

GLOBAL DRUG DEVELOPMENT:

Issues for the pharmaceutical industry and the regulatory authorities

CMR INTERNATIONAL INSTITUTE WORKSHOP
26-27 May 2004, Tokyo, Japan

WORKSHOP REPORT

Margaret Cone
Stuart Walker

September 2004

**GLOBAL DRUG DEVELOPMENT:
Issues for the pharmaceutical industry and the regulatory authorities**

CMR INTERNATIONAL INSTITUTE WORKSHOP

26-27 May 2004, Tokyo, Japan

WORKSHOP REPORT

Margaret Cone and Stuart Walker

SECTION 1: OVERVIEW

Although most of the major pharmaceutical companies are moving towards simultaneous development and registration of new drugs in Europe and the US, the full integration of Japan into global development plans has yet to be achieved by many companies. It was therefore appropriate and timely that the CMR International Institute Workshop in *Global Drug Development* should take place in Tokyo, providing an opportunity for senior executives from industry and regulatory agencies to discuss the scientific issues and perceived regulatory hurdles to be overcome, on the way forward, towards fully integrated drug development.

Among the concerns that were discussed was the so-called 'Japan gap' – the lag time between filing new drug applications in the Western world and filing in Japan, which can result in a delay of several years before Japanese patients benefit from medicines that are available to patients in other parts of the world.

New Japanese Agency

The timing of the Workshop was also particularly opportune as it took place less than two months after the inauguration of the new Japanese Pharmaceuticals and Medical Devices Agency (PMDA), in April 2004. The Keynote presentation by the Senior Executive Director of PMDA, Dr Osamu Doi, gave delegates the opportunity to learn, at first hand, about the structure and objectives of the new agency. Of particular interest were plans to streamline the review process, to introduce a fast track system for the clinical investigation and registration of priority medicines, and to strengthen safety monitoring.

Syndicate recommendations

Following the customary format for Institute Workshops, all participants were involved in lively interactive Syndicate discussions. The Syndicates were asked to look at the immediate steps that could be taken to overcome barriers to global development and also to develop a vision for the future. Among the areas identified for action in the short to medium term were improving safety monitoring and information exchange through a global safety

database, and taking steps to maximise the benefits of the harmonisation achieved through ICH, by improving the consistency of interpretation and implementation of guidelines. The need to develop guidance on establishing clinical endpoints and on adopting surrogate markers was also among the recommendations from the Syndicates.

A new development paradigm

Looking to the future, there was consensus that the time is right to initiate an international debate on a 'new paradigm' for drug development and regulatory review. It was recommended that the CMR International Institute for Regulatory Science should take a lead in this and build such discussions into its work programme for the coming years.

Among the visions for the future were proposals that a formal review of new medicines should take place at the end of Phase II rather than waiting for completion of Phase III, and that some innovative products that address unmet medical need could be released for early marketing on a 'trial' basis, with intensive safety monitoring. It was proposed that 'rolling reviews', as established in the US, should become the norm and even taken a stage further. It was envisaged that data could eventually be held in a central 'data warehouse', accessible to the authorities, that allowed reviews to take place on a continuous basis, ultimately obviating need for conventional submissions or final study reports.

Innovation and change

In a thought-provoking presentation, Dr Murray Lumpkin, Principal Associate Commissioner, FDA., underlined the obligations of regulators to engage with industry in a debate on how to bring about change where this would optimise the development and review of innovative new therapies. He encouraged companies to become involved in the debate generated by the FDA white paper *Innovation or Stagnation: challenge and opportunity on the critical path to new medical products*¹.

The belief that the time is right to start discussing some radical changes of philosophy and practice in global drug development was one of the main themes to emerge in the Workshop discussions.

Workshop Report

This report is presented in three sections:

Section 1: Overview

Section 2: Outcome, summarising the main points and recommendations from the Syndicate discussions

Section 3: Meeting Summary, giving information on the individual presentations and the subsequent questions and answers that they generated.

CMR INTERNATIONAL INSTITUTE FOR REGULATORY SCIENCE

The CMR International Institute for Regulatory Science has been set up as a not-for-profit division of the Centre for Medicines Research International Ltd in order to continue its work in the regulatory and policy arena, and to maintain the well established links that the Centre has with regulatory authorities around the world. The Institute operates autonomously, with its own dedicated management, and funding that is provided by income from a membership scheme. The Institute for Regulatory Science has a distinct agenda dealing with regulatory affairs and their scientific basis, which is supported by an independent Advisory Board of regulatory experts.

CMR International, Institute for Regulatory Science,

Novellus Court, 61 South Street Epsom, Surrey KT18 7PX, UK

Tel: +44 (0) 1372 846100, Fax: +44 (0) 1372 846101

E-mail: institute@cmr.org

Website: www.cmr.org/institute

Workshop Organisation

Workshop organised by: Neil McAuslane, Margaret Cone and Stuart Walker, CMR International, Institute for Regulatory Science.

Report prepared by Margaret Cone

Reference (Overview, page 1)

1. Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products, published by the US Department of Health and Human Services and the FDA, March 2004, www.fda.gov

**GLOBAL DRUG DEVELOPMENT:
Issues for the pharmaceutical industry
and the regulatory authorities**

CMR International Institute Workshop, 26-27 May 2004

Workshop Report

SECTION 2. OUTCOME

Session 3 of the Workshop, during which the syndicate discussions took place, was chaired by **Dr Hatsuo Aoki**, *President & Chief Executive Officer, Fujisawa Pharmaceutical Co Ltd, Japan*. There were four Syndicates that addressed two topics:

Topic A: *Integrated drug development in ICH regions: What does a current regulatory development roadmap look like for true simultaneous development today, where are the hurdles and what are the practical solutions?*

Syndicate 1: *Chair: Professor Thomas Kühler, Director of Operations, Medical Products Agency, Sweden*

Rapporteur: Dr Simon Larkin, Director, Drug Development, Europe, Kyowa Hakko UK Ltd

Syndicate 2: *Chair: Dr Bernd-Günter Schulz, Head of Global Regulatory Affairs, Schering AG, Germany*

Rapporteur: Professor Samuel Vožeh, Head Business Unit Prescription Medicines, Veterinary Medicines and Pharmacovigilance, Swissmedic

Topic B: *Looking towards the next 10 years, with advances in technology, continuing resource constraints and increased globalisation, what would an ideal regulatory landscape look like and how could this be achieved?*

Syndicate 3: *Chair: Dr John Lim Director, Centre for Drug Administration, Health Sciences Authority, Singapore*

Rapporteur: Dr Paul Huckle, Senior VP, European and International Regulatory Affairs, GlaxoSmithKline, UK

Syndicate 4: *Chair: Dr Graham Burton, Senior Vice President, Regulatory Affairs, Pharmacovigilance and Project Management, Celgene Corporation, USA*

Rapporteur: Dr Leonie Hunt, Director, Drug Safety and Evaluation Branch, Therapeutic Goods Administration, Australia

The outcome of the Syndicate discussions is summarised in this section.

1. DEFINING THE GOALS FOR GLOBAL DEVELOPMENT

The current goal of Global Drug Development was defined as a single integrated development programme, leading to a single set of data (including bridging studies) within a timetable that would allow simultaneous submission (within one month) in the major markets.

Some participants were of the view that simultaneous submission was not such a critical factor but all were agreed that the ultimate goal was earlier access to significant markets. Furthermore, looking ten years hence, one cannot assume that those markets will be the same 'big three' of today – USA, Europe and Japan. The growing importance of the emerging markets, especially China must be a factor in the future goals of global development.

2. A NEW PARADIGM FOR DRUG DEVELOPMENT AND REGULATORY REVIEW

The Workshop arrived at the conclusion that, over the next ten years, there needs to be a fundamental move away from the traditional, conventional way that new medicines have been developed and reviewed over the past 20 to 30 years.

Proposals for the future included:

- A formal regulatory review of data at the end of Phase IIb;
- A rolling review of data after Phase IIb;
- Early controlled marketing for some medicines, at the end of Phase IIb with the equivalent of the current Phase III development being carried out in a 'real-world' patient population;
- A central 'Data Warehouse' that would allow regulatory authorities to access and analyse data on new medicines during development and would obviate the need for formal regulatory submissions;
- Joint, coordinated reviews with the possibility of mutual recognition of the assessment and evaluation of the sections on quality (Chemistry and Manufacturing Controls – CMC) and on non-clinical studies.

