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INNOVATIVE DRUG DEVELOPMENT APPROACHES

**FINAL REPORT FROM THE EMEA/CHMP-THINK-TANK GROUP ON
INNOVATIVE DRUG DEVELOPMENT**

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ABBREVIATIONS

| | |
|-----------|--|
| BWP | Biologics Working Party |
| CAT | Committee for Advanced Therapies |
| CHMP | Committee for Medicinal Products for Human Use |
| COMP | Committee for Orphan Medicinal Products |
| CPWP | Working Party on Cell-Based Products |
| EC | European Commission |
| EMA | European Medicines Agency |
| ENCepp | European Network of Centres of Pharmacovigilance and Pharmacoepidemiology |
| EW | Efficacy Working Party |
| FDA | Food and Drug Administration |
| GMP | Good Manufacturing Practise |
| GTWP | Gene Therapy Working Party |
| hERG | Human Ether-a-go-go Related Gene |
| ICH | International Conference on Harmonisation |
| IMI | Innovative Medicines Initiative |
| IND | Investigational New Drug Application |
| LOCF | Last Observation Carried Forward |
| MA | Marketing Authorisation |
| MAA | Marketing Authorisation Application |
| MAH | Marketing Authorisation Holder |
| MHLW/PMDA | Ministry of Health, Labour and Welfare (Japan)/ Pharmaceutical and Medical Devices Agency |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MoA | Mode of Action |
| NCA | National Competent Authority |
| QP | Qualified Person |
| PA | Protocol Assistance |
| PgWP | Pharmacogenetics Working Party |
| PhVWP | Pharmacovigilance Working Party |
| QSAR | Quantitative Structure-Activity Relationship |
| RA | Regulatory Authority |
| R&D | Research & Development |
| RMP | Risk Management Plan |
| SA | Scientific Advice |
| SAWP | Scientific Advice Working Party |
| SME | Small and Medium-sized Enterprise |
| SRA | Strategic Research Agenda |
| WP | Working Party |

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1. EXECUTIVE SUMMARY

One key objective of the European Medicines Agency (EMA) is to make safe and efficacious medicines available to patients. Better medicines should reach the market timely and their evaluation use state of the art methods. One of the key goals of the EMA Road Map 2010 is to foster research and innovation in the pharmaceutical industry across the European Union. In this context, an “EMA/CHMP think-tank group on innovative drug development” was set up. The group comprised EMA staff and several members of different scientific Committees/working parties of the Agency acting as an internal focus group. These experts aimed at identifying scientific bottlenecks to the development of innovative medicines, both in the industry’s R&D and in the academic environment.

The group organised a series of meetings with individual pharmaceutical companies and academic groups or learned societies over the year 2006.

The purpose was to offer these stakeholders the possibility to present and discuss informally their views on evolving strategies in drug development. Not only the identification of bottlenecks was on the agenda, but possible redundant or irrelevant requirements would also be considered as well as modernisation of methods and procedures to develop and regulate medicinal products.

Large multinational pharmaceutical companies as well as small and medium-size enterprises (SMEs) were listened to. Academic groups and learned society groups active in the areas of diabetes, neurology, oncology, and infectious diseases shared ideas with the think tank group. A written procedure was also organised to extend the range of the consultation; this took the form of a questionnaire sent to about 200 pharmaceutical companies having used the EMA procedures previously.

The current report describes the technical and scientific highlights of all these consultations, incorporates reflections and draws recommendations from the think-tank group. Areas for improvement in the operations of the EMA and its scientific Committees include strengthening of both the informal and formal dialogue already in place, in order to ensure a continual exchange throughout the life-cycle of the products. Additional focussed and flexible guidance is expected to better reflect the views of the EMA. Likewise further considerations should focus on biomarkers, modelling & simulation, and emerging clinical trials methodology.

As a word of caution, the present report does wittingly not consider the impact of the recommendations on resources. Prioritisation within a following action plan will be done by the EMA at a later stage.

1.1 Areas for improvement in the EMA/CHMP operations

1.1.1 Communication

Companies brought up strong views on the need for improved communication with regulators, especially *during* drug development. The current pathways for communicating with the EMA regulators were considered slow, not sufficiently personalized and too formal or cumbersome.

The think-tank group recommends that companies make a better use of advice procedures provided by the Agency [Scientific Advice (SA) and Protocol Assistance (PA) for orphan drugs]. Meetings during or immediately after major development phases are particularly encouraged. Results of non-clinical trials and early clinical trials will improve the shape of ensuing development plans.

The future peer-reviewing of SAs by CHMP (Committee for Medicinal Products for Human Use) members will create natural bridges with subsequent (Co-) Rapporteurships.

The Scientific Advice Working Party (SAWP) should create additional flexible ways to communicate with companies for minor advices and for follow-up clarifications, particularly for the benefit of SMEs.

Less formal and less binding “Briefing meetings” are currently developed in collaboration with some Working Parties (WPs) like the Pharmacogenetics Working Party (PgWP), Gene Therapy Working Party (GTWP), Cell-Based Products Working Party (CPWP) through the EMEA Innovation Task Force.

This initiative should be facilitated and extended to other WPs.

Overall, the group recommends that the EMEA expands its life-cycle approach to innovative drug development.

1.1.2 Guidelines

Companies expressed a need for continuous global harmonisation of guidance on drug development. The biggest needs seem to lie in the special new areas, like validation of biomarkers, novel study designs & statistical methods, advanced therapies, modelling & simulation, development of a drug and its companion diagnostic products, etc.

The think-tank group acknowledged that scientific guidelines constitute a good basis for harmonised evaluation and will promote predictability and consistency of EMEA scientific opinions. However excessive reliance on guidelines can disconnect regulators/companies from evolving science.

The think-tank group recommends the following when preparing guidelines:

- to establish priorities for scientific guidelines on the basis of actual scientific needs, in consultation with stakeholders and with WPs experts, especially the SAWP;
- to reconsider the balance between general guidance (retrospective) and individual (prospective) advices;
- to limit development of guidelines allowing for a more focussed work of experts also on more specific topics;
- to create quick, targeted and limited in scope “guidance documents” delivered by the WPs on recent/”burning” issues ;
- to organize on European scale therapeutic area-specific networks to optimise the scientific input in to the guideline;
- to consult such experts in the field in an earlier phase of a guideline development.

1.2. Scientific topics

1.2.1 Biomarkers

The qualification of biomarkers and surrogate endpoints was brought up by all major pharmaceutical companies as one of their most important topics. To gain efficiency, the collaboration between individual companies, as well as between industry, academia, and regulatory agencies is acknowledged. Industry would particularly welcome harmonisation between the EMEA and the FDA.

The think-tank group recommends that the EMEA commits itself to this global collaboration through the establishment of regular discussion fora and the implementation of global scientific guidance.

An industry consortium should apply for “topic-related” scientific advices on these general issues, involving possibly also FDA.

The research on qualification of biomarkers planned under the EC DG Research’s 7th Framework Programme / Innovative Medicines Initiative is welcomed and needs long-term support. Whilst the

responsibility to generate the data adequate for biomarkers qualification lies with the sponsors, participation of the EMEA in the actual qualification and validation processes is considered important. Further reflection is needed to develop such a concept based on the experience gathered within the EMEA participation in the joint activities with the FDA and in the C-Path initiative.

