

3 Improved Predictivity of Efficacy Evaluation

3.1 Summary

This chapter describes how academic clinical and pharmaceutical expertise can be brought together to identify the required biological tools, and to advance the use of emerging technologies including omics and imaging that will be required for their successful implementation. Multidisciplinary groups with expertise in cancer, brain disorders, inflammatory diseases, diabetes and infectious diseases reviewed the current state of knowledge, and outlined a strategy to address the key bottlenecks in drug discovery. It has become clear from the series of workshops on efficacy bottlenecks that there are overarching needs, common to all disease areas, which illustrate the challenges of improving efficacy such as to:

- Develop better understanding of disease mechanisms;
- Develop *in vitro* and *in vivo* models predictive of clinical efficacy;
- Develop *in silico* simulations of disease pathology;
- Stimulate translational medicine in an integrated fashion across industry and academia;
- Create disease-specific European Imaging Networks to establish standards, validate imaging biomarkers and develop regional centres of excellence;
- Create disease-specific European Centres for validation of omics-based biomarkers;
- Co-ordinate the development of national patient networks and databases to develop a true pan-European organisation for patient selection and clinical trial analysis;
- Form a European stakeholder consortium to address value demonstration, including quality of life issues, patient reported outcomes and burden of disease;
- Develop a partnership with regulators to devise innovative clinical trial designs and analyses, to aid acceptance of biomarkers, and to promote data sharing and the joint consideration of ethical issues.

Without exception, these common needs would apply equally to other disease areas, and the creation of European-wide networks and centres will form the basis by which the work of the initiative will spread beyond its current confines. It needs to be stressed that the work is, necessarily, pre-competitive from the pharmaceutical industry standpoint and, therefore, cannot concern itself with specific drugs or with issues that relate to the behaviour of individual molecular entities. Therefore, the absence of certain diseases from the scope of the initiative does not in any way imply that research on these will be starved of resource and interest. The initiative is a small part of the total effort invested in biomedical research in Europe, but we expect that this small part, focused as it is on technical and procedural bottlenecks, will have a disproportionately large effect on future success in all disease areas.

3.2 Introduction

Advances in knowledge and technology have greatly increased our expectations of improved healthcare. The investment into R&D of new medicines has seen spectacular growth over the past decade. Despite technical progress in drug discovery technologies, there has not been a concomitant increase in R&D productivity. The current developments in the basic discovery sciences have not been mirrored by concomitant progress in understanding the clinical basis of disease and, therefore, the development of novel effective therapies. This situation needs to be addressed and a better integrated approach to innovative medicines R&D is required.

The objective of the Innovative Medicines Initiative is to accelerate the process of bringing new medicines to market, and to increase the efficiency of drug development. This chapter will provide a framework of recommendations and inputs for enhancing the predictability of success by focusing on the relevant bottlenecks in the drug discovery and development value chain (Figure 1). For this purpose, the major bottlenecks have been grouped into four key areas; pharmacology, biomarkers, patient recruitment and regulatory approvals, as illustrated in Figure 21 below.

It should be remembered that the benefit of a new drug to the patient and its approval involve, of course, not just its clinical activity, but also its safety. Several of the bottlenecks defined in Figure 1 apply to both of these aspects, and come together in the risk–benefit analysis of the regulatory approval process and in post-marketing pharmacovigilance. The detailed analysis of safety is presented in Chapter 2 of this document.