It was recommended that the CMR International Institute for Regulatory Science should build these concepts into its future work programme in order to allow the ideas to be discussed and refined further.

2.1 Review at the end of Phase IIb

This is proposed on the premise that there would be a more significant body of data available at end of Phase II than has, historically been the case, with more work being done to reach a more robust end-point and a much earlier focus on safety issues. With these provisos, it was felt that new medicines could be subject to a formal regulatory review and appraisal when proof of concept is achieved at the end of Phase IIb.

At this stage the non-clinical studies, with the possible exception of carcinogenicity studies are normally complete and the final formulation and accompanying CMC data should also be available. The company should also have a clear proposal for the labeling (Summary of Product Characteristics).

The outcome of a successful Phase IIb review would then determine the way in which the product moves forward:

- An agreed Phase III development plan with a rolling review of the data as it is generated, leading to a final assessment for marketing at the end of Phase III. (The safety and CMC data would not be re-assessed unless new issues arose); *or*
- Early marketing with a specific agreed programme of investigations to be carried out in the patient population, in the market place; *or*
- Conditional marketing authorisation with specific limits on use and patient population, etc. (equivalent to current orphan drug programmes and conditional approvals).

2.2 Rolling Review

This would start with early consultations and scientific advice being sought from the start of the clinical programme. After the formal end-of-Phase IIb review described above, a rolling review of data, and consultations on the development programme would continue until full marketing is achieved.

This paradigm envisages that the phases of development would become more 'blurred' with review opportunities being dictated by the availability of data rather than the more traditional milestones. For example the review opportunity might be the completion of a particular study rather than a collection of studies. It was noted that there is precedent for this in some processes for the approval of orphan drugs, HIV and oncology products.

The rolling review would have the intention of satisfying technical requirements for product approval and it was recognised that it was a quite separate exercise from generating the data required for pricing and reimbursement discussions.

2.3 Early Marketing under controlled conditions

There was strong support for the concept that, for products where the data is sufficiently robust at the end of Phase II, a 'probationary' approval for marketing should be possible. The conditions attached to early marketing would include studies to confirm efficacy and also to test the safety hypothesis and the risk management programme proposed at end of Phase II. The product would be subject to regular safety reviews (perhaps through a system of periodic safety update reports (PSURs)). This would not, however, merely be a larger Phase III trial; the drug would be exposed to a population of 'real life' patients with concomitant illness and use of other medicines.

It was recognised that this model would not be appropriate for all indications and target populations but would apply primarily to medicines addressing unmet medical need. (It may not, for example, apply to some 'lifestyle' drugs).

It was also recognised that early marketing release would involve a degree of risk to the companies and regulators along with both benefits and, to a certain extent, risks for patients. It would be important to ensure that both the benefits and risks are understood by prescribers and patients, who would need to be fully informed and involved in the development and risk management programme. It was acknowledged that issues of informed consent would need to be addressed.

There would need to be an agreed way of designating products that were under 'probationary' marketing release in order to make this clear to physicians and patients. Once the post-marketing programme had fulfilled its obligations and met expectations the product would be cleared for full marketing under normal conditions.

Marketing trials in partnership with government and other agencies

It was suggested that government and other healthcare providers, for example HMOs in the US, could partner with industry in the programme for early marketing access for medicines and their further clinical development. It was noted that the Japanese government had recently invested heavily in building up the infrastructure for clinical trial development in Japan and was encouraging companies to allow the government to become a partner in trials on products before full market release

2.4 Data Warehouse

This proposal envisages a departure from the convention that data must be analysed by the company and collated into a dossier for submission to the regulatory authority at a specific point in the drug development programme. Instead, all the safety and efficacy data concerning a product would be held in a central, electronic 'data warehouse' accessible to regulatory agencies at all stages of development. The concept derives, in part, from the fact that the FDA reviewers currently carry out their own analysis of the data as part of the review process, rather than relying on the company interpretation.

This proposal takes the concept of the 'rolling review' a stage further, and is not limited to a review process that starts at the end of Phase II. Data would be submitted to the data warehouse from the outset and reviewed once. There would be no large submission at the end of the development process, containing all the data from discovery to marketing. Instead companies would issue a notification that the final case report had been entered.

The body of knowledge about the product would be built up between the regulators and companies working in partnership through the one database. The stages at which the data should be reviewed would be a matter for agreement between the company and regulators. For example, as data comes in from dose-ranging studies there could be agreement reached between regulators and the company on what would be the ideal dose and what should consequently be the next direction for clinical development.

Potential disadvantages

It was noted that, if only 55% of Phase III compounds proceed successfully to marketing, there is a risk that the rolling review and data warehouse would create extra work for the agencies, reviewing products that are not viable. In the new paradigm, however, the data is only reviewed once and this review starts at an early stage in development. Many of the 45% of Phase III failures might, in fact, be due to reasons that might be picked up if there had been a rolling review and serial assessment early in the process. If that were the case the proposed new system would prove more efficient for both companies and regulators.

2.5 Joint review of applications

The ultimate objective of harmonising procedures and data resources between regulatory agencies is the joint review and evaluation of medicines. A situation could also be envisaged where a surrogate review is accepted in which one agency carries out a review on behalf of other agencies, and this would be possible because of the degree of harmonisation that has been achieved.

As the first step towards this, it was suggested that, in the review envisaged at the end of Phase IIb, it would not be necessary for each agency to carry out a separate review of the non-clinical and CMC data. There could be 'mutual recognition' with a single review, by a designated agency that was accepted by other agencies.

In order to build the mutual confidence and harmonisation required to implement joint or surrogate reviews, a 'hierarchy' of harmonisation was identified starting with the work of ICH on data requirements and guidelines, followed by steps to ensure uniform interpretation and leading to harmonised procedures for scientific evaluation and decision making. The latter would need to be supported by a commonality of reviewing tools and decision making tools that are already being integrated into the review processes used by agencies.

3. IMPROVING THE CURRENT ENVIRONMENT FOR GLOBAL DEVELOPMENT

The Syndicates identified short and medium-term changes and developments that would facilitate an integrated approach to global drug development and pave the way for the more radical approaches described above.

3.1 Human Safety: Global Safety Database

Public confidence in both regulators and industry would be enhanced by improved management of drug safety issues both during development and after marketing. Workshop participants recommended that there should be a single, global safety database that would operate from the time of first development of a medicine to its launch and throughout product life.

There was acknowledgement of the work of ICH to harmonise the collection and electronic exchange of data on adverse events (ICH guidelines in the 'E2: *Management of Clinical Safety Data* series and establishment of the MedDRA terminology) and the work of the Uppsala Monitoring Centre in, Sweden, established under the auspices of WHO.

It was felt, however, that a new initiative was needed to establish – or designate - a single database where industry could file its safety data once, enabling it to become immediately available to all agencies and interested parties, rather than the current system of multiple filings to different agencies. The data would also include events reported directly to agencies that had not come through the company reporting system. It was recognised that the ability of different agencies to maintain and interrogate local databases is very variable, depending on resources, and it was felt that having a single database would remove some of these differences between agencies.

Among the advantages identified were that it would:

- Enhance the transparency of data to all parties;
- Facilitate a single risk management protocol that could be utilised worldwide, whilst allowing local or regional implementation;
- Encourage pan-regional and regional discussions between agencies and industry on emerging safety issues, at an early stage.

3.2 Synchronised timelines

The ability to obtain joint scientific advice from agencies, under bilateral confidentiality agreements, followed by simultaneous submissions are recognised as key factors in successful global drug development. It was suggested that, in addition, agencies should harmonise their timelines for submissions and synchronise the clock times when simultaneous applications are made.

This synchronisation would help companies to deal more efficiently with questions on applications, as these would arise within the same time frame. It would allow for more interagency discussions and better resource planning. The need to abide by internationally agreed timelines would also assist agencies in justifying the additional resources that may be required to meet these objectives.

The current CMR project on *Benchmarking Regulatory Review Processes* could help provide a basis for agreeing realistic, harmonised timelines for review.

3.3 Maximising the benefits of ICH

The Workshop felt that the full potential of the ICH harmonisation achieved to date is not being realised and that there is a need for programmes of re-education on the concepts and details of the ICH clinical guidelines among regulators and industry. Some guidelines need to be revisited to ensure that they are being interpreted and applied in a consistent and even-handed manner. It was recognised that industry might need to provide funds for appropriate training programmes.