In addition *the think-tank group recommends* that the EMEA should continue to organise regular discussion meetings with regulators, academia and industry on these issues.

1.2.2 Statistical methods and clinical study designs

Most companies brought up the need for interaction and guidance with regard to innovative statistical approaches and clinical study designs.

The think-tank group recommends that the issues be addressed in the CHMP/Efficacy Working Party (EWP) guideline on “Flexible Design”.

The CHMP/EWP should also consider establishing a specific subgroup to collate overall experience in adaptive / flexible designs. The agency together with the group could host a workshop for stakeholders and help in training. CHMP members and assessors across the EU experts network could thereby benefit from sharing up-to-date scientific knowledge in this fast developing area.

A workshop involving all interested parties should be also considered addressing the use of ‘Bayesian’ methodology in confirmatory clinical trials. More generally, the think-tank group recommends that the CHMP consider whether sufficient and relevant expertise is made available in the EU experts network as to inform its decisions in the area of statistics/clinical trial methodology.

1.2.3 Faster access tools

Companies were keen to learn how the new procedures for faster access of innovative medicines to the market, such as conditional approvals, will be implemented by the EMEA/CHMP.

The think-tank group recommends

Based on early experience at the SAWP (e.g. strong anticipation of exceptionally promising results), it seems reasonable to continue to gain experience on the scientific principles applicable within the scope of conditional marketing authorisation and explore scientific issues which may be common also to some more common and/or less serious diseases.

But such approach should focus on further refined, carefully set-out post-approval conditions tailored to the appropriate means becoming available as more practical experience is accrued.

Clarity and efficiency in delivering the drug information to health professionals and patients is one of the many crucial elements to ensure that the use of these products is strictly compliant with the approved indications and label recommendations.

This approach should be further explored and discussed to assure that the benefits of such an early access to a new drug would clearly supersede potential drawbacks (confirmed positive benefit risk/balance).

1.2.4 Risk Management Plans

The understanding of the Risk Management concept and the associated Risk Management plans (RMPs) raised important concern from industry. Companies shared the view that faster access to the market means reduced safety knowledge at the time of first marketing.

The think-tank group recommends actions to clarify and evaluate the Guideline on the Risk Management System. Amongst post-authorisation activities, Marketing Authorisation Holders (MAHs) should in particular strengthen signal detection. It is also suggested to put in place an easy

access to the SA procedure for questions regarding RMPs. CHMP (Co-)Rapporteurs should promote early discussions with MAHs on drug safety and facilitate early reviews of selected RMPs by the Pharmacovigilance Working Party (PhVWP).

The Agency should make any effort to strengthen resources gained from all parties and coordinate efficiently major data sources for pharmaco-epidemiology in the EU.

The EMEA is also in charge of giving MAHs access and guidance to use the Eudravigilance signal detection tools. This achievement when effective will facilitate companies' own signal detection activities. The true effectiveness of RMPs needs evaluation and discussions with stakeholders (e.g. in a workshop).

The ongoing initiatives to build up a network of centres for pharmaco-epidemiological studies are highly supported. These activities should benefit on the long term from public support such as the pharmacovigilance initiatives of the 7th Framework programme / Innovative Medicines Initiative.

1.3.1 Clinical trials

Most if not all companies and academic groups brought up the need for development of tailored scientific guidance for quality, non-clinical and reporting requirements for clinical trials with investigational medicinal products.

Lack of clear EU scientific position on these matters is perceived as a practical obstacle in conducting research and clinical development in Europe, particularly critical for certain types of products such as paediatric, orphan and other selected and innovative products.

The think-tank group recommends to the CHMP to consider the development of tailored scientific guidance for quality and non-clinical requirements for clinical trials with certain types of medicinal products.

In addition, common EU scientific position on non-clinical requirements prior to conducting early phase I clinical trials with low doses of pharmaceutical compounds needs finalization and urgent implementation. This EU-position should tentatively reflect the outcome of the ongoing ICH updating of the M3 guideline. The scientific opinion should incorporate the final conclusions of the draft guidance on 'first-in-man' trials with "potential higher risk" products.

1.3.2 Global aspects

Most companies active at international level upholding a worldwide dimension insisted on the importance of global harmonisation with regard to innovative drug development approaches.

Further ICH initiatives in this domain should be strongly supported.

Additional scientific international fora may be considered with the aim to validate the use of new tools like biomarkers or new methodological/statistical approaches and to consolidate the handling of advanced therapies.

The think-tank group recommends that EMEA also promotes scientific discussions on novel drug development strategies within the framework of the current bilateral arrangements EC-EMEA/FDA and with the MHLW/PMDA. Therein EMEA should actively encourage parallel/joint scientific advice with the FDA whenever possible along a SA/PA request.

1.3.3 Interaction between Industry and Academia

Academic and learned society representatives were generally in agreement with the needs expressed by the pharmaceutical industry. However they brought a few more issues to the forefront. Academia

expressed a global wish to be increasingly involved in scientific research efforts in collaboration with industry. Some investigational fields were quoted, especially in the area of biomarkers, pharmacovigilance, new statistical approaches, predictive non-clinical safety testing, and antibiotics. Academia supported the DG Research / Innovative Medicines Initiative.

The think-tank group recommends that the EMEA/CHMP could actively contribute in some well-defined consortia (e.g. related to biomarkers, pharmacovigilance, paediatrics). EMEA might occasionally take the lead e.g. in studying the natural progression in important diseases through analyses of the placebo-arms of major clinical trials.

The group also recommends close future collaboration between the EMEA and DG Research, not only in relation to the Innovative Medicines Initiative, but also in relation to other existing DG Research initiatives (Innomed from the 6th Framework Programme, clinical trial networks, etc). Flexible ways of improved interaction with scientific societies should also be considered.

1.3.4 *Advanced Therapies and emerging treatments*

Companies involved in development of advanced, cell and gene therapies welcomed the planned Regulation for Advanced Therapies expected to bring valuable harmonisation. Industry emphasised the need for flexible scientific guidelines and adapted requirements able to cope with the rapidly developing field of advanced and emerging therapies.

The think-tank group recommends

The CHMP and its working parties should draft scientific guidelines on the quality and non-clinical requirements for clinical trials with advanced therapy products.

2. INTRODUCTION

2.1 *Background*

One key objective of the EMEA is to make safe and efficacious medicines available to patients without unnecessary delays. The number of new molecular entities reaching the market has been decreasing in the past years, whereas pharmaceutical industry investment in R&D has been constantly increasing. Promising medicines discovered using “new science” are being developed and regulated under the traditional paradigm, and the influence of this on the attrition rate is unclear. However, initiatives are ongoing to identify and propose remedies for the bottlenecks in drug development.

As part of its proactive attitude towards the continuing evolution of the pharmaceutical field, the EMEA has developed its Road Map, which shows how EMEA will contribute to better protection and promotion of public health, improve the technical environment for medicinal products, and help to encourage and facilitate innovation, research and development in pharmaceutical, biotechnology and healthcare arenas.

With this aim in mind, the EMEA and its Committee for Medicinal Products for Human Use (CHMP) established a think-tank group on innovative drug development approaches, which organised a series of meetings with individual pharmaceutical companies and academic groups/ learned societies offering the possibility to informally present and discuss their views on innovative drug development strategies and how they intend to develop medicinal products in the future, considering the evolving science.