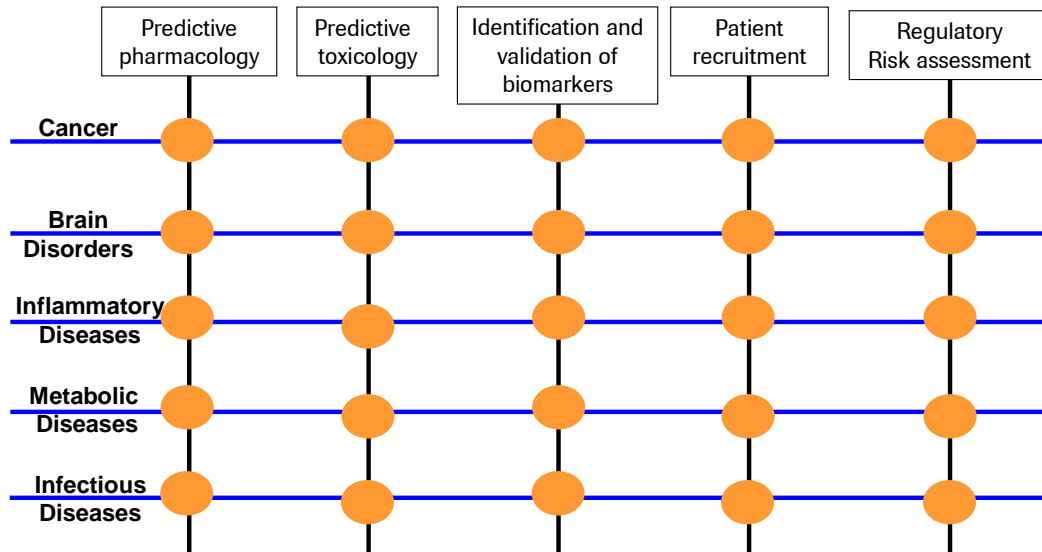


Figure 21 : Efficacy Issues are Often Disease Specific

Following an extensive consultation process, this SRA focused on the following disease areas:

- Cancer;
- Brain disorders;
- Inflammatory diseases;
- Metabolic diseases;
- Infectious diseases.

These diseases have been chosen because they are, primarily, important areas of unmet medical need, affecting the lives of millions of European citizens. We do realise, however, that there are many other medical conditions that the SRA could also have addressed which remain problematical in our society. The disease areas were chosen because this Technology Platform provides the opportunity to address challenges that have so far prevented or impeded progress in the development of better treatments, and to encourage research, which we predict will have a real impact within the time frame of this programme. In other words, significant progress in these areas is expected if the SRA is implemented.

Although there are elements that are common to all therapy areas and may also be common to other medical conditions, each disease has a unique combination of issues. In one disease, it might be a lack of predictive animal models in which to test putative treatments. In another, it might be the heterogeneity of the patient population and the inability to recruit the right patient group for clinical trials. In a third, it might be the failure to consider quality of life measures in the demonstration of clinical efficacy, and inadequate attention being paid to patient needs. Addressing these issues in the context of one major disease thus informs others, and provides a framework for change that will improve and guide the drug discovery process for all disease areas. This will be particularly powerful if the science to be undertaken is able to streamline the clinical trials and regulatory processes. It will reduce not only failure rates, particularly in late clinical development, but also the time and cost. Such a sea change in the business would greatly encourage research into other diseases, particularly those that have been hitherto neglected on the grounds of the high cost of R&D.

3.2.1 Pharmacology

While infectious diseases remain a major threat to the health of Europe's citizens, the challenges to an ageing population are the chronic, degenerative diseases. Many of our approaches for chronic diseases focus on control of symptoms, and novel drug development should be targeting treatments that affect disease progression and ultimately, cure the disease. Advances in basic science in the past few years have indicated that most common diseases have extremely complex patterns of pathogenesis, involving the regulation of dozens, or even hundreds, of genes and their protein products. In the light of advances in genomics, proteomics, and bioinformatics, the basic science of the 1980s and 1990s where single or small numbers of pathways were investigated would currently seem naïve at best.

New treatments will, therefore, only emerge from a better understanding of the pathophysiology of disease. This work will not only point the way to treatments with more predictable efficacy, but will also create the biological tools required to facilitate the drug discovery process, and the diagnostic agents needed for early detection of the disease and prediction of treatment responsiveness. Out of this initiative, we will gain an insight into how to prevent disease, but the challenge of discovering disease-predicting biomarkers of sufficient precision and accuracy to justify pre-emptive treatment is considerable. It is inconceivable that such markers would be acceptable, unless firmly based in an understanding of disease mechanisms.

Whether for treatment or for prevention, these biological tools are needed to allow a rational and well-informed choice of molecular target, for the development of *in vitro* screening methods to discover promising drug leads, and animal models that demonstrate pharmacological action and predict efficacy in the human disease. These are not trivial undertakings, and past inadequacies in this regard are responsible for a significant proportion of the drugs that have failed in clinical trials to meet their endpoints.