When new ICH topics are addressed, it was suggested that academia should be involved at an early stage in the discussion in order to help generate guidelines that start from a therapeutic rather than a regulatory point of view. Academia would also have a role in international arbitration when trying to bring together different medical views and opinions on essential matters in ICH.

It was recommended that a study should be carried out by CMR on the implementation and interpretation of the ICH guidelines in the different regions in order to identify the major causes for concern among pharmaceutical companies and regulatory agencies.

3.4 Endpoints and surrogate markers

There was agreement that priority should be given to harmonisation, possibly through ICH, of guidance on the establishment of clinical endpoints and the use of surrogate markers. Discussions would, however, need to involve other stakeholders besides the industry and regulatory agencies, including academia, patient groups and practising clinicians. Although some general guidance would be appropriate, guidelines, or preferably 'points to consider' would need to be agreed, separately, for different therapeutic areas.

It was recommended that the CMR International Institute should include the topics of clinical endpoints and surrogate markers in its programme of work for the near future.

3.5 Acceptance of Foreign data

Renewed efforts are required to improve the use of bridging studies and clarify the situations in which they are considered necessary. It was felt that the ICH E5 guideline on the acceptance of foreign clinical data was not being implemented in a harmonised manner and

that repetition of clinical studies is still being required in many situations where they are not necessary. In the case of diseases with a well-established diagnosis and course, where there are no pharmacodynamic or pharmacokinetic differences between ethnic groups, data should be accepted without the need for either bridging studies or repetition of clinical programmes.

It is important that further clarification and interpretation of the conditions under which foreign clinical data is accepted should focus not only on the acceptance of Caucasian data in Japan but also on the acceptance of data from Japanese and other Asian patients, in the EU and USA.

3.6 Training and accreditation of reviewers

Considerable responsibility is assigned to individual assessors during the review of an application but it was noted that there are no international agreements on requirements for training, competency or accreditation.

Support and encouragement was expressed for the current schemes for exchange of regulatory personnel between agencies as part of training programmes and in order to gain experience of, and insight into, regulatory procedures in a different culture. Such schemes should enable staff not only to be observers but also to have 'hands on' experience by being involved in actual reviews.

Several agencies have internal procedures for peer review of assessments, quality management systems and competency programmes but consolidated information on these is not readily available. **It was recommended that** the CMR International Institute should collect such information and it was noted that this would also be relevant to the Institute Workshop, December 2004, on quality aspects of regulatory review and submission processes.

4. FURTHER OBSERVATIONS

The following summarises further points raised by the Syndicate groups in discussion of regulatory hurdles in the way of global development and possible remedies:

- **Use of comparator products:** Differences in requirements between the Europe and the US over the use of active comparator *versus* placebo remain an impediment to the design of global clinical protocols and even within Europe differences in views on the dose and type of comparator can be an impediment to trial design. International discussions on this topic need to continue whilst, in individual cases, the subject should be addressed in consultations with regulators at the end of Phase II;
- **Quality specifications:** The lack of harmonisation between pharmacopoeias and differences in the implementation of ICH quality guidelines are resulting in the same products being authorised with different specifications leading to increased costs, increased resources needed for maintenance and difficulties in compliance. Renewed international harmonisation efforts are needed to address these problems;
- **Pre-clinical testing:** Animal data is generally regarded as having less value once clinical data and experience accumulates. The lag time between filing an application in the West and in Japan has, however, resulted in instances where the Japanese authorities have asked for additional animal studies to be carried out on products that are already established on the market in the other regions;
- **Clinical trial authorisations:** The need to make multiple applications for clinical trial authorisation in different regions and countries is a time-consuming impediment to global clinical programmes. A system that would allow a single filing, that was mutually recognised in other regions would be a major benefit;

- **GCP and GMP inspections:** Further mutual recognition agreements (MRAs) should be implemented to avoid the current need for repeated inspections by regulatory authorities;
- **GCP in Japan:** Many outside observers feel the implementation of GCP in Japan to be complex and it would be helpful if PMDA could draw up guidelines for the conduct of multinational trials in Japan.

CLOSE OF THE WORKSHOP

In his closing remarks, Professor Stuart Walker, thanked the Chairmen, Speakers, Syndicate leaders and Institute staff for their contributions to the success of the Workshop. He assured participants that the proposals and recommendations from the Syndicates would be taken up in the next three-year work plan for the Institute that was currently being developed.

Professor Walker reminded participants of the opportunities to discuss some of these matters again at the two further Institute Workshops to be held in 2004:

- ***Beyond Benchmarking: What are the key performance metrics that agencies and companies should use to measure performance?***, Monday 4 and Tuesday 5 October 2004, Lansdowne Resort, Virginia (Washington D.C. area) USA; and
- ***'Knowing and meeting customer expectations': The quality of dossiers and the review process***, Thursday 2 and Friday 3 December 2004, Woodlands Park Hotel, Cobham, Surrey, UK

Delighted by the success of holding the current Workshop in Japan, Professor Walker also predicted that the CMR Institute would be seeking the opportunity to return to the country for a further Workshop, in the near future.

**GLOBAL DRUG DEVELOPMENT:
Issues for the pharmaceutical industry
and the regulatory authorities**

CMR International Institute Workshop, 26-27 May 2004

Workshop Report

SECTION 3: SUMMARY REPORT OF THE WORKSHOP PRESENTATIONS

PROGRAMME

SESSION 1: REGULATORY AND SCIENTIFIC APPROACHES TO GLOBAL DRUG DEVELOPMENT

Chairman:	Dr Murray Lumpkin, Principal Associate Commissioner, FDA, USA	<i>Page</i>
KEYNOTE PRESENTATION: The role of the new Japanese regulatory organisation in bringing global medicines to the Japanese patient	Dr Osamu Doi, <i>Senior Executive Director, Pharmaceuticals and Medical Devices Agency (PMDA)</i>	2
Global Cooperation in Drug Development: A US viewpoint (<i>by video</i>)	Dr Lester Crawford, <i>Acting Commissioner, US Food & Drug Administration, (FDA)</i>	5
<i>Strategic Approaches to Global Drug Development: Advantages and Disadvantages</i>		
Integrating Japan into global development: A multinational company perspective	Dr Mike Ferris, <i>Head of Drug Innovation and Approval, Aventis Pharma Japan</i>	6
Working in a western environment: A Japanese company perspective:	Dr John Alexander, <i>President, Sankyo Pharma Inc., USA</i>	11

SESSION 2: GLOBAL DEVELOPMENT PROTOCOLS: SCIENTIFIC AND REGULATORY ISSUES

Chairman	Dr Robert Peterson, Director General, Therapeutic Products Directorate, Health Canada	
Factors that impede or assist true global development in the ICH regions	Professor Stuart Walker, <i>President and Founder of CMR International</i>	14
What are the key questions that need to be addressed in a global development plan to utilise a single protocol?	Dr Christine Cioffe, <i>Vice President Project Management, Merck and Company Inc.</i>	17
Dialogue with regulators during global development: When, why and how?	Dr Stewart Geary, Deputy Director, Corporate Regulatory Compliance and Quality Assurance Headquarters, Eisai Co Ltd, Japan, Eisai Co Ltd, Japan	20
The regulators; role in enhancing medical science innovation	Dr Murray Lumpkin, <i>Principal Associate Commissioner, FDA, USA</i>	24

SESSION 3: THE GLOBAL DOSSIER AND ITS REVIEW

Chairman	Dr David Jefferys, <i>Department of Health, Special Adviser – Healthcare Industries, UK</i>	
Construction of a Global dossier: what needs to be considered, and what are seen as the critical success factors?	Dr Tim Franson, <i>Vice President, Global Regulatory Affairs, Eli Lilly & Company Limited, USA</i>	28
Same dossier, same data: but three reviews in three regions: Is this a valuable exercise or wasted resource?	Dr George Butler, <i>Vice President and Head, Worldwide Regulatory Affairs, AstraZeneca Pharmaceuticals, USA</i>	31
Global Cooperation in Drug Development: A European viewpoint (<i>by video</i>)	Mr Thomas Lönnngren, Executive Director, European Medicines Agency, (EMA)	36

SESSION 4: SYNDICATE DISCUSSIONS

Chairman's Introduction	Dr Hatsuo Aoki, President & Chief Executive Officer, Fujisawa Pharmaceutical Co Ltd, Japan	38
--------------------------------	--	----

KEYNOTE PRESENTATION: THE ROLE OF THE NEW JAPANESE REGULATORY ORGANISATION IN BRINGING GLOBAL MEDICINES TO THE JAPANESE PATIENT

Dr Osamu Doi

Senior Executive Director, Pharmaceuticals and Medical Devices Agency (PMDA)

In his presentation Dr Osamu Doi described the establishment of the new Pharmaceuticals and Medical Device Agency (PMDA) that had been inaugurated in April 2004 and discussed the changes and improvements that can be expected with the new organisation and the performance goals that were being set.