As it was not possible to invite all companies and academic groups to these discussion meetings, the EMEA also opened a written consultation procedure to obtain input from EMEA users.

Based on all this information and its own assessment of requirements, the EMEA/CHMP has discussed if and how the scientific requirements could be adapted without compromising the safety of patients. This dialogue on the development of new medicines could result in development of better product development toolkit, able to address the bottlenecks during the development of innovative medicines. All this while improving and stimulating innovative drug development in general, could contribute to more efficient and accelerated drug development process to the benefit of patients.

2.2 Goals

The EMEA created the “think-tank group on innovative drug development” in order to form a view both on the current and emerging scientific approaches in the development of medicinal products and on the related standards in Europe to identify what is needed in terms of science uptake for their scientific evaluation purposes.

Thus, the approach was to identify bottlenecks in the development of medicinal products and possible redundant scientific requirements, as well as to discuss the application of new methods and procedures to support the sound scientific development and approval of medicinal products.

Based on this the goal was to make recommendations on what should be done and in what time frame to encourage and facilitate innovation and research in the field of pharmaceutical products development. In this context preliminary consideration was given also on how to benefit from and provide support to the European Commission in its 7th Framework Programme, especially the Innovative Medicines Initiative (IMI) technology platform and its Strategic Research Agenda (SRA).

2.3 Working Methods

The think-tank group was established in June 2005 and following a few internal organisational meetings, the group met with a number of pharmaceutical companies and academic groups/ learned societies between December 2005 and November 2006.

Invited companies ranged from large multinational companies to small and medium-size enterprises. In addition a questionnaire on innovative drug development approaches was sent to about 200 pharmaceutical companies using EMEA procedures (scientific advice procedure, orphan drug designation procedure, centralised Marketing Authorisation procedure) and to some pharmaceutical associations.

The group held meetings also with a number of EU academic groups or learned societies. Invited academic groups were active in the area of diabetes, neurology, oncology or microbiology/ infectious diseases.

This report is based on the discussion meetings with the different groups, both from academia and industry, as well as on the questionnaire replies: there was a remarkable consistency between the findings identified in the oral discussion meetings and the input received from the questionnaire respondents, including detailed suggestions of scientific and procedural nature.

The think-tank group, in its preparatory activities, also held internal discussions after each meeting with external parties, and four meetings dedicated to discussing the relevance of the findings and to prepare this report and its recommendations.

The current report brings forward the highlights of these meetings, incorporates reflections from the think-tank group and interested parties that have sent comments, and draws recommendations to improve the development and approval of innovative medicinal products in Europe. The think-tank group discussed and agreed with the CHMP the recommendations contained in this report prior to its publication.

The most important scientific topics that came out in these discussion meetings with industry and questionnaire replies are described in the subsequent sections of this report.

2.4 General remarks

The EMEA/CHMP, will discuss prioritisation of the recommendations contained in this report. This will need to take into account not only the importance of each of these recommendations, but also the financial and human resources needed to implement the proposed actions since no consideration has been given to the impact on resources related to the different recommendations at this point.

3. SYNTHESIS OF DISCUSSION MEETINGS WITH PHARMACEUTICAL COMPANIES AND OF QUESTIONNAIRE REPLIES

3.1 General industry trends

It is noteworthy that only 14 selected pharmaceutical companies were invited to these discussion meetings, and only 22 replies on the questionnaire were received. Thus, the views may not represent the views of the whole pharma industry in the EU. However, industry opinions, needs and requirements towards regulators were very similar among all these concerned groups.

In general, different trends in overall drug development strategies could be seen among the companies. Many companies seemed inclined to continue developing medicinal products “as before”, without engaging in too many new, modern “high risk” advanced (often initially cumbersome) drug development methods/ fields.

On the other hand, many were clearly changing their drug development views from conservative “one drug fits all” blockbuster model towards targeted treatment solutions for patients within particular disease and particular molecular marker profile or otherwise defined disease pathology.

For this type of targeted drug development various new scientific approaches seem to be desirable such as validation of biomarkers, identifying biomarker-defined populations in adaptive study designs; also increased interaction with regulators to discuss these new approaches is of utmost importance.

There was a trend to identify substances with unsuitable safety profiles as early as possible by the use of new screening methods, e.g. toxicogenomics, Human Ether-a-go-go Related Gene (hERG)/QT assays, Quantitative Structure-Activity Relationship (QSAR) for detection of active metabolites etc during the discovery phase.

There were also companies focusing purely on certain new, high risk advanced therapies and technologies; these companies seem to be in the biggest need for advice and support from regulators. Finally, some companies were clearly aiming at a “mixture” of all the above, developing traditional products with classical methods, as well as engaging in development of new, advanced therapies with very modern techniques.

Importantly, most companies seem to have realised, that collaboration between different companies and academic groups, in addition to regular dialogue with other stakeholders like regulators, is the key in tackling today’s bottlenecks in drug development. Furthermore, companies seem to think about competition differently today: the real inventions are the compounds, and this forms the competitive area. However, in other areas science should probably not be completely competitive. The companies and academia should collaborate and invest in understanding the mechanisms of diseases. *Collaboration among different parties through European Commission/ DG Research’s 7th Framework Programme/ Innovative Medicines Initiative-project is an awaited important opportunity.*

Another key trend seemed to be that the amount of pharmaceutical research carried out in Europe is decreasing. Some pointed out that EU has been, until recently, a very attractive location for early clinical trials (many Contract Research Organisations with world class clinical pharmacology capabilities, good academic centres with translational biology/ experimental medicine strength, well

motivated volunteers, regulatory authorities experienced in early phase guidance). Some companies were clearly focusing on carrying out research and development within Europe, also in the future, “*as pharma industry can still be developed within the EU.*”

However some companies signalled issues such as lack of treatment-naïve patients, underperformance of some study centres, as some of the aspects which may reduce the attractiveness of Europe as a key player in clinical research.

3.2 *Communication/ interactions with regulators*

3.2.1 *Industry views*

One of the most prominent views companies brought up was the need for improved communication and exchanges with regulators. Many companies considered that the current pathways for communicating with the EMEA regulators were:

- slow: requesting a written Scientific Advice (SA) was considered useful but felt as taking several months to obtain a response;
- not sufficiently personalised, especially at the pre-submission stage. Many companies thought the designation of Rapporteurs [long] before the Marketing Authorisation Application (MAA) is submitted should be considered;
- sometimes too formal or cumbersome; comparisons were made with the FDA where “telephone calls” to obtain “quick advice” or scientific view or reflections from regulators are said to be common.

3.2.2 *Think-tank group’s recommendations*

Taking into account the many opportunities currently available at the EMEA to improve communication with stakeholders, the think-tank group’s opinion is that:

Briefing-meetings which are possible currently with the EMEA-Innovation Task Force and with some Working Parties like PgWP, GTWP and CPWP, should be further developed to support and complement formal early dialogue procedures. Briefing meetings could be organised also with some other Working Parties than those mentioned; awareness of the enforcement of informal briefing meetings on emerging therapies and technologies should be increased.

Overall, the whole EMEA/ CHMP SA-system may have to be strongly enlarged and EMEA should invest further in SA support, especially in peer-review and in scientific coordinators system.

The SAWP should create some additional flexible yet organised ways to communicate with companies for minor advices/clarifications during and following up on a major SA procedure.

Companies should increase their use of the SA and PA procedures, from an early development phase on, as such meetings will provide opportunities for a more continuous, easier, long-term dialogue with companies.