A major key to reducing attrition is the development and use of pre-clinical models that are more predictive of efficacy and safety in clinical trials. In order to enhance the predictive ability of pre-clinical models, we must utilise technologies and endpoints that most closely reflect those that are, or could be, used in clinical trials. Potential new therapies are frequently reported, yet most of these exciting new discoveries never advance beyond the laboratory bench. A critical component to the successful deployment of translational medicine research in drug development to deliver these new medicines is the focus that must be given to comparative medicine, physiology and pharmacology.

For many diseases, we have an imperfect understanding of the relevance of pre-clinical experiments and their relation to clinical experience. Relevant animal models, as well as early predictive clinical endpoints, are needed to allow a wider testing of novel hypotheses. Key to this is the development of comprehensive disease lifecycle models that directly link the rationale in pre-clinical modelling to the treatment of clinical disease. Further, developing, refining and validating complex animal models that directly link therapeutic targets to the phenotype of disease (confidence in rationale) and developing and refining animal models of toxicity that allow earlier prediction of human response to medicines and identification of safety biomarkers (confidence in safety) are key enablers to successful translational medicine research in drug development. The technologies and endpoints that most closely reflect those that are, or could be, used in clinical trials should be utilised in order to enhance the predictive ability of pre-clinical models. This will encourage technology transfer in both directions: technologies and biomarkers that are currently used in clinical trials can be more directly adapted to pre-clinical models and novel technologies and biomarkers being developed in animals may be efficiently validated and introduced to clinical trials.

A critical need will be access to human tissue banks and biobanks linked to medical records containing information on phenotype. This will be essential for understanding the link between molecular targets for drug intervention and the fundamental pathophysiology of disease, for testing and validation of biomarkers, and for translating the results of clinical trials into a molecular understanding of responsiveness and side-effects. European-wide co-ordination of existing national efforts is crucial to establish common standards, definitions, diagnostic criteria, protocols, data standards, data mining tools and so on. The organisational effort will be considerable, and will need to encompass, in addition, the ethical, legal and societal issues around ownership, consent and confidentiality of the data.

A better understanding of disease pathophysiology will provide the basis for the predictive pharmacology that is essential to reduce attrition rates in clinical trials. A key output of this research will be the discovery and validation of biomarkers, which are seen as critical to the success of modern drug discovery.

3.2.2 Biomarkers

A biomarker is defined as 'a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention'³⁸. Biomarkers are quantitative measures of biological effects that provide informative links between mechanism of action and clinical effectiveness. They can provide new insights into a drug's mechanism of action, metabolism, efficacy and safety, and into disease mechanisms and disease course. They can play multiple roles during the R&D phase of a drug. Biomarkers can be used as tools to understand the biology of a disease, but also to understand the effects of a new drug. Biomarkers may also provide information on patient sub-populations that might respond to a new drug or be susceptible to side-effects. This

³⁸ Biomarkers and Surrogate Endpoints: Preferred Definitions and Conceptual Framework,' Clinical Pharm. & Therapeutics, vol. 69, N. 3, March 2001

approach is known as patient stratification, and is the basis of the future concept of personalised medicine.

The value of biomarkers is that they hold enormous potential to point us in the direction of critical information for developing better diagnostics and medicines, and for helping the industry to manage the innovation process in a more cost-effective manner. Thoughtful and proactive use of biomarkers can improve the mechanistic information generated in drug development, allowing a better understanding of the sources of variation and the correlation between discovery, pre-clinical and clinical information. This will result in better early decision-making, reducing late-stage attrition when the costs are greater.

With the deployment of validated biomarkers, one could expect better clinical study designs in more suitably defined populations, with endpoints yielding improved labelling and marketing information. In short, the application of biomarkers in the drug development process will translate into such benefits as:

- Increasing the probability of programme success and reduced cycle times, matching patients with therapy;
- Faster optimisation of therapy;
- Improved compliance with therapy;
- Reduced complications of therapy and disease;
- More efficient drug development;
- More efficient healthcare delivery;
- Reduced societal healthcare burden.