Dr Doi set out the overall mission of PMDA to ensure the timely introduction of innovative new drugs and medical devices that are safe and effective in order to improve therapy and contribute to a better quality of life. The agency will take over Japan's role in ICH and continue the initiatives, started 13 years ago, to implement harmonised standards for pharmaceuticals.

Requirements and Goals for PMDA

Outlining the progress that had been made even before the establishment of the new Agency, Dr Doi referred to the increase in human resources that had been assigned to new drug review since 1997, the reduction of the target review time from 18 months to 12 months in 2000 and the revision of the Pharmaceutical Affairs Law in 2002. With the establishment of the PMDA in 2004, specific requirements had been identified:

- Reliable reviews based on a high level of expertise;
- An integrated organisation to carry out NDA reviews that are consistent with pre-NDA (clinical trial) consultations;
- Introduction of a Japanese Fast Track system which will reinforce priority review procedures and introduce priority clinical trial consultation;
- Setting up the necessary infrastructure for the implementation of the revised Pharmaceutical Affairs Law in April 2005;
- Establishment of transparent management systems for the review of NDAs allowing information to be disclosed on performance and with procedures for hearing complaints and for appeals.

Dr Doi also discussed the short-term goals that were expected for the PMDA. The first was to set review times and definitions for prioritised NDAs as well as an overall improvement in the speed of reviews with targets set for overall elapsed review time. Better performance would be sought for the system of consultation and guidance provided at the pre-NDA stage, which will require closer integration of the pre-NDA and NDA review teams. This will also be essential for the Fast Track scheme for priority, innovative medicines.

Integral to bringing about these changes will be improvements in quality of service, including an increase in the number of review personnel with relevant expertise, more reliable quality assurance of the review process and improved pharmacovigilance.

Structure of PMDA

The establishment of the PMDA represents a major reform of the regulatory system in Japan but, as Dr Doi explained, there had been the step-wise changes and improvements introduced into the system since 1997 (see box).

Changes leading to the formation of PMDA

In July 1997, MHW set up a new system for pharmaceutical regulation consisting of:

MHW (Evaluation and Licensing Division)

PMDEC (Pharmaceuticals and Medical Devices Evaluation Center)

OPSR (Organization for Pharmaceutical Safety and Research)

JAAME (Japan Association for the Advancement of Medical Equipment))

In November 1999, MHW reformed the Central Pharmaceutical Affairs Council (**CPAC**)

In April 2004, **PMDA** was established

Taking over the functions of PMDEC, OPSR and JAAME, the PMDA has been organised into five sections:

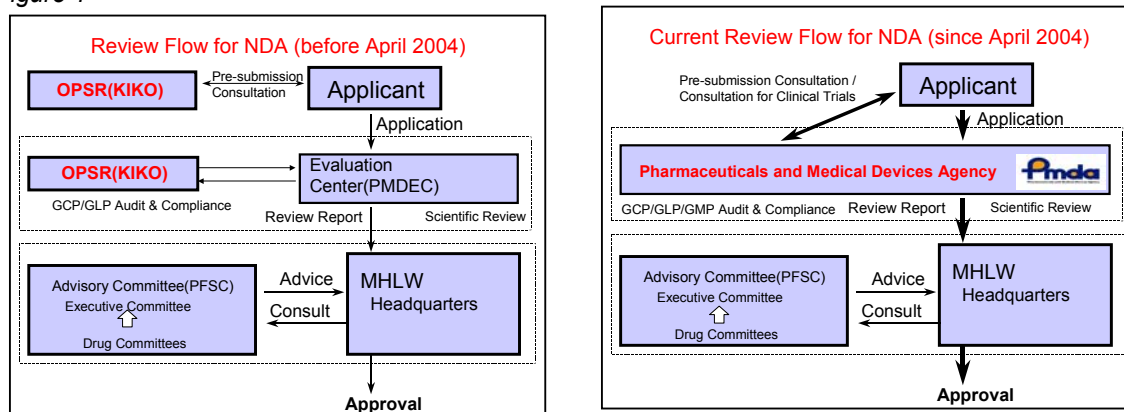
- *Office of Review*: Responsible for the review and consultation for new drugs, new medical devices, biologics, generics and OTC products and carries out GLP, and GCP audits
- *Office of Postmarketing*: This has taken over work previously handled by MHLW and OPSR and is responsible for collecting safety information and ADR reports as well as GMP audits and enforcement of product quality standards;
- *Office of Relief*: This is responsible for the system of relief (compensation) provided for victims of serious adverse drug reaction and, more recently, infectious diseases;
- *Office of Research Promotion*: This is currently incorporated within PMDA but will be moved to a new research-oriented agency which is yet to be established;
- *Office of General Services*: This provides the technical and administrative support required to run the agency.

A five-year medium term management plan has been set for the Agency with targets to increase staff levels from 240, before PMDA was established, to 357. PMDA is designated as an *Independent Administrative Agency* that has autonomy but remains under the auspices of the government. Its performance is subject to regular scrutiny by the *Independent Administrative Agency evaluation Committee*. It is funded in part by user fees for consultations, reviews and audits, and also by an appropriation from the national budget. Industry also contributes funds for postmarketing and relief activities.

Changes in the review process

Dr Doi explained the changes to the review system as a result of the establishment of PMDA (see Figure 1) and emphasised the high expectations that the streamlining and simplification of the process would improve speed and efficiency.

Figure 1



The mid-term objectives and plans for PMDA have been elaborated and Dr Doi provided a summary of these:

- *Accelerate Review Process*: Shorter target review times for innovative new drug/new device applications (NDAs) in order to have more effective and safer pharmaceuticals and medical devices accessible in a timely manner. Introduction of a priority pre-NDA clinical trial consultation system in order to reach NDA submission earlier.
- *Safety assurance for general public*: Review and postmarketing vigilance sections working closely together. Expedited review processes require strengthened procedures to reduce risk and a new, proactive system is being established in cooperation with health professionals and clinics;

- *Public benefit from new technologies*: Strengthening the review resources and enhancing the knowledge base in order to provide appropriate guidance for the development and review for the products using new biotechnological and genomic technologies;
- *Review Target Times*: Revised targets for the regulatory review time:
 - 80% of NDAs: outcome of review within 12 months
 - 50% of priority review products: outcome within 6 months

New targets, which will be introduced from the next mid-term plan (starting from 2009) will be set in terms of overall review elapsed time (sum of the regulatory review time and the applicant time) in order to match the performance of the US/European agencies.

Dr Doi emphasised that achieving the latter targets would also depend upon encouraging applicants to improve the quality of the dossiers submitted. He also noted that, in order to qualify for a Fast Track consultation and review, a product needs to be innovative and to be for the treatment of a serious disease for which no other comparable therapy is available in Japan. As noted earlier, accelerated review needs to be backed up by strengthened safety monitoring and Dr Doi explained the ways in which the system for the flow of pharmacovigilance information is being streamlined and improved.

In conclusion

Dr Doi summarised the benefits that could be expected from the new review and pharmacovigilance procedures established under the PMDA. He felt that, under the previous system, there were too few reviewers and too little time to be able to listen fully to the opinions of companies and he was confident that this would change with increased human resources and the ability to have more frequent and meaningful discussions between the two parties.

At a global level, Dr Doi looked forward to even closer cooperation with counterparts in the EU and USA. This is not just a responsibility to the Japanese people but also to the world as Japan has an important contribution to make in the field of new medicine development. PMDA will improve the quality and quantity of Japanese reviews and safety measures and, to respond to the expectation of the people, will base its operations on the most advanced science and technology in order to deliver the fast and appropriate judgment that is required.