Systematic end of phase II-type meetings or meetings scheduled after and/ or during any major decision-making step during development, should be considered for certain selected groups of products and companies. These meetings with companies, even not being “pre-approval meetings”, might address key elements of the planned phase III trials rather than responding only to questions posed by the companies as currently done under SA procedure.

Some of these aspects have already been taken into account in the new SA procedure (published in June 2006). Results of non-clinical trials and early clinical trials are regularly discussed between companies and the SAWP as they shape ensuing development plans. Resource implications could be significant, as a change towards more systematic evaluation of existing data would be needed.

These measures should be further tested especially with SMEs involved in the development of most innovative therapies.

Peer-reviewing of SAs by CHMP members will create exchange of knowledge and natural bridges with subsequent (Co-) Rapporteurships. However, nomination of the Rapporteurs for the centralised procedure Marketing Applications evaluation should continue to be done independently, to ensure objectivity in the assessment of the final data gathered and according to best relevant available expertise at the time of the MAA.

In conclusion, the possibility for a more continuous, easier, long-term scientific relationship and dialogue (sharing more information during development) with the CHMP and its working parties at different steps of product development could be supported and should be explored. This would facilitate the progress of product development from one phase to another phase. Further, a benefit to EU of ongoing dialogue would be that differences in FDA / EU development strategies might be highlighted earlier.

3.3 *Clinical trials*

3.3.1 *Industry views*

One of the topics spontaneously brought up by most companies (and academic groups, see later) was related to clinical trials, in particular with reference to the need of a more harmonised scientific evaluation of pre-clinical requirements and clinical protocols.

3.3.2 *Think-tank group's recommendations*

The group recommends that the CHMP might consider development of tailored guidelines for quality and non-clinical requirements for clinical trials especially for certain types of innovative products, to harmonise the requirements within the EU. This effort shall be complemented by appropriate training of assessors and the building up further special assessor-networks.

Furthermore, a harmonised EU-position taking into account the ICH discussions on M3 guideline, should be expressed soonest on non-clinical requirements to support clinical trials, as well as recommendation on early clinical trials with low doses of pharmaceutical compounds. This is of utmost importance for the selection of the most promising molecules and for speeding up drug development.

3.4 *Global harmonisation*

3.4.1 *Industry views*

Most companies brought up the importance of global harmonisation of technical requirements with regard to innovative drug development approaches. For example, global discussion on the development and qualification of biomarkers/surrogate endpoints and novel study designs and statistical approaches should be facilitated. A regular forum for such type of scientific discussion between the FDA and EMEA/CHMP should be established. Also collaboration (e.g. joint SA) with Japanese regulatory authorities was recommended. Other topics in need of harmonisation that were brought up were risk management plans, environmental risk assessment and paediatric development plans.

3.4.2 *Think-tank group's recommendations*

The think-tank group is of the opinion, that global harmonisation of technical requirements for the development and evaluation of medicinal products should be pursued at different levels, depending on the topic. While the discussions within the ICH are continuing on certain topics, some other topics could be discussed at other levels.

For example, the EMEA should reinforce or establish with the FDA additional routine fora for scientific discussion, e.g. on biomarkers, new methodological/statistical approaches, modelling and

simulation, risk management plans, and on other new technologies/ advanced therapies in addition to the existing clusters on pharmacogenomics, oncology, paediatrics, vaccines.

EMA should also participate more actively in different international workshops dedicated to specific scientific topics.

The EMA should actively, suggest joint scientific advice with the FDA, when biomarkers, new statistical methods, or other new innovative drug development approaches are included into the SA request. Establishment of the process for joint SA with Japanese regulatory authorities should be facilitated in the future.

Harmonisation and consistency within the EU remains the foundation for a proper contribution to global harmonisation.

3.5 *Translational medicine, biomarkers/ surrogate endpoints, new imaging techniques*

Biomarkers are measurable characteristics that reflect physiological, pharmacological, or disease processes. The discussion in this field includes two different issues: first, selection of subpopulations that have different benefit/risk and secondly, use of biomarkers as surrogates for hard clinical endpoints. It is recognised that whilst novel biomarkers as surrogate endpoints require most extensive clinical data acquisition, substantial new knowledge is rapidly becoming available about biomarkers with predictive value in terms of drug response or in terms of disease progression.

Usually efficacy and sometimes safety biomarkers are developed in animal models and then translated and validated into the clinical development in humans. Use of biomarkers in early non-clinical and clinical development to provide a more informed scientific basis for the design of pivotal trials has already proven useful in streamlining the development of targeted therapies.

The identification and validation of predictive efficacy and safety biomarkers in particular could be very important in future drug development as changes in biomarkers following treatment may reflect the pharmacodynamic/clinical response to the product.

Often, changes in such biomarkers can be detected earlier, or more readily, than the corresponding clinical endpoint (an outcome being used to measure drug effect). A biomarker that can be used to accurately predict and quantify clinical benefit (a direct measurement of how a patient feels, functions, or survives) or harm, can be used as a surrogate for clinical outcome. Before a biomarker can be accepted as a surrogate endpoint, there is a need to have confidence that changes in the marker reliably predict the desired clinical endpoints. Furthermore, new imaging techniques and imaging endpoints in treatment trials build confidence in the biological rationale as they are often more sensitive than usual clinical measures, thus holding potential for use as biomarkers to measure treatment efficacy. This is particularly important for the development of disease-modifying products.

3.5.1 *Industry views*

The question of how to qualify biomarkers and surrogate endpoints was one of the most important scientific topics brought up by all major pharma companies. This is one of the challenges where collaboration is needed between individual companies, as well as between industry, academia, and all regulatory agencies. According to industry, harmonisation between the EMA and the FDA would be particularly welcome.

Examples of innovative biomarkers currently used in drug development and presented by companies during the meetings are: (pharmaco-)genomic markers; histology; PET imaging endpoints in oncology; serum biomarker and imaging of unstable atherosclerotic plaque in cardiovascular disease; imaging markers of early neurodegenerative diseases (e.g. mild Alzheimer's disease); osteoarthritis skeletal biomarkers and imaging etc.

Importantly, in the area of pharmacogenomics, major disharmony exists between Member States in technical guidelines (e.g. on genetic sampling, coding, etc).

3.5.2 Think-tank group's recommendations

The think-tank group's opinion is that EMEA/ CHMP should now commit itself to this global collaboration through different actions. Regular discussion fora should be established. The EMEA (e.g. SAWP) should continue to organise regular meetings with regulators, academia and industry, on these issues (see, e.g., the successful Biomarker meetings organized in December 2005 and December 2006). EMEA/CHMP could act here as the facilitator for data mining and for data exchanges (e.g. in liaison with Innovative Medicines Initiative). Reflection papers should be written sooner, to provide orientation to industry on how to move forward and develop in this field. Industry, both as individual companies and as consortia, is encouraged to apply for (EMEA/FDA) advice on these issues.

The research on qualification of biomarkers planned under the EC DG Research's 7th Framework Programme / Innovative Medicines Initiative is welcomed and needs long-term support. Whilst the responsibility to generate the data adequate for biomarkers qualification lies with the sponsors, the role of the EMEA in the actual qualification and validation processes is considered important. Further reflection is needed to develop such concepts based on the experience gathered within the EMEA in the area of pharmacogenomics biomarkers in the joint discussions with the FDA within the C-Path initiative.