Furthermore, the identification of diagnostic biomarkers will be essential for improved early intervention in disease, and will be a key technology in the development of more focused drug prescribing. However, the vision will only be achieved if there is the right approach to optimisation of biomarker investment, performance and application. This is a core deliverable of translational medicine research.

The issue is how to validate biomarkers. This is a very lengthy and expensive exercise, involving many patients and years. The FDA has proposed different steps in the validation process, but there is no real consensus among all partners. For example, a validated biomarker is defined as 'a biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results'. Proper validation is essential if biomarkers are to develop from being tools for internal use by the pharmaceutical industry to measures that can be used to drive approval decisions.

The successful development of biomarkers and their integration into the drug discovery process also requires current technology to be developed, and access to it improved. The use of genetic variables for patient stratification is in its infancy in many therapeutic areas, but there is already an emerging literature and clinical evidence on the power of pharmacogenetics to predict efficacy as well as side-effects. The omics technologies are seen as essential for the discovery of accessible biomarkers, for example in blood, urine or cerebrospinal fluid. These would be used for diagnostics, disease progression, prediction of treatment outcome, and measurement of treatment effectiveness.

The other essential technologies are bio-imaging methods such as MRI or PET scanning. As with other biomarker methods, the development and validation of imaging biomarkers in animals is an important precursor to the use of such techniques in man. There is a need for further refinement in the technologies, such as improvements in resolution, sensitivity and comparability, and a pressing need for greater access for patients to centres of excellence in imaging methods.

For this to happen, standards and registries of biomarker and clinical data will need to be agreed upon, and existing European-wide national networks will need to be co-ordinated. In the case of both imaging and omics technologies, the creation of disease-specific European Networks/Centres will be proposed. These will establish standards, validate imaging biomarkers and encourage the development of accredited regional centres of excellence.

3.2.3 Patient Recruitment

The next challenge to accelerating the delivery of safe, effective medicines to the market is patient recruitment. There are two key aspects here: speeding up the recruiting process, and recruiting the right patients. Solving these issues addresses a further question relating to the ability of Europe to compete with the Far East in clinical research. This was a major topic of discussion in the workshops on drug efficacy, and the key to the retention of a thriving clinical trials environment in Europe was seen to lie in the active involvement and collaboration of patients and patient organisations, in the creation of pan-European networks. and in the quality of patient and trial data. In this regard, it will be important to develop clinical research capability and capacity in the new member states.

Clinical trials consume a major proportion of the time required for medicine development, on average more than 50% of the total. Some trials are performed in parallel, while others are performed sequentially relying on scientific results from previous trials. A clinical trial consists of the approval to start the trial, patient recruitment, treatment duration, and reporting. One of the major components is the patient recruitment phase. Composite benchmarking data show that more than one-third of the total time for a trial is spent in the recruitment phase, which lasts, on average, one year. Reducing the duration of this phase will have a substantial effect on the time a medicine takes to develop, and will provide a competitive edge in terms of performing clinical trials.

Strategies will be developed with clinicians and patient associations to improve patient recruitment. Consideration should be given to the benefits of advertising for recruitment into clinical trials. A potential approach could be through educating patients about the benefits of participating in research. Furthermore, patient organisations can be pro-active in the setting up of registries, databanks and/or biobanks to support clinical research. Therefore, the early involvement of patient organisations is crucial in the development of strategies towards fast and effective recruitment.

Patients should not only be informed about the outcome of the clinical research, but also be involved in the design of the study. Their involvement is important for developing a more patient-centric approach to treatment, and for their participation in an educational process involving patients, carers and researchers to ensure best treatment outcomes. In this respect, some initiatives have already proved useful, for example the participation of patient organisations in study groups to reflect upon trial strategy for therapeutic and diagnostic innovations, and participation of patients at various stages of the clinical trials elaboration process. A systematic analysis of patients' participation needs to be performed with the relevant European medical research and patient associations. As the concept of personalised medicine becomes a reality, the understanding and willing participation of patients will become ever more important in analysing the relation between genetics and responsiveness. Their influence will also be felt in promoting research into quality-of-life measures and their incorporation into clinical trials.