DISCUSSION

Regulatory Review times: Dr Doi was asked to comment on review times in Japan especially in comparison with the procedures in the FDA. In replying, he pointed out that it is important to ensure that similar data is being compared, for example whether the time for a review includes the time taken by companies to respond to questions. Differences in the review processes can make such comparisons difficult. PMDA will, however, give priority to making the review process more efficient and reducing delays. Dr Doi noted that the improved review times achieved by FDA in the year 2000 had been an incentive to improve the performance of the Japanese review and that it was disappointing when the average time for review subsequently increased. Targets had, however, been set by PMDA and it was hoped that, by offering consultations at the development stage, and redundancy in the drug development process could be reduced, particularly in relation to additional clinical trials.

User Fees: Reference was made to the consultations that had taken place between the Japanese authorities, FDA and the US industry (through PhRMA) over the implementation of user fees in Japan and Dr Doi was asked to comment on this. He replied that the exchange of information had been extremely valuable and that the official exchange of letters on the subject had been an important driver in revising methodology and establishing a definite review time within the procedures.

GLOBAL COOPERATION IN DRUG DEVELOPMENT: A US VIEWPOINT

Dr Lester Crawford

*Acting Commissioner, US Food & Drug Administration, (FDA)
(Presentation made by video)*

On behalf of the FDA, Dr Lester Crawford extended best wishes and congratulations to Mr Akira Miyajima, Chief Executive, and Dr Osamu Doi, Senior Executive Director of the new Japanese Pharmaceuticals and Medical Device Agency (PMDA). He was sure that it would provide outstanding science-based, public health promotion and protection for the people of Japan and would be one of the premier drug regulatory agencies for years to come.

Dr Crawford referred to the long and valued history of successful interactions between FDA and Japanese regulators in the regulation of medical products, including bilateral agreements and several multilateral initiatives such as those under the auspices of APEC and ICH. As successful as those initiatives have been, however, he believed that one of the most remarkable and most productive interactions with Japanese regulatory colleagues has been through the Mansfield Fellowship Program.

Exchange Programs

The Mansfield Fellowship Program is a special program in which US government officials compete for selection to spend a year working in their counterpart agency in the Japanese government. Prior to their time in Japan, they must undergo a year-long, intensive Japanese language course that enables them to participate to a much greater degree in the work of the host agency. These are much sought-after postings and FDA has been privileged to have had several candidates selected in recent years and has been able to send chemistry reviewers, medical officers, and pharmacists to work in the Japanese drug regulatory agency. These officers have been able to learn at first hand how their counterparts approach scientific, regulatory, and policy issues and how regulatory decisions are made in Japan. Returning FDA colleagues, said Dr Crawford, had consistently reported rewarding professional experiences of working with their Japanese counterparts and of the extraordinary personal experiences of living in Japan for a year.

FDA had similarly been honoured to host exchange visits from many Japanese colleagues and Dr Crawford expressed his personal thanks to Japanese regulatory authorities for making these exchanges possible. Considering this long history of mutual respect and productive collaboration, he was confident that this very positive spirit will continue with the new PMDA and he was very much looking forward to continuing to work together.

Global drug development

Drug discovery, development, authorisation, marketing, sales, and utilisation are now global functions that should benefit people around the world, said Dr Crawford, and he emphasised the need for regulatory processes to be tailored to meet the challenges of such an open 21st century world and marketplace. The impact of biomedical technology over the past century is profound and unmistakable, he said, but as we look to the future, many feel that the best is yet to come. The world of genomics, proteomics, nanotechnologies, and biomedical information technologies will surely usher in new areas of health promotion that can only be barely imagined, at present.

The task of such innovation is, however, becoming increasingly difficult. It requires heavy investment and can be an increasingly lengthy and costly business that involves a great deal of risk and unpredictability – much of it based simply on the unknowns of disease, but some also based on regulatory environments that can seem opaque and unresponsive.

The regulatory role

With so much hope and promise on one side, and so much risk and unpredictability on the other, Dr Crawford discussed what the regulators could do to help address the issue.

It is imperative, he said, that medical product regulators around the globe foster innovation and improvements in citizens' health by working together to develop the kind of transparent, science-based quality standards that industry and the public alike know must be met in order to bring a new medical product to market. In this way, all stakeholders can have confidence in the medical products on the markets and we can give assurances to:

- patients and practitioners that they have access to quality products with demonstrated positive benefit-risk profiles;
- payers, whether private or public, that they are getting good value for their money;
- companies that they can have confidence that there is indeed a fair, level playing field for market entry; and
- our citizens that what is billed as 'innovation' is indeed innovation and not exploitation.

This, suggested Dr Crawford, is what our citizens pay us, as regulators, to do and it can only be better when regulators work together; 'The sum of our parts together is greater than the sum of our individual components, alone' he said.

Facilitating innovative drug development

Dr Crawford referred to the paper recently published by FDA that describes the 'critical pathways' to successful development and authorisation of innovative medical products. This document emphasises that new development tools are needed to improve the predictability of the drug development process and lower the cost of research by helping industry identify product failures earlier in clinical trials. The end result, he said, will surely be a 'win' for public health if truly innovative products can be developed and brought to market as quickly, safely, and efficiently as possible. This critical path, however, also entails regulators working more closely with their counterparts in other agencies to achieve this public health benefit on a global scale.

In order to help facilitate this FDA has recently concluded several important agreements with counterpart agencies that will allow the parties to work together more closely than in the past. Under these agreements, agencies will be able to share confidential, pre-decisional and investigative information and to leverage to a greater degree the resources of each other's agencies.

Whilst acknowledging that some companies might see this as 'threatening', Dr Crawford argued that the converse is true. These agreements allow partner agencies around the world to interact in real time in order ensure that the benefits of the exciting new world of biomedical technology are secured more quickly and that the known risks associated with them are reduced even further.

In closing

In closing, Dr Crawford again thanked the organisers for the opportunity to share his thoughts, with the Workshop, on how all parties can work together to encourage medical product innovation and advance public health worldwide. 'I pledge to all of you', he said, 'that during my tenure as leader of the US Food and Drug Administration, this will be our policy and our goal'.

STRATEGIC APPROACHES TO GLOBAL DRUG DEVELOPMENT: ADVANTAGES AND DISADVANTAGES

Integrating Japan into global development

Dr Mike Ferris

Head of Drug Innovation and Approval, Aventis Pharma Japan

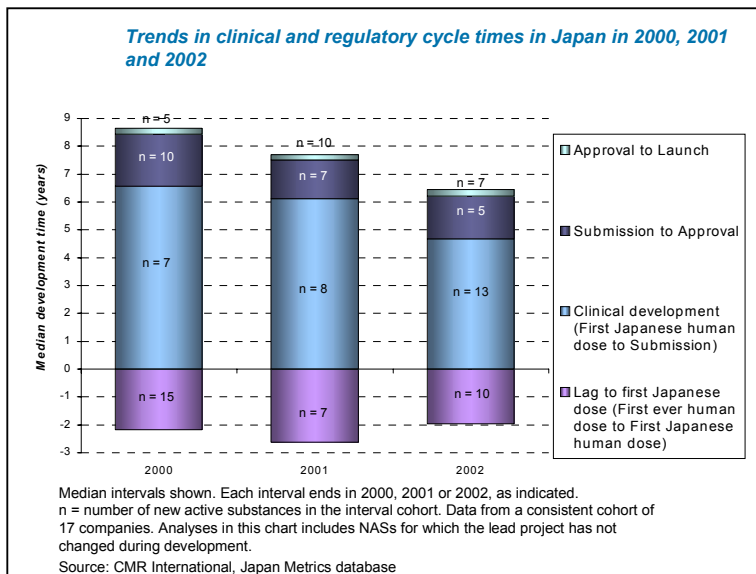
Dr Mike Ferris opened his presentation by discussing a working definition of global drug development. This could, he suggested, be 'the development of a new drug in the three major ICH regions (US Europe and Japan) in a single integrated development programme thereby generating a single set of pivotal data to be used as the basis for the CTD to be submitted in each region'. The objective of such a definition could be a simultaneous *launch* in the three regions, but this is not necessarily realistic, especially in Japan, because of the need to negotiate reimbursement before marketing. Even an objective of simultaneous *approval* might not be possible to achieve because of the different regulatory systems and, within his own company, Dr Ferris had reached agreement that a realistic goal for the present is integrated development leading to simultaneous *submission* in the three regions.