3.6 Modelling and simulation (M&S)

3.6.1 Industry views

A model is a mathematical construct to mimic reality, built based on data, from the given drug and similar compounds and the current scientific understanding of the process involved.

Simulation involves use of the model to play various "what-if" scenarios in order to determine the best one. M&S can provide information to inform different types of decisions, identify sub-populations, provide understanding of exposure-response relationships, dose selection for Phase I/II/III, dosing strategies in sub-populations etc. It was proposed by one company that in the future, M&S might even provide confirmatory evidence for filing.

Modelling and simulation have become an integral part of all new drug development programs in many companies, who would also aim to include such data in a scientific dossier, as a replacement for other required data. This would require constructive dialogue between regulators and industry in order to agree on the level of decision-making that is appropriate with the data at hand; it also requires capacity and expertise on both sides.

3.6.2 Think-tank group's recommendations

The think-tank group is of the opinion that a regular discussion forum on M&S (global, with regulators, academia and industry) should be established to learn from experience, and to move the evolving science rapidly into practical applications.

However the view that M&S might replace confirmatory evidence of efficacy and safety, currently is not shared by the think-tank group.

Training for assessors on these M&S aspects should be organised. Additional expertise for scientific appraisal as well as creation of networks of excellence should be considered. Written CHMP-guideline, in addition to the recent population-PK guideline, should be considered where appropriate. Especially in the paediatric field regulators should be pro-active, e.g. in defining how to validate different models, identifying academic partners not only in the medical field but also in other fields more experienced with computerised programmes and starting collaboration in some pilot projects in the area.

3.7 *New scientific models for clinical development and regulatory approvals*

3.7.1 *Industry views*

New models for clinical development were suggested during the discussion meetings and are represented below.

Model 1/ Learn and confirm: This model represents a transition from the current phased approach for clinical development to an integrated process moving seamlessly from non-clinical models to proof of concept in early clinical trials (learn) to expansion to global clinical trials (confirm). The design of the early studies is characterised by accelerated testing in patients vs. healthy volunteers, use of adaptive methodologies in trial design, elimination or decreased use of blinding and continuous assessment of data.

If a new compound does not live up to predefined criteria in specially designed phase I trials (see below), the project may go back to the preclinical stage for further refinement.

Model 2/ Build, confirm, expand: This is a three-stage model with a concept of more efficient early clinical development but with late stage development carried out in a “real world” population: A disease model of the potential safety and efficacy of the drug in the disease state is developed with increased use of biomarkers supported by epidemiology (discovery to proof of concept); a provisional approval phase follows with controlled early market access and strict safety management; full approval is achieved after updated safety assessment and clinical outcome.

Changes in phase I development were also presented: formal phase I clinical development of a selected compound may be preceded by “phase I clinical discovery/research studies” with doses in the lower pharmacological range to carry out e.g. pharmacokinetic/receptor occupancy experiments with many compounds, before the actual phase I formal development starts with only one of the candidate compounds. This concept was considered very important, and guidance documents with some flexibility here were considered of importance.

It was proposed that new development approaches might establish efficacy more rapidly (e.g. in 200 targeted biomarker-defined patients). The question is does the safety and exposure database need to be of the same size as currently required for usual approval or could that database be more limited at the time of a partial/provisional marketing authorisation? Could risk management plans help in early approval? Drug development should be considered as a “continuum” throughout the life-cycle of the product, including post-approval risk management plans (RMP) with real-life use of the drug. Consideration of conditional marketing authorisation mechanisms with further safety data generated via post-approval commitments and RMPs was suggested to be broadened.

3.7.2 *Think-tank group’s recommendations*

The think-tank group is of the opinion that a common EU-position should be developed as soon as possible on non-clinical requirements to support early phase I clinical trials with doses in the low pharmacological range of pharmaceutical compounds, taking into consideration the ongoing discussion at the ICH level to update the M3 guideline, and the ongoing preparation of guidance on first in man trials with “potential higher risk” products. This is of utmost importance to allow companies to “kill/fail fast” the non-optimal molecules. Further, industry is encouraged to more proactively search for potential safety problems with new molecules. Realistically the overall safety requirements will not become less stringent while they might, though, become different and more tailored.

It is clear from the proposals presented that the importance of phase II / exploratory data is appreciated by many companies and this is wholly supported by the think-tank group. Certain methodological approaches suggested, including the use of adaptive trial designs, decreased use of blinding and

continuous assessment of data might be permitted, even encouraged, in early phase, exploratory development.

Further, the think-tank group is of the opinion, that currently a “provisional approval” (two-stage marketing authorisation approval process, i.e. initial provisional approval at the stage where a positive benefit/ risk is not yet completely established followed by strong RMP and later full approval) for all diseases even with very controlled approval only, is not feasible/ recommendable. This would not be compatible with the obligation for regulators to base the benefit-risk consideration on the best and sufficient safety data.

Enhanced post-marketing safety follow-up should be considered to complement and strengthen the safety during the life-cycle of the product, but could not substitute for what needs to be known before placing the product on the market.

However, the scientific principles of conditional marketing authorisation (already positive benefit/ risk) could be in the future applied to cases of unmet medical need where there are exceptionally promising therapeutic results. This would, however, require enhanced and more efficient provision information to health care professionals and patients, better defined, carefully set out post-approval conditions so to ensure clinical use be strictly restricted to only the approved indication.

Especially, advancement of new risk management methods, validated surrogate/ biomarker endpoints, etc, in the future, could further support the applicability of the scientific principles in terms of benefit/risks evaluation underpinning conditional approval. The feasibility of this approach should be further explored and discussed in the light of the further experience acquired in this area.

3.8 Statistical aspects/ study designs

3.8.1 Industry views

A number of companies propose a more seamless and flexible approach to phases II and III of drug development in preference to the current ‘phased’ approach. In a classical full drug development programme, the design features of a given clinical trial are usually fixed (sample size, patient population, treatment arms) and the development phases are strictly separated. The evaluation of data and learning is possible only after full completion of a development phase, and the resulting gap between the phases of development adds to the length of the whole development process. New approaches, using more efficient clinical trial designs, might shorten development times, while maintaining the integrity of the data. In particular, the so-called ‘seamless’ phase II/phase III trials, where ‘phase III’ continues without a pause in recruitment following ‘phase II’, could expedite drug development significantly and might increase the information available on dose-response.

Integral to this concept is the use of adaptive / flexible designs. These trials permit changes to important design characteristics based on accumulating (i.e. interim) data, thus allowing for uncertainties in factors influencing the trial design to be addressed during the trial. Examples might include, choosing one from a number of doses in stage 1 of a trial, then confirming the efficacy of the chosen dose in stage 2; refining the definition of the patient population; re-estimation of sample size; amending statistical methodology.

There are both methodological / statistical and practical issues relating to the implementation of such trial designs. Consequently, there exists the need for increased interaction with, and guidance from, regulators. The need for guidance on a case-by-case basis was highlighted, where possible, such guidance should be ‘global’.

Also discussed was the role of ‘Bayesian’ statistics. There are advantages to including properly quantified existing knowledge in the design and analysis of future clinical trials. It is argued that Bayesian methods can provide a more natural framework for assessments of futility, selection of dose / patient population in trials with an adaptive design and in quantifying efficacy and safety in small populations.