From the outset, the Innovative Medicines Initiative emphasised the need to involve patients actively in the R&D process of new medicines in order to ensure a more patient-centric approach. During discussions at the first efficacy workshop on April 4–5 2005, it became clear that patients' needs were not being adequately addressed by current practice. An issue that seriously impedes the potential of patients' organisations is the precariousness of their funding. Sponsorship by the pharmaceutical industry lays them open to accusations of bias in favour of their funders, and the possibility of core funding by the Innovative Medicines Initiative for their involvement in innovative therapy development is a proposal that should be further considered.

The value of continuing to run clinical trials in Europe, despite the higher cost per patient compared with the Far East, will depend on the quality of the trials and the added value created by having first-class electronic patient records and biobanks allowing intelligent patient selection and investigation of the basis for response and non-response. Essential to this process will be the creation of pan-European networks of academics, physicians, patients and industry, a pan-European IT infrastructure for clinical trials and pan-European research hubs that will become centres for translational medicine research. These will need to be developed out of existing national networks, encouraging them to adopt common standards and protocols across all the member states.

The causes, clinical manifestation, consequences and treatment of disease and disorders often differ between women, men and children, and the possibility of such differences will therefore be taken into account in the research that is carried out. Partnerships with parent/patient organisations are crucial to address ethical questions and public trust issues in these circumstances.

3.2.4 Regulatory Approvals

Regulatory authorities are the final judge of the risk–benefit ratio for each new application. The perception is that the regulatory authorities are becoming more risk-averse, translating into increasing risk management planning which can include requirements for expanded studies to quantify potential serious adverse events. The reasons for this may include increased public and media scrutiny of pharmaceuticals and regulatory decision-making, and a perceived lack of robustness in the post-marketing monitoring processes. In addition, there is an increasing tendency for medicines to be given approval with more restricted indications, with requests for more data if approval is to be given for a broader range of indications. This can lead to significant delays in gaining marketing authorisation, and delay patient access to innovative medicines that address medical needs. A set of recommendations for reducing the time to market, but ensuring the safety of new medicines, will be developed and discussed with the relevant stakeholders and, particularly, the EMEA, in a spirit of co-operation and transparency. A detailed list of topics for dis-

ussion will be drawn up within the first months of the project but may include, among others, proposals on how to:

- Improve dialogue with regulators during development prior to regulatory approval, in order to reduce requests for additional data and regulatory questions following submission. The EMEA Pipeline Project is a welcome opportunity for the industry to work more closely with the EMEA to help expand and improve the range of guidance available in Europe, by sharing the industry's view formed through R&D experience in different therapeutic fields. In this context, collaboration with other regulatory agencies, for example the FDA, in order to improve consistency across regions and share best practice will add further value. The EMEA's ongoing dialogue with the FDA on harmonising regulatory practices is laudable.
- Increase the acceptance by regulatory authorities of biomarkers and surrogate clinical end-points. New biomarkers have the potential to speed the availability of medicines to patients if they can also be used for regulatory decision-making. They are already used to inform development decisions in industry, and there is a progression and continuum from 'biomarker' (used as a development tool) to 'surrogate end-point' (sufficiently widely accepted to be used as the clinical basis of approval). This should be done on the basis of the new procedure for European Union Guidelines, recently published by the EMEA. This guidance is a clear improvement of the procedure for a transparent development, consultation, finalisation and implementation of new guidance documents in the EU.
- Increase the involvement of other stakeholders, such as patients, in the regulatory review process. Patients often take a different view from the regulators of the risks that they are prepared to take when weighed against the potential benefits of a new medicine. However, to safeguard patients, this must go hand-in-hand with appropriate support, information and surveillance after drug approval. An important research area will be the quantification of quality-of-life measures. The development of ways to measure drug efficacy beyond the usual primary efficacy end-points is important to prevent potentially valuable medicines falling by the wayside but only if such measures are incorporated into the clinical trials process. Such studies can be used to inform future health economic considerations of new therapies. To promote this, a European Stakeholder Consortium, consisting of patients, regulators, health care providers, industry, physicians, and medical insurance companies will be established. This will address quality of life issues, cost and burden of disease.
- Develop methods to collect data on the risks and benefits of medicines once they are available in a real-world setting. Evaluation of the long term and real life benefits and risks of medicines after launch should use information from randomised clinical trials and from observational and epidemiological studies that use electronic patient-level data (for example, data from medical records). It is therefore important that databases containing this information are developed and these resources are made available for academic and industry research. Improvement in post-marketing surveillance methods should speed up the approval process by providing reassurance that risk-benefit issues will be properly considered, and could reverse the current trend to increase the scope and size of clinical trials. We envisage that this initiative will assist the EMEA in its efforts to improve risk management, and the measurement of the behaviour of drugs in a real-world setting.
- Develop and ensure appropriate use of early conditional approval for innovative new medicines with an adequate safety profile. Improvements in risk management processes, including pharmacovigilance, would certainly encourage such approvals. The use of such procedures needs to be balanced, encouraging development of innovative medicines where further post-approval work is justified, while avoiding unnecessary application of post-submission conditions to other products, serving only to extend the current trend to limited approvals. Alongside this, there is a need to develop new tools for regulatory review (for example, a rolling review) with entry criteria that allow reasonable numbers of products to benefit. The EMEA's responses to the new EU Pharmaceutical Legislation and its Road Map to 2010 already describe grounds for conditional accelerated and compassionate use approvals. The basis is, thus, already in place for discussion on how their current restricted applicability could be widened in the future.
- Develop proposals with the regulators to increase the sharing of data, for example on the placebo arms of clinical trials. There is a huge reservoir of data held in EMEA and national agencies that could be pooled to provide baseline information to guide clinical trial design for new treatments, for example calculating statistical power. Similarly, the regulatory bodies hold data on the pharmacokinetics of a large number of drugs. Collective analysis of the data for all substrates of a particular metabolising enzyme, for example cytochrome 2D6 or 3A4, should provide information not only on the inherent functional variability of these enzymes within the patient population, but also allow one to determine quantitatively the contribution to the variability of such factors as age, gender, disease, and inhibitors of these enzymes. Armed with this generic information, one