The 'Japan Gap'

The challenge for those trying to achieve simultaneous submissions, however, is the so-called 'Japan Gap' resulting from the lag time between the first human dose anywhere in the world and the start of clinical development in Japan. A study carried out by CMR International, some years back showed that, added to more protracted development times in Japan, this lag was resulting in a gap of over four years between the first submission in the rest of the world and in Japan.

Dr Ferris referred to a more recent CMR study of 2002 data indicating that the clinical development times, at that time, were closely comparable between the US and Japan and slightly longer in Europe, probably because many companies do their first-time-in-man studies in Europe. Review times were found to be much the same for all three regions, at about 18 months. There remained, however, a gap of some two years before products reached the Japanese market as a result of the lag from first-ever human dose to first human dose in Japan. Data from the CMR International Japan Metrics database (Figure 2) on trends in clinical and regulatory times for the years 2000 to 2002, in Japan, showed a steady decrease in clinical development times, resulting from the use of bridging studies. The 'message', however, as Dr Ferris pointed out, lies below the line that shows a lag time of some two years before clinical development commenced in Japan.

Figure 2



At Aventis, he said, they had made a retrospective study of the strategy for clinical development and registration of their own new products in order to gain further insight into the 'Japan gap' and the options for reducing or eliminating it. Illustrating the point with a comparison of 'idealised' key performance indicators (KPIs) from the EU, US and Japan Dr Ferris showed that a fully integrated programme in the EU and US could bring a product from first time in man to NDA submission in four and a half years, but development in Japan did not even start until proof of concept had been reached in the West. Then, if the clinical work in Japan led to a decision that bridging was possible, the minimum 'Japan gap' was 2.9 years, otherwise the need to carry out a full development programme in Japan resulted in a gap of 4.4 years, as found in the data discussed earlier. These 'Japan Gaps' were then built into the company decision-making process.

Dr Ferris then addressed the question of the stage at which Japan should join a Global Drug Development programme and discussed the options for eliminating the Japan 'lag'.

Option 1: Include Japan at Global Phase 1

If Japan is included in global first-time-in-man studies this can be regarded as true global development and some of the benefits are obvious. Theoretically it should be fastest and will generate early data on intrinsic ethnic factors - whether the drug is handled differently in Japanese and Caucasian subjects. There is also the advantage that, by involving local company personnel and opinion leaders from the beginning, there will be enhanced knowledge, interaction and interest.

One of the first decisions is the design of the Phase I study and whether to opt for a single protocol, with Japanese and Caucasian subjects studied in a single-centre trial, or to carry out a two-centre study. The advantage of the former is that it avoids the risk of site or investigator bias and, logistically, the study should be much easier and probably cheaper. The problem is that one of the cohorts of subjects will be in an alien ethnic environment and there may also be issues around limited availability of volunteers. In the two-centre study, both cohorts are in their home environment and it should be relatively easy to get volunteers. On the other hand there are the normal risks of site bias investigator bias and, logistically, the trials are more complex especially from a regulatory point of view.

Dr Ferris suggested that there were other disadvantages of including Japan in the global Phase I study, one being the problem that it is unlikely that the final formulation will be available at that stage and it is almost certain that the study will have to be repeated to generate definitive pharmacokinetic parameters in Japanese subjects. Another issue is the conservative attitude of local ethics committees, but Dr Ferris had been encouraged by Dr Doi's assertions that PMDA would be taking steps to encourage early drug development in Japan. Lastly, an important consideration is the high attrition rate for projects with only one in nine that enter Phase I actually reaching the market. The likelihood of eight out of nine studies being wasted has led many companies to delay the start of development in Japan.

Option 2: Include Japan from Global Phase IIa (*proof of concept*)

The next option discussed by Dr Ferris was to carry out a Phase I study in Japan at the same time that, globally, proof of concept studies are being undertaken in Phase IIa. This then allows a fully integrated Phase IIb programme to be set up. The benefits of this are the ability to focus, at an early stage on extrinsic ethnic factors that will influence the programme in Japan and to 'tailor' the programme to include Japan specifics such as clinical endpoints. As with Option 1, it also involves relatively early involvement of local company personnel and opinion leaders.

Dr Ferris pointed out, however, that including Japan in a multi-country study in a global Phase IIb presents some significant challenges. Firstly, which countries should Japan partner with in such a study; the US, Europe or other Asian countries. On the basis of intrinsic ethnic factors there are arguments for partnering with Asian countries but when looking at extrinsic factors such as medical practice Japan is much more similar to the Western world, in many aspects. Other extrinsic factors to be taken into account in designing a multi-country study

include the question of comparators, regulatory acceptance of endpoints, patient background and language issues, and differences in disease definition

Disease definition

Dr Ferris illustrated the issues surrounding disease definition with two examples, diabetes and obesity. Whilst the Japanese diagnostic criteria for Type II diabetes are similar to those of the American diabetes Association and WHO, the difference in body mass index (BMI) between patients in Japan (22-24 kg/m²) and in the US (30-32 kg/m²) is considerable. There is also an extensive literature that suggests that insulin secretion greater, and insulin resistance is higher, in Caucasians than in the Japanese. Furthermore, the therapeutic approach and use of concomitant drugs differs considerably between the regions. The significance of such factors needs to be considered when trying to integrate Japan into the global protocol.

Turning to obesity, Dr Ferris pointed out that patients with a BMI of 25-<30 are classified as obese in Japan and pre-obese by WHO criteria, under which obesity starts at 30 Kg per m². If the inclusion criterion for a global study is set at a BMI of 30, fully 20% of the US population will qualify, and only 2% of Japanese. Furthermore, if this BMI is carried through to the label, the product may not be viable for the Japanese market.

Other disadvantages of Option 2

Option 2 means that development in Japan jumps from local Phase I studies to inclusion in a global Phase IIb study, generally double blind and placebo controlled. Dr Ferris suggested that PMDA might be cautious, as KIKO had been in the past, about this jump to a global programme with a drug that is still regarded as 'experimental', especially since the transition will often involve changes in dose and possibly definitions of endpoints.

There is also, as in the previous option, the question of attrition rates. CMR data indicate that only one in six products that reach a successful proof-of-concept will reach the market, on which basis five in every six Phase 1 studies carried out in Japanese cohorts will be wasted.

Option 3: Include Japan from Global Phase IIb

For many of the reasons outlined above, most companies have tended to delay their decision to commit to a development programme in Japan until Phase IIb is underway in the rest of the world. The potential wastage is reduced by starting Phase I in Japan, at this stage, and carrying out Phase II/III or bridging studies whilst Phase III is underway elsewhere, since data indicate that 55% of projects entering Phase III reach the market.

The strategy can follow two paths: use of bridging studies (Option 3a) or full development in Japan (Option 3b). If bridging is feasible, the strategy can work well as there should be plenty of time, whilst Phase IIb studies are in progress elsewhere, to examine extrinsic ethnic factors. As data from other regions becomes available it will help the company to work with local opinion leaders and in consultation with PMDA. Dr Ferris cited an example from Aventis' experience with a disease-modifying drug for rheumatoid arthritis, originally planned as a full stand-alone development. By bridging, it was possible to eliminate an early Phase II study, two bioequivalence studies and two Phase III studies that were planned for Japan, with a very substantial savings in time and money.

Disadvantages of the Option 3a approach are that it results in repeating work that has been carried out in the West, that local opinion leaders have not been involved from the beginning and that it results in a steep learning curve for local company personnel. If a long-term treatment study is needed in Japan this can become an issue since it can become rate limiting and jeopardise the overall objective of simultaneous global submissions.

This, Dr Ferris pointed out, brings one to the final 'Option 3b' scenario in which, having left it until Phase IIb (post-proof of concept) in the rest of the world before finding that bridging into Japan is not possible, the only course remaining is stand-alone development in Japan. This is not Global Drug Development, he said, and it is much too late to achieve it.