Other, very specific comments, were received from more than one company in the following areas: discontinue the preference for / reliance on Last Observation Carried Forward (LOCF) for imputation of missing data; increase the use of longitudinal methods rather than analyses at single time points; amend the current scientific guidance which advises against the use of minimisation as a means of randomised treatment allocation; offer greater assistance in terms of selecting non-inferiority margins; relax requirements in areas of high unmet medical need and increase the use of the “putative placebo” approach.

There was also a clear demand for increased statistical resource to be made available to CHMP via individual Member States and / or the creation of an EU Statistics Advisory Board / Working Group.

3.8.2 *Think-tank group’s recommendations*

The think-tank group understands the level of interest from industry in novel approaches and feel that the use of adaptive / flexible clinical trial designs can be supported in certain situations. However, adaptive designs are not viewed as a panacea for all ills of clinical drug development.

Giving general guidance on the acceptability of adaptive designs is complicated by the breadth of the definition, which includes widely-accepted group-sequential methods and sample-size re-estimation as well as changes to inclusion / exclusion criteria, primary endpoints and methods of statistical analysis based on accumulated data on efficacy. As a general principle, it is clear that the concept of ‘adaptation’ fits better within the learning / exploratory phase of drug development than in the ‘confirming’ phase.

Certain adaptations should be acceptable in confirmatory studies (for example group-sequential methods and blinded re-estimation of sample-size): these are not controversial.

Indeed, there is precedence for trial designs within the spectrum of ‘adaptive / flexible’ designs being received positively by SAWP and CHMP. It is important that both the treatment and the indication can be clearly identified, therefore, adaptations which lead to testing a global hypothesis without clear clinical meaning, including, but not limited to major changes to posology or patient population, should not be accepted as confirmatory evidence.

With regards to the promotion of novel adaptive designs in confirmatory studies (e.g. seamless phase II/III designs incorporating dose selection at interim), a number of issues are clearly emerging where scientific guidance would be beneficial. One relates to when stage 1 (‘phase II’) data should be used in the primary data analysis of the trial, and when stage II (‘phase III’) data should be stand-alone.

A related issue is the involvement of sponsor personnel in decision-making based on access to unblinded, accumulating data on efficacy and safety. A third, broader, issue is whether data derived from an adaptive / flexible design is thought sufficiently reliable for approval.

It is recommended that these issues be clearly addressed in the EWP reflection paper currently under development. To further inform the development of this paper, it is recommended that EMEA promotes a workshop on these topics, involving regulators, academia and industry.

Given that these designs are likely to become commonplace in the Marketing Authorisation Applications, CHMP should consider establishing a small subgroup on adaptive designs (under the auspices of EWP /SAWP), to collate experience in adaptive / flexible designs from SAWP, external conferences / meetings and assessment of applications. This group could be charged with developing an agenda for the proposed workshop and with organising training for assessors / CHMP members across European regulatory authorities. The group would take responsibility for ensuring that scientific knowledge and guidance stays up-to-date in this developing area.

Bayesian methodology does have a place in drug development, for hypothesis generating in earlier phases, in the assessment of futility and potentially in ‘small populations’ where there is no possibility to perform an adequately powered randomised controlled trial. However, with regards the use of

'Bayesian' methodology in confirmatory clinical trials, at present the think-tank group does not recommend the use of *informative priors* in Phase III trials, which should provide stand-alone, confirmatory evidence of efficacy and safety.

With regards the other comments received, CHMP may wish to consider whether guidance need to be revisited and further developed on missing data and minimization, selecting non-inferiority margins in disease-specific areas and using putative placebo to define non-inferiority margins.

Finally, CHMP may wish to consider whether a sufficient quantity of relevant statistical expertise is available across each Member State on this topic (statistics, clinical trial methodology) to inform its decisions, and to inform the activities of its working parties.

3.9 *Pharmacovigilance/ risk management*

3.9.1 *Industry views*

The area of pharmacovigilance is a very important aspect of post-authorisation activities. The main challenges in this area, which were brought up by some of the companies in these discussion meetings, were the practical questions relating to the design of RMPs, as well as the need for possible discussion of product-specific RMP issues, e.g. with the CHMP-Pharmacovigilance Working Party. Also a larger discussion forum (workshops) would be needed to share and learn from the experience on RMPs in general, and to discuss the EMEA expectations on RMP and on the tools to measure effectiveness of RMPs.

3.9.2 *Think-tank group's recommendations*

The think-tank group is of the opinion that several actions should be undertaken in order to clarify and evaluate the recommendations of the Guideline on the Risk Management System, to support and strengthen post-authorisation activities of MAHs, in particular signal detection and tailored pharmacovigilance activities in well designed pharmacovigilance plans. Post-authorisation safety studies should be of the highest needed standard and be conducted in EU Member States where resources are available. The think-tank group was also of the opinion that it is important to clarify factors that may lead to disharmony of post-marketing safety (risk minimisation) activities in RMPs. The goal should be that a number of key elements of the Risk Minimisation Plans should be specified at approval for Marketing Authorisation, to ensure the safe and effective use under approved indications, and that they can be satisfactorily applied in Member States.

Recommendations include:

- To consider revisiting the CHMP Guideline on the Risk Management System and improving working procedures for handling EU Risk Management Plans, building on emerging experience and on findings from the CHMP Review and Learning Project, ongoing since 2006;
- To promote the use of Scientific Advice regarding RMPs, to encourage early discussions between MAHs and (Co-)Rapporteurs, and to facilitate early reviews of selected RMPs by the Pharmacovigilance Working Party;
- To collect and analyze available information on different approaches in relation to risk minimisation activities in different Member States, and to consider principles for acceptable standards to ensure safe and effective use;
- To support strengthened resources and methodologies for pharmacoepidemiology in the EU;
- To facilitate MAH's access to Eudravigilance data and to signal detection tools in order to support early signal detection, and to provide guidance on the principles and practical aspects of the use of these tools;
- To discuss expected outcomes and measures of effectiveness of RMPs in a Workshop between regulatory agencies and pharmaceutical companies;
- To consider developing new techniques and methods to address new risks potentially associated with emerging new therapies. Enhanced risk management shall be developed for medicinal products that have special characteristics, e.g. unpredictability of effects/ side

effects, possible long-term effects, use in special and serious medical conditions. Products in advanced therapies and, in general, those using new mechanisms of action, will need special attention. Both collection of safety data for characterisation of risk profiles and risk minimisation in individual patients will dictate the need for intensive monitoring of exposed patients in their clinical setting. Data collection and analysis through well designed pharmacoepidemiological studies are needed;

- To put further efforts for the finalisation of the project to build up a network of centres for pharmacoepidemiological studies in the EU (ENCePP);
- To follow the implementation of the 7th Framework programme/ Innovative Medicines Initiative and to actively promote initiatives to strengthen resources and methodologies for Pharmacovigilance.

3.10 *Advanced therapies and other emerging treatments*

3.10.1 *Industry views*

New (or advanced) therapies in the broad sense include cell and gene therapies, anti-sense molecules, products based on xenotransplantation, tissue engineering, medicines based on nanotechnology etc. There are particular challenges related to the introduction of these therapies to the market.

In view of the fact that most of the emerging therapies aim to act as diseases modifiers, major benefit for public health is expected. At the same time however, such therapies trigger new considerations for the safety as well as uncertainties about the applicability of diverse technical and scientific requirements.

