for pharmaceutical biotech products included the production of compounds under GMP conditions to obtain an early proof of concept in clinical trials. In Europe, such facilities are virtually non-existent. Special considerations and rules for conducting clinical trials and registration procedures may further be enforced for incipient compounds where clinical significance, i.e. orphan drug status, must be demonstrated.

Considerations regarding substance purity, e.g. the presence of DNA residues or differences in the glycosylation of recombinant peptides and proteins, need special attention.

4.7.2 Research and technology aspects

More specific research and the development of new methods are required regarding the transportation of pharmaceutical biotech products across biological barriers. New concepts and adequate targeting and delivery systems are needed for this purpose.

Artificial gene-delivery systems, particularly *non or pseudo-viral* ones which appear to be safer and easier to manufacture than the presently favoured viral vectors, will be the key to the success of any *in vivo* gene therapy, such as the treatment of cystic fibrosis by CFTR-transfecting inhalation aerosols. Novel carrier systems, such as nanoparticles, liposomes and micelles, also have to be investigated and developed. In this context, the emerging, novel tools of bioinformatics and nanotechnology have to be integrated in pharmaceutical sciences and technology. Similarly targeting and stealth technologies, addressing the various barriers imposed by the body's immune system, will be essential and have to be combined with the novel carrier systems. The clarification of general structure-function relationships is another need.

What research will bring regarding drug delivery through modified cells and organs, newly designed peptides and proteins or special medicotechnical devices can, at present, only be imagined. But technologies that overcome biological barriers by facilitating cell entry or modulating tight junctions in a physiologically acceptable way will have to be developed in order to allow convenient, needle-free administration to the patient. So-called alternative routes, e.g. pulmonary, buccal and nasal, have to be explored physiologically and technologically.

Analytical methods for the quantification of biotech molecules still often have to rely on complex and non-precise bioassays. These should be replaced by modern alternatives, based on novel and emerging instrumental analysis tools, including surface plasmon resonance, fluorescence correlation spectroscopy, confocal laser and atomic force microscopy, matrix-assisted laser desorption ionisation time-of-flight mass spectrometry (MALDI-TOF-MS), possibly in conjunction with secondary ion mass spectrometry (MS-SIMS). Valuable characterisation of biomolecules will be performed by combining separation methods with various mass spectrometric techniques.

Medium to large-scale production requires new production and purification methodologies, e.g. inducible expression systems, chemically defined, serum-free media and inducible or infection systems, the latter replacing transfection systems. Novel technologies, such as molecular imprinting and transgenic animals, have to be adopted and further developed.

4.7.3 Interface areas

The remarkable complexity of pharmaceutical biotech products within analytical science, immunology, delivery/targeting and so on represents particular scientific challenges. These can be solved by industry-academia partnerships. The EU RTD programme should therefore address the administrative and economic requirements which will make such collaboration possible.

A holistic training approach to drug development requires further expansion from the initial gene to product, including the process system engineering necessary for biopharmaceuticals. Training networks need to be established for on the job training in pharmaceutical biotechnology and educational networks, too, for graduate students, such as the European Masters Programme in Pharmaceutical Biotechnology with its Ph.D. curriculum, visiting projects and summer schools.

Platforms for discussion and partnership between regulators, academia and industry along with concerted actions to co-ordinate and discuss transdisciplinary research programmes spanning from engineering to cell biology are considered important tools. The rise of start-up companies, particularly spin-offs from academic institutions, holds great potential for the creation of new jobs for European society. These enterprises, however, need funding to develop the necessary core technologies and facilities to produce material that accords with GMP for subsequent clinical trials.

4.7.4 Deliverables

Provided the proposed measures of this key action are implemented and fulfilled during the coming 6th EU RTD framework programme, significant progress may be expected for new pharmaceutical biotech products. These will address the medical treatment needs of a variety of diseases with a high impact on quality of life. Improved collaboration between academic institutions, industrial companies and regulatory authorities in relation to pharmaceutical biotech products will lead to sustainable economic growth and create new job opportunities within both large and small pharmaceutical companies in Europe.

5. Conclusions

“New Safe Medicines Faster” gained the full support of workshop participants and several industrial, regulatory and academic organisations as a key action in the coming 6th EU RTD framework programme. Further backing from the cystic fibrosis patient organisation was obtained.

With only 10 to 20 researchers per workshop session, it was not possible to cover all aspects of the topics up for discussion. Nevertheless, through the hard work and commitment of the participants, the required input was produced. The discovery, pharmacogenetics and clinical research aspects of the drug development process were also not subject to direct analysis, the first being deliberately excluded and the latter failing to receive necessary attention due to the lack of clinicians at the workshop. Additional workshops in these three aspects are, then, required to gain a complete picture of the road ahead for drug development as a whole.

During the two days in Brussels, the following general conclusions were drawn:

5.1 The drug development process

The future prosperity of the European pharmaceutical industry is dependent on the reshaping and optimisation of the drug development process based on an integrated approach involving industry, academia and regulatory authorities. While industry and academia have a tradition for co-operation, direct interaction with Europe’s regulatory bodies lags behind. The involvement of these authorities from the outset of the changes of drug development process is considered vital.