DISCUSSION

Emerging markets: It was noted that the current emphasis is on the three ICH regions that make up a substantial part of the contemporary market but it may not necessarily take into account future markets where substantial percentages of the World's population live. Dr Ferris was asked whether he had given consideration to the time when China, for example, becomes a major target market and the extrapolation of data will need to incorporate another area of the World. Dr Ferris agreed that these markets will be of key importance in future and that there is particular interest in the expansion of studies into Asia. Although the Japanese market has, historically, been very attractive it will not be possible to continue the 'stand-alone' approach to studies there, particularly in view of the cost of carrying out clinical trials in Japan. He believed that the future lay in carrying out Asian studies, with Japan as a leading participant in those programmes. China, he said, is a very exciting and challenging objective

Options for development: Dr Ferris had discussed three specific options for development programmes that incorporate Japan but he was asked whether the 'cookie cutter' approach of making each programme fit one of these models was practical. Should each programme not be individualised on a case-by-case basis? Dr Ferris agreed that the options he had discussed set out the framework of issues faced by all companies, but that the individual strategies adopted by companies were where the competitive advantage lay. Each company has its own decision-making process but the main message is that the structure for the development plan needs to be in place as early as possible in the data-collection process.

Patient variability and ethnic differences: A participant noted that North America has a substantial Asiatic population, which is one of the factors to be taken into account when determining, for example, dose levels. One of the emerging observations, however, is that variability in individual responses is more of an issue than ethnic differences. Dr Ferris agreed that considerations of ethnic differences need to be kept in proportion. One of the concepts of the ICH E5 Guideline, he noted, is that the variability within a population is similar to the variability between populations and it is important to keep in mind the clinical significance of those differences. He felt that there was an increasing tendency to become diverted into hypothetical and irrelevant discussions around minor differences that are not clinically relevant. Developing early data on intrinsic ethnic factors is obviously important but he had tried to present the commercial reality and the caution with which companies might approach investing in studies on Japanese cohorts at an early stage for every product.

Impact of gender: Reference was made to the increasing expectations that gender factors should be investigated and analysed, in addition to ethnic factors, as part of the clinical development. It was suggested that this could double the complexity, not only of the development process but also the review. Dr Ferris agreed that this was a looming issue but not one to which he was able to suggest a solution except to note that it underscores the need for a paradigm change in the way drugs are developed and reviewed in future. Development costs are escalating and output decreasing, as the process becomes ever more complex and the situation is becoming untenable.

STRATEGIC APPROACHES TO GLOBAL DRUG DEVELOPMENT: ADVANTAGES AND DISADVANTAGES

Working in a western environment:

Dr John Alexander

President, Sankyo Pharma Inc., USA

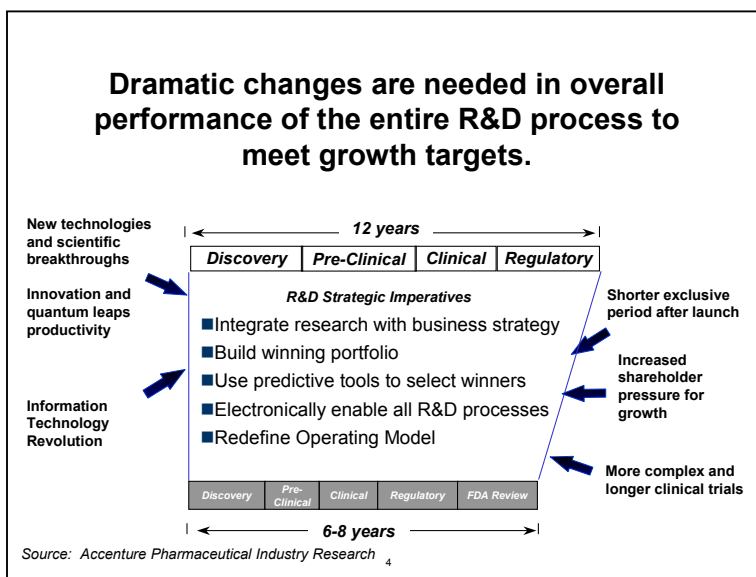
Dr John Alexander looked first at the factors that are facing all pharmaceutical companies involved in global drug development, before turning to the particular challenges for a Japanese company. The general picture shows healthcare costs outstripping resources, a deficit of innovative drug discoveries, soaring development costs and intense competition. Most Japanese companies are small to medium-sized by pharmaceutical industry standards and face the challenge of very limited R&D budgets compared with the major players. The problems of low productivity and soaring development costs are shared by companies in Japan, which also face intense competition from the Western companies that are starting to dominate the Japanese market. Whilst there is an expectation that companies should do well in their own country, Japanese companies are facing the same problems of patient recruitment and approval as other companies operating in the country.

Referring to figures for World pharmaceutical sales for 12 months to October 2003, (North America \$168 billion, Europe \$72 billion, Japan \$51 billion) Dr Alexander suggested that there arguments for saying that money should be spent in roughly the same proportion as the eventual return, that is, approximately half in the US and a quarter in Europe and Japan. The somewhat depressing scenario illustrated by CMR International data, however, is that, although R&D global expenditure is increasing in line with global sales, the global output of new molecular entities (NMEs) has fallen dramatically and does not represent a satisfactory return on investment. At the same time, the development time for NMEs remains constant at 10-12 years, with a longer time needed to reach the market in Japan as a result of the 'Japan gap'¹.

Reducing development times

Most companies, said Dr Alexander, are trying to reduce the development time by half and he referred to the different strategic imperatives shown in Figure 3, and the other factors that were impacting on efforts to shorten development.

Figure 3



¹ Discussed further in the presentations by Dr Ferris, page 7, and Professor Walker, page 14

Looking at the overall picture, Dr Alexander suggested that, compared with the past, the 'R&D bottleneck' has moved from discovery to the pre-clinical stage. A large number of new molecules are being created through new technologies for discovery, including combinatorial chemistry and high throughput screening and many candidates move to the discovery-to-development interface (DDI), the period between discovery and phase II, but the attrition rate at the DDI is high. The question is whether this attrition rate can be improved through using genomics and other technologies to predict the 'winners' better. So far there has been little evidence that this is happening but Dr Alexander believed that the DDI is where most companies would be expending a large part of their R&D resources.

Challenges of integrating Japan into global development

Dr Alexander itemised the main hurdles in the way of integrating Japan into global drug development programmes. Slow enrolment of patients into clinical trial in Japan has, historically, been a major problem but he believed that the situation was improving with local CROs playing a valuable part in recruiting patients, for example in such fields as hypertension.

Another issue is the dose for patients in Japan which is usually about half that of Western countries. This is often dismissed as being related to body size but Dr Alexander's own impression was that this was the result of the emphasis being placed much more heavily on safety, in Japan. In relation to ethnic differences, an area that should be taken into account is the difference in diet. Dr Alexander referred to his experience of the development of anti-platelet drugs where a dramatically lower dose was needed in Japan. The response was much greater than could be predicted from differences in body weight and it was postulated to be related to the high fish content in the diet. Such extrinsic factors can justify early study of drugs in Japan.

Different disease classifications and endpoints in Japan and the problems of 'bridging' data from the West also present challenges to global clinical development. The difficulties of global project management are also a factor, not least because of differences in language and time zones.

Dr Alexander drew parallels between the changes that the Japanese industry is currently undergoing and the evolution in drug development in the US that he had seen during his career. These included moving from:

- Working in 'silos' to working in multidisciplinary teams;
- Local companies operating nationally to global companies;
- Commercial involvement only in Phase III to involvement throughout the R&D process
- Doing everything within the company to outsourcing.

Differences between clinical research in the US and Japan

Dr Alexander made further comparisons between carrying out clinical research in the US and in Japan. As mentioned earlier, there is a greater emphasis in the US on efficacy, whereas the emphasis is on safety, in Japan. The vast and diverse patient pool in the US is a real attribute as is the large infrastructure of investigators, clinical research coordinators, and CROs/SMOs available to conduct studies in the US. He also paid tribute to the FDA for working closely with industry on drug development issues and he welcomed the changes in Japan that he felt would greatly help the pharmaceutical industry in the future.

Strategies for global development

Turning to the question of research strategies, Dr Alexander suggested that 'strategy' is about being different, by choosing to perform different activities, or similar activities in a different way from competitors. It is important to distinguish operational effectiveness from strategy; Operational effectiveness means achieving similar goals, such as development times, better than ones rivals.

When Sankyo management were considering appropriate strategies for research, they had studied other successful Japanese companies, and found parallels in the automobile industry, with a company such as Honda. This has successfully moved from a position of having almost no sales in the US in the mid-1970s to its current leading position, by focusing on five key business areas: Fast product development; A global, but flexible approach to local markets; High quality products; Strong leadership; and Effective outsourcing and alliance management.