should be able to predict *a priori* the likely variability of the pharmacokinetics of a new drug within the patient population, under a variety of situations, thereby facilitating future design of clinical studies and subsequent product labelling. It will also improve the cost-efficiency of such studies. This proposal will require not only inter-company collaboration but also the agreement of EMEA and national bodies to release these data (Figure 22). EMEA's proposal that it will undertake out-comes research using the vast data pool it has available is encouraging in this respect.

- Encourage discussion on a more flexible approach to clinical trials that reflects the individual needs of particular disease areas. This would include not only the proposals above about surrogate endpoints, quality of life measures and baseline data, but rethinking the classic Phase I, II and III design and to modify this where opportunities arise to streamline the process. There are arguments that the whole statistical basis of clinical trial design needs to be reassessed, for example the investigation of Bayesian approaches in order to increase the effectiveness of trials, and reduce their size and cost.

Recent announcements by EMEA on transparency, harmonisation of regulatory procedures and improvements to risk management bode well for future co-operation in the regulatory domain. Particularly encouraging are the proposals to include representatives from patient organisations on the EMEA Management Board, and the setting up of scientific advisory working parties (SAWPs) and scientific advisory groups (SAGs). The SAWP of the CHMP provides guidance on the conduct of tests and trials to demonstrate the quality, safety and efficacy of medicines. The SAGs provide independent recommendations to the CHMP on scientific and technical matters in specific therapeutic areas. The aim to provide top quality scientific advice and assessment is an excellent one.