The workshop deliberately focused on the development issues that follow the discovery phase, all of which are of equal importance. Instead of being viewed as a series of consecutive steps, drug development requires parallel thinking to get the process to accelerate. At present, the large number of lead candidates results in bottlenecks in the ensuing development phases. What is required, then, is not just more candidates, but candidates of a higher quality. IT is of paramount importance for further integration of all the elements of the drug development process.

5.2 Focus research areas and technology development

The multitude of research topics related to the drug development process gives rise to a plenitude of interdisciplinary research areas. Academia should take these topics on board with an early involvement by regulatory authorities.

The following focus areas were mentioned:

- Functional gene analysis
- Pathophysiological understanding of diseases for target prioritisation
- *In vivo* and *in vitro* disease models and transgenic animals
- Pharmacogenetic profiling and population genetics
- Predictive biomedical markers and surrogate end points

- Drug and gene delivery systems
- Modelling tools for *in silico* testing to be applied wherever possible in the drug development process
- Toolboxes containing predictive methods and seamless scaling techniques
- Miniaturised fast screens with a robotic base to be applied wherever possible in the drug development process
- Pharmacometrics including non-invasive testing methods and sensor technologies
- Process measurement technologies to enable rational manufacturing
- Implementation of IT solutions throughout the drug development process
- Science-based regulatory guidelines reflecting the latest scientific developments.

5.3 Networking

Networking secures the exchange of information between scientists. More networking is, therefore, highly desirable between European pharmacy schools and faculties and other institutions involved in the drug development process. In addition, European consortia incorporating academia, industry and regulatory authorities should be established to promote evidence-based clinical pharmacology, data collection and analyses of drug effects, interface process and management research, electronic drug development and so on.

5.4 Education and training

The need for trained staff who can deal with all the new disciplines and technologies related to drug development was repeatedly emphasised at the workshop. Training and education were viewed as essential for the implementation of new knowledge in research. This means more postgraduate education in drug development sciences is needed. As part of this, a Centre of Excellence equipped to provide training in cutting edge technologies and with a holistic training scheme should be established.

More education is required within the following disciplines:

- Mathematics (modelling, simulation, statistics)
- Bioinformatics (prediction)
- Genetics (human polymorphism)
- Information technology, including pharmacometrics and information management (data handling).

5.5 Infrastructural needs

In addition to calling for more European networking and Centres and Excellence, the workshop revealed a great need for the establishment of public databases. These databanks should contain results from exploratory safety and efficacy investigations and patient data from clinical trials of drugs. In this connection, a Centre of Excellence focused on pharmaco-IT solutions is required.

5.6 Innovation

There was no doubt among workshop participants that the drug development process contains huge potential for new start-up companies and SMEs. Any area in which fast technological process takes place offers such possibilities. A boom in pharmaco-IT solutions is anticipated when the IT sector starts to recognise the many opportunities in this field.

5.7 Involvement of European citizens

Clinical evaluation is the last stage in the development of new medicines. Here European citizens have an important role to play in relation to understanding the importance of the drug evaluation process and their willingness to take part in clinical trials. Patient enrolment will often limit the progress of clinical trial programmes. In this, patient organisations are a key partner as they request new treatment opportunities, provide patients with information and education and mediate easy access to a large number of patients. The availability of well-qualified physicians willing to act as investigators in clinical trial programmes is another key factor.

5.8 Summary

Research activities are vital to facilitate the development of innovative, high quality medicines which are both effective and safe. These include functional gene analysis, the development of disease models, modelling, simulation and prediction techniques, automation and high throughput methods, non-invasive measuring, IT and process optimisation.

Inclusion of the key action “New Safe Medicines Faster” in the 6th EU RTD Framework Programme would undoubtedly spur the pace of change in the European pharmaceutical sector – within academia, the pharmaceutical industry and regulatory authorities by creating pan-European networks that deliver new treatments faster to the citizens of Europe.

6. Recommendations

“New Safe Medicines Faster” is recommended for incorporation in the 6th EU RTD Framework programme, preferably as an independent key action.

By focusing on the procedures involved in drug development, this key action simultaneously promotes basic research, new leading technologies and deliverables in the form of new safer medicines. This process-oriented approach also favours new interface research, including management of the enormous quantity of diverse data that the development of medicines delivers. In this way, new standards could be set for handling complex data.

The workshop revealed a great demand for competent, highly trained drug researchers, both specialists and generalists within the pharmaceutical sciences and related disciplines – a need that should be met by the key action.

The strict regulations imposed on drug development make it particularly unique. The key action would create new European platforms for regulators and researchers to design the necessary changes to the drug development process in partnership and bring about the much-needed improvements in capacity, efficacy and speed. Only in this way can the European pharmaceutical industry exploit the enormous opportunities created by the genomic revolution and achievements of modern chemistry for the generation of new medicines to the benefit of European citizens.

This report, though, cannot stand alone, as it does not place equal weight on the various aspects of the drug development process. Additional information about the critical issues and bottlenecks related to the clinical phase of drug development and the new, very important area of pharmacogenetics should be sought separately. Many of the technological issues also require further analysis and consideration.

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