Industry pointed out that simplification and adaptation of requirements would be beneficial in order to encourage development and to increase confidence of sponsors.

Companies involved in development of cell and gene therapies welcomed the proposal for a Regulation of the European Parliament and of the Council on advanced therapy medicinal products since it would bring harmonisation that is beneficial for industry.

As the nature of the advanced therapy products presents some unique challenges, it was emphasised that the scientific quality and non-clinical requirements, the controls of the manufacturing process as well as the applicability of GMP should be adapted to the nature of the products.

The need for a thorough characterisation of the cell-based products, understanding of the mechanism of their action and the use of relevant animal models and pre-clinical new development strategies were discussed.

Further scientific guidance at EU level is needed on borderline issues, such as:

- scientific characteristics of classes of products;
- level of applicability of GXP at the various stages of development;
- risk minimisation, monitoring and requirements for traceability of patients after treatment prior and after approval;
- adaptation of the “ancillary” aspects of the main legislation” (e.g. Braille, paediatrics, etc);
- non-clinical requirements before starting clinical studies with advanced and emerging therapy medicinal products are needed.

In summary, industry requested continued dialogue and advice to be provided to both reduce industry uncertainties and maintain confidence of the public in the development of emerging therapies and technologies. In this context the following product-specific scientific support was indicated as necessary to boost the development of such products:

- scientific guidance on the eligibility to the evaluation procedures as “medicinal products” of certain new therapies;
- continuous scientific discussion and “rolling evaluation”;
- harmonised EU scientific input into clinical trials ,design and methodology for emerging and advanced therapies.

3.10.2 *Think-tank group's recommendations*

The think-tank group recommends that the ongoing activities at the level of the EMEA and CHMP in support of the development of emerging therapies and technologies should be reinforced.

The EMEA-Innovation Task Force and the Scientific Committees and the Working Parties specialised in new therapies such as SAWP, the Biologicals Working Party (BWP), the Cell based Products Working Party (CPWP), the Gene Therapy Working Party (GTWP) should further develop their activities to provide both for early identification of areas in need of scientific guidance and specialised expertise and to respond timely to such needs with CHMP advice, scientific guidelines (including Q&A-documents) and development of new expertise within the network.

CHMP and the relevant working parties, BWP, GTWP and CPWP, should aim to build adaptation of scientific guidelines to the wide variety of advanced therapy products.

Selected opportunities for “rolling” scientific discussion and evaluations as already announced in the EMEA Road Map and prompted in the current legislative proposal for Advanced Therapies, i.e. through certification of quality and non-clinical safety data by the EMEA during development, to provide guidance and assess the compliance with scientific requirements, might be offered.

New processes should be developed in order to allow a closer scientific input into design, methodology and conduct of clinical trials for such emerging and advanced therapies.

In view of the complexity of the emerging therapies a “one stop approach” (for all scientific evaluation procedures to be channelled/ advised through one entry point) for most/ all of these products would support development, and ensure scientific predictability and maintain public confidence in the science underpinning emerging therapies. This would also provide consistent interpretation of borderline technical requirements.

Special consideration for the pharmacovigilance of these products is reported in section 3.9.

3.11 *Guidelines*

3.11.1 *Industry views*

With regard to guidelines, the overall need seemed to be in further global harmonisation of different aspects of drug development. Otherwise the need for guidance documents was related to special new areas, like validation of biomarkers, new study designs/ statistical methods, advanced therapies, modelling and simulation, technical guidance on the development of a drug and companion diagnostic. In addition, certain other topics were raised, which will be further discussed and considered in different work plans.

Perceived problems with guidelines included the fact that commonly guidelines are written when some experience in the area or indication has been already gained, and are thus focused mainly on the already available dossiers. Therefore guideline might not be available when the truly innovative products are being developed. The usefulness and scientific value of available guidelines might be questioned or perceived as limited as not always reflecting the recent knowledge and latest science.

Industry was also asking for priorities for different guidelines within a Working Party, and for pan-European discussion before guidelines are adopted (or even before the first draft is published). Also comments like the following were heard: *“More and more Guidelines and Points to Consider tend to be considered as kind of rules/laws. More flexibility and creativity should not be discouraged (spirit of the guideline should account). Guidelines do not take into account real innovations (innovations do not fit into the guidelines, usually)! Regulators tend to add, but never remove requirements. Guidelines should be reviewed with respect to the changing science and medical need, so that they not only keep pace with, but also anticipate developments.”*

3.11.2 *Think-tank group's recommendations*

CHMP guidelines are the basis for harmonised, consistent and transparent evaluation resulting in predictable scientific responses to uncertainties surrounding innovative medicines within the EU. Guidelines reflect the current scientific policy and thinking. The goal of a guideline is also to guide and facilitate drug development. However, it is conceivable, on occasion, that the presence of a guideline hinders due consideration of the science, which may have evolved since the guideline was drafted. Guidelines, however are recommendations and deviations could be accepted if justified on the basis of sound science reasoning.

Based on the discussions with industry, academia and within the group, the think-tank group recommends, that:

- Scientific guidelines development should be done in a shorter time frame with more intensive work of participants (this would require proper allocation of resources and time, including consultation of the external experts).

- Priorities for guideline development should be established on the basis of the needs of product development. These needs and their priority should be established in consultation with stakeholders. The current (recently published) procedures will guarantee that industry and health care professionals will get an early signal of emerging guidelines (through Work Programmes of Working Parties, and through concept papers). Importantly, when issuing a guideline, it should be considered whether a guideline is the most appropriate tool to support product development, or whether individualised advice (through continuous dialogue with applicants, especially for those situations for which existing guidance is not applicable or a science-based alternative approach is adopted) would be more appropriate. Finding an appropriate balance between producing guidelines and providing more individual advice will be the key here.

- Brief and specific documents, e.g. Question and Answer-documents created by the SAWP or other WPs on current issues (e.g. based on SA-requests by the companies on non-product specific topics, or based on expert-meetings on “currently debatable”, “hot” topics) and prepared in a short time-frame could be helpful in producing public guidance quickly.

- When a guideline is to be issued, experts in the field should be consulted in an early phase of development. For this, further development of national expert networks is of vital importance. Early consulting of academic groups as well as patients is also highly recommended. In controversial areas different sides of controversy should be taken into account as much as possible.

- Therapeutic area specific European-wide networks among assessors should be created, to build more standardised way to view and evaluate different drug development topics in that particular therapeutic field. Such network would also act as a forum for discussion and brainstorming around particular topics, including guidelines, in the field.

- A shorter procedure and time frame for updating a guideline for focussed revisions and on a limited scope should be considered (e.g. if triggered by new considerations emerging from CHMP or SA discussions or when new knowledge becomes available).

3.12 *European Commission, Dg Research/ 7th framework programme, Innovative Medicines Initiative*

3.12.1 *Industry views*

Some of the companies brought up the European Commission DG Research's Innovative Medicines Initiative. All of them welcomed the initiative, especially in forming a common platform for different stakeholders to collaborate.

3.12.2 *Think-tank group's recommendations*

The group was of the opinion, that especially in the areas of predictive safety testing, biomarkers, pharmacovigilance and new statistical approaches collaboration with DG Research and its Innovative Medicines Initiative should be highly supported and encouraged.