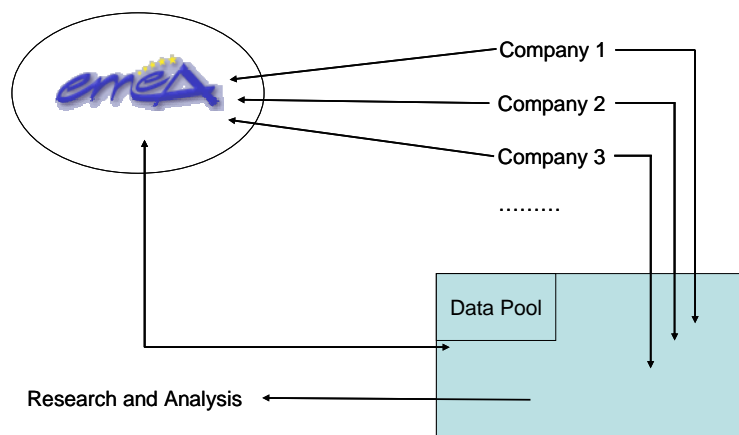


Figure 22 : Potential Data Sharing Model

3.2.5 Rare Diseases and Orphan Drugs

Rare diseases are a diverse group of diseases, which are severe, life-threatening and chronically debilitating. The majority of rare diseases are of genetic origin, and usually prevalent in families. Others comprise rare variants of non-rare disorders. In addition, big footprint diseases, such as cancer, can be broken down in smaller, so-called orphan indications, that affect only a limited number of patients. Thousands of rare diseases are known and, collectively, 20–30 million Europeans are affected, causing a major health problem.

Orphan drugs are medicinal products intended for the diagnosis, prevention or treatment of life-threatening or very serious illnesses that are rare. This designation is awarded as a result of relatively small numbers of patients and limited market potential. With Europe lagging more than 10 years behind the US in the development of orphan drugs, the European Parliament approved legislation in 1999 aimed at stimulating the development of orphan drugs by providing various incentives to companies. These are:

- Market exclusivity for 10 years;
- Protocol assistance by the CHMP of the EMEA to optimise development plans and clinical trials;
- Access to the centralised procedure for marketing authorization (MAA);
- Fee reductions and access to grants from the EC and member states.

In Europe, the COMP is the dedicated committee within EMEA which reviews and approves applications for orphan drug designation.

In regulatory terms, orphan diseases are defined by a prevalence of fewer than five in 10,000 in the European Union. The incentives now available to companies for the development of orphan medicinal products have created opportunities specifically for biotech companies. Many biotech companies, both

larger international bio-pharmaceutical companies and SMEs, have ongoing R&D programmes for orphan drugs. Only a small number of companies, however, have as yet been able to develop and commercialise products for orphan indications. This is primarily caused by the difficulties encountered for the efficient development of such drugs compared to traditional medicines.

For a heterogeneous group of diseases, the development of diagnostic tools and therapeutic compounds shares a common approach, and is threatened by similar hurdles. For orphan diseases, there are usually no validated and predictive biomarkers. Pre-clinical models are difficult to generate, and large, randomised clinical trials are not possible. Because of the limited availability of patients for enrolment in clinical trials, orphan medicinal products are usually based on limited data, often employing surrogate end-points from clinical trials in small populations. Frequently, marketing authorisations are granted under exceptional circumstances, which require post-approval commitments to perform additional clinical trials. The clinical development of orphan drugs, therefore, requires alternative methodological approaches.

The successful improvement of the R&D process by addressing major bottlenecks in safety and efficacy, as proposed in the SRA, will be directly applicable to the development of orphan drugs. The improvement of predictive pharmacology and toxicology by applying genomics, proteomics and metabonomics technology applications should help address the current safety concerns regarding data obtained from small trials in orphan indications.

The SRA also addresses the improvement of clinical research with regard to efficacy. First, a better understanding of disease mechanisms and the identification and validation of biomarkers should enable translational research in orphan indications, and lead to better pre-clinical models being established. It will also improve clinical outcome trials in small and specific patient populations. Second, the strategies that will be developed to promote the discovery of medicines better adapted to patients' needs should, similarly, be applicable to rare diseases and benefit the development of more orphan drugs. Finally, patient selection and recruitment in trials for orphan drugs may be improved by the development of biomarkers, consultation with patients and patient organisations, and enhanced interactions with regulatory authorities, as proposed in the SRA.

3.2.6 Data Sharing

A critical issue for the future success of this initiative will be the willingness of all stakeholders to share pre-competitive data much more freely than before. The advantages to be gained have already been illustrated above by the example of sharing baseline data, however, the issue is not one that can be decided simply between the industry and the regulators. To create the intelligent clinical trial environment so vital to the initiative, it will be necessary to agree on the kinds of data that will be required to build the patient databases of the future, to whom the data will be made available, and to understand the IP implications of biomarker data, as well as the ethical and legal issues around patient consent and confidentiality.

3.2.7 List of Contributors

Improved Predictivity of Efficacy Evaluation: Introduction			
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