In some areas the EMEA should consider actively advising consortia to facilitate research and innovation in the EU. For example collaboration related to biomarkers, paediatrics, pharmacovigilance, or to study natural disease progression through placebo-arms of significant diseases is recommended. Also contribution in defining data standards to enable efficient data sharing between regulatory authorities, pharma, and 3rd parties (academia) could be useful. Similarly, contribution in formulating guidance on study designs on meta-analyses on different companies' datasets (how to collaborate in a standardised way, how should the companies collect data from studies in the same indication, for later pooling of data) could be useful.

In general the think-tank group also recommended close collaboration in the future between the EMEA and DG Research, not only in relation to the Innovative Medicines Initiative, but also in relation to other existing DG Research initiatives (clinical trial networks, etc).

4. SYNTHESIS OF DISCUSSION MEETINGS WITH ACADEMIC GROUPS/ LEARNED SOCIETIES

It was very valuable to discuss the topic of new innovative drug development approaches with academic groups and learned societies, as they have a lot to offer to regulators, as well as to other stakeholders involved in drug development. They have deep and updated scientific knowledge on major diseases, unmet medical needs, clinical and scientific developments including information on epidemiological projections, integration of non-pharmacological and pharmacological interventions, therapeutic trends, pharmaco-economic methodologies. Further, with regards non-industry sponsored clinical studies, these can benefit society through defining new standards of care, addressing key public health questions in large collaborative international studies, addressing also rare indications, and in defining sensitive populations.

4.1 *Clinical trials*

4.1.1 *Views from academic groups/ learned societies*

In order to avoid repetition of studies unlikely to be useful, they suggested that it should be made compulsory to publish results from negative clinical trials, to avoid repeating the same trials in the future.

Discussion with regulators on minimal clinically relevant differences and possible guidance on this would be useful. Academics considered that it would be very valuable if a systematic consultation of health care professionals on new CHMP-guidelines were to take place in the future.

Much of the comments from learned societies on methodological aspects of clinical trials mirrored the comments from the pharmaceutical industry discussed above (use of adaptive trial designs, use of dynamic treatment allocation etc.) and therefore are not presented in further details here.

European guideline for acceptance of large academic trials and for the transfer and retrospective use of these non-commercial databases by industry should be written.

Building up European-wide clinical research networks would be very helpful. Any facilitation here by regulators would be appreciated.

4.1.2 Think-tank group's recommendations

Guidelines on the criteria for the scientific evaluation of results of large academic trials should be provided to increase awareness of the possible impact of those trials on the benefit/risk evaluation of on medicines.

4.2 Biosamples

4.2.1 Views from academic groups/ learned societies

Biosamples of human origin are essential for a rapid development of new diagnostic tests and individualised therapies. However, in Europe there are no clear scientific guidelines in this area. This creates practical difficulties in collecting sufficient information in certain types of clinical trials

4.2.2 Think-tank group's recommendations

Further scientific guidelines on specific topic will be considered.

4.3 Special topic: antibiotics

4.3.1 Views from academic groups/ learned societies

In the area of microbiology and infectious diseases, the biggest public health concern is that antibacterial resistance has spread globally at an alarming rate, continues to increase, and presents a tremendous public health problem. Multi-drug resistance has become a very common problem. Thus there is a huge need for novel antibacterial agents (especially against Gram-negative bacteria) and for prudent use of currently available drugs. However, major pharmaceutical companies have reduced their involvement in the field due to high risks (e.g. rapid change in resistance, market, commercial considerations, etc).

There is also a major unmet medical need for new rapid diagnostic tools, to provide quick diagnosis (bacterial vs. viral infection) without the need for bacterial culturing.

It was also pointed out, that there are many old antimicrobial compounds discarded from development long time ago due to e.g. poor bioavailability/ toxicity, which should be reconsidered in light of new scientific developments in the field to overcome these earlier development problems.

It was suggested that costs of clinical development of antimicrobials could be reduced by allowing extrapolation from one indication to another (e.g. sinusitis and otitis, or intra-abdominal surgical and gynaecological infections, respectively, since caused by the same organisms in similar compartments) or by PK/PD-studies (smaller studies in patients with verified aetiology generating drug concentration data, could in some situations replace classical phase III efficacy studies).

Overall, there will be more and more infections caused by organisms resistant to all available drugs and without active search for new antibiotics the overall health threat will increase rapidly.

4.3.2 Think-tank group's recommendations

Strong research support is needed in the area of antimicrobials, directed both to academia and industry. The 7th Framework Programme/ Innovative Medicines Initiative will address this topic and collaboration here is strongly recommended. Also development of diagnostic tools should be encouraged.

New antimicrobials are required to demonstrate non-inferiority to a licensed control. This can require hundreds, even thousands of patients across a development programme. Requirements for evidence of efficacy in phase III might be re-considered. It should be further discussed whether it might be preferable to relax the currently tight requirements for active comparator trials, so that less stringent

demonstration of non-inferiority could be acceptable (especially) if absolute efficacy is clearly established (i.e. versus placebo).

With the recently updated guideline on antibacterials, the question of extrapolation (from one indication to another, or by PK/PD-studies) has been addressed. The revised Note for Guidance on antibacterial medicinal products is promoting drug development in indications of medical need (niche indications) accepting a limited database. In principle, such limited databases should be discussed with the EMEA as a part of a scientific advice procedure.

A gap analysis on the unmet medical needs for antibiotics and a priority list of pathogens could be performed, and more tailor-made requirements (what kind of clinical trials are needed for these) could be considered. Incentives for developing old antimicrobial compounds or compounds for niche areas (also those not meeting criteria for orphan drugs) should be considered. The EMEA should consider hosting meetings around this topic together with relevant experts.

4.4 *Other topics*

4.4.1 *Views from academic groups and learned societies*

Some groups were working on biomarkers and new end-points, and were requesting guidance on what would be scientific requirements in this field. In many therapeutic areas, the focus is currently on pre-symptomatic stages of diseases. Imaging techniques will be of increasing importance; collaboration between all stakeholders (including regulators, academia and industry) should be facilitated to validate these “imaging biomarkers” (e.g. using placebo-patients).

Some are developing sophisticated mathematical models for clinical trials. These models can be currently used to guide proper trial designs or for targeting the right population (e.g. certain age group), but not yet to replace other clinical trials. How to integrate risks into these models is one key issue. A need for global guidance on general principles on how to validate a new model and for clarification about what is the standard here was apparent.

It was questioned how could academics/ physicians/ patients/ regulators encourage development of combination therapies of existing products, if they have been developed and owned by two different companies?

Also the question how could a new indication be formalised (MA granted), if data became available from non-commercial research and an official indication/MA would be in the major interest of patients?

Clear minimum criteria should be established for mode of action (MoA) studies, supported by MoA based screening platforms (e.g. non-commercial) to rapidly select relevant agents and optimise their development e.g. testing many different tumour types at the same time for a new anti-cancer agent in order to clarify specifically enough the actual MoA.

4.4.2 *Think-tank group’s recommendations*

As described in 3.5.2, different actions related to biomarkers are recommended. Also a discussion forum and guidance on validation of new modelling and simulation models could be considered (see also 3.6.2). Establishment of minimum criteria for MoA-studies should be discussed and considered by the Safety Working Party. Interaction with EU clinical research networks is encouraged (especially in the area of paediatrics and pharmacoepidemiology). Also the interactions with other learned societies should be strengthened and flexible ways of improved interactions considered.