Sankyo came up with a management model that is based on one global R&D Management Committee, with an Integrated Development Team (IDT) being formed for each product coming out of discovery. The company has acknowledged that there are cultural differences between Japan and the West when it comes to the process for, and speed of arriving at decisions and the procedures are designed to facilitate decision-making. It is team-based and coordinated by the Management Committee, which includes all key representatives from the commercial and technical areas. The Committee meets monthly and the Chairman reports to the President of the company.

Dr Alexander described the R&D structure that has recently been reorganised at Sankyo. Within this structure is the Sankyo Pharma Development in which US Development and EU Development has been merged into a single organisation. As a result, most of Sankyo's research is invested in the US with a relatively small group in Europe. Within Pharma Development, the four global departments – Project management, IT, Medicinal Safety and CMC – are usually headed by Japanese staff. This is for two reasons; not only to ensure Japanese personnel bring expertise in their own field, but also to enable them to learn about drug development in the West, since the individuals in these posts are seen as the future R&D leaders for the company.

Models for global drug development

Acknowledging that any model for efficient drug development must depend on the particular type of drug, Dr Alexander outlined the general philosophy followed by Sankyo for global drug development. Phase I is carried out in the US where Sankyo has a 32-bed clinical pharmacology unit. Placebo controlled studies are normally carried out in the US as they are not so well accepted in Japan and Europe. Trials against comparators are, however, essential for Europe, he noted, not least because of the implications for pricing and reimbursement.

Traditionally, Sankyo has been one of the companies following the established pattern of carrying out Phase I and II studies in the West before starting development in Japan but this has recently been questioned by the top management as it seems anomalous for a Japanese company. This policy is therefore being reviewed and the new strategy will probably be still to carry out Phase I studies in the US but then to start work much earlier, in Japan, to determine the impact of intrinsic and extrinsic ethnic factors. It is accepted that many products may fail, but any wasted investment would soon be offset if a successful product is speeded to the market.

Whilst it is important to determine, at an early stage, the factors that will determine whether it is possible to 'bridge' Phase III data into Japan from Europe or the US, the ideal situation, in many ways, is for Japan to be included in global Phase III trials. Dr Alexander noted, however, that one of the downsides is the expense of carrying out clinical studies in Japan. There are also the problems mentioned earlier of disease classification and selecting the right dose.

Dr Alexander noted that Sankyo has little interest in developing products for a single or regional market and the other elements of their globalised development strategy include:

- Allocation of resources to key regions (US 50%, Japan 25%, Europe 25%);
- Providing global management experience for future leaders;
- Creating a strong project management function with decentralised global project teams;
- Developing global information systems; and

- Providing training for staff to understand the cultural differences between Japan and the West.

In conclusion

Dr Alexander summarised by underlining the fact that Japanese companies are expanding their development and commercial presence in the West, especially in the US. Unless they move from local to global they will not survive. Slowing pharmaceutical growth rates in Japan and the challenges of clinical trial enrolment are driving these changes. It is a particular challenge for Japanese companies to move from being local to being global but any company that wishes to become truly global must address the cultural and organisational challenges that are involved.

DISCUSSION

Language: Asked about the language that is used in the Global R&D Management Committee, Dr Alexander replied that there is always simultaneous translation although any slides are almost always presented in English. He remarked that the translation is so good that one forgets about it. It has been suggested that, as a global company, the language should be English but this impedes discussion. Translation is a significant investment but one that is considered worthwhile.

FACTORS THAT IMPEDE OR ASSIST TRUE GLOBAL DEVELOPMENT IN THE ICH REGIONS

Professor Stuart Walker

President and Founder of CMR International

Professor Stuart Walker introduced his presentation with an overview of the current trends in global drug development in terms of R&D investment, number of new molecular entities (NMEs) being developed and development times. In 1992, he noted, the industry worldwide was spending about 25 billion US\$ on research and development and by 2003 the figure had risen to 50 billion US\$ with predictions that it would reach some 60 billion by 2006/2007.

Whilst such investment might be expected to show a concomitant increase in the number of NMEs being placed on the market this has declined from a peak of 46 in 1997 to an all time low of 26 in 2003. At the same time the industry and regulatory agencies have been unable to improve drug development times that have remained fairly constantly between 12 and 14 years. Professor Walker pointed out, however, that the apparently lower productivity of industry, in terms of the declining number of NMEs, says nothing about the value of those products and it may well be that they are more innovative or more valuable in terms of their medical benefit compared with the more numerous products introduced in earlier years.

Data that compared overall development times from first synthesis to launch onto the market in Japan, the USA and Europe, showed that the time taken for products to reach the market in Japan was between two and four years longer compared with products launched in the US and Europe. Patients in Japan were therefore waiting a considerable time to benefit from new medicines launched in other major markets and the so-called 'Japan gap' was one of the items investigated in a survey on *Current Strategies in Global Drug Development* carried out by the CMR International Institute, in preparation for the Workshop². Replies to the survey had been received from 17 pharmaceutical companies including eight out of the top 15 in the world, by R&D expenditure.

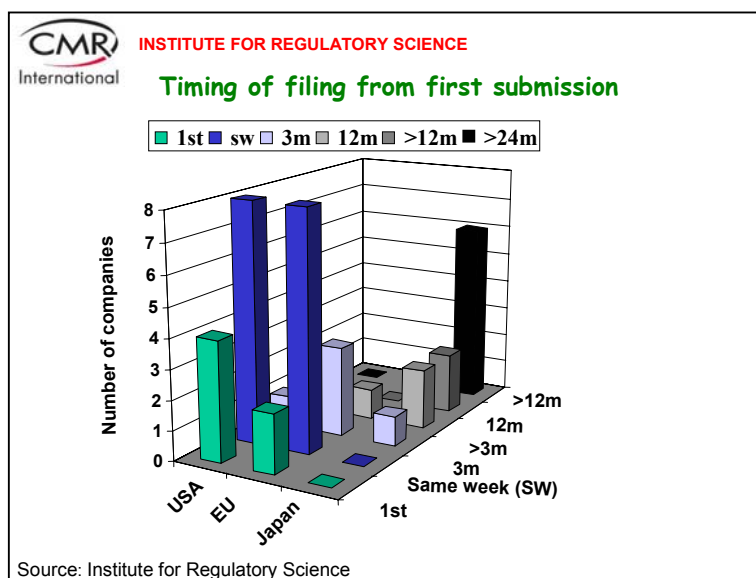
² Professor Walker acknowledged the work of Dr Neil McAuslane who had carried out the survey and prepared the analyses reported in this presentation.

Strategies for the timing and sequence of submissions

Asked about strategies for the timing of submissions to regulatory authorities in the three ICH regions, about one third of companies gave simultaneous filing as their current preference, one third indicated a sequential approach and the remainder preferred to decide on a case-by-case basis. When asked to predict their strategy in 2010, however, the vision of the large majority of companies was that they would be filing simultaneously in the three regions.

When the order of filing was examined it was found that a large majority of companies submit to the US and Europe first and this is often followed by submissions to Canada and Australia. Professor Walker noted, with concern, applications were rarely, if ever, submitted to Japan as the first country and, for many companies, it appears that Japan is fourth to sixth or even ninth in terms of the order of filing applications. When the timing of submissions was examined, a similar pattern emerged with applications often being filed within the same week, in the US and Europe, whilst some 60% of companies reported that they had filed applications in Japan more than two years after the first submission in the rest of the world. These findings are illustrated, schematically, in Figure 4.

Figure 4



Companies were asked about their clinical development strategy and whether this was integrated between different regions, was sequential or whether development was simultaneous but not integrated. Seventy percent of companies indicated that they had an integrated approach for the US and Europe only. It is not, however, only Western companies that are studying new drugs in the US and Europe first and then bridging into Japan at a much later stage, Japanese companies are also following this strategy.

In summary, the survey indicated that most companies have significantly different development programmes between the West and Japan with simultaneous data generation in the Western world and a lag before work commences in Japan. Similarly there are simultaneous submissions in the Western world with a delay before filing in Japan. The vision for the future (by 2010) is, however, for a single global development plan with simultaneous data collection, simultaneous submission and, more importantly, simultaneous approval and timely access to new medicines for all patients.

Interaction with agencies

Professor Walker referred to a previous CMR International Institute Study³ that had been carried out in preparation for an earlier Workshop in which companies had identified three main Critical Success Factors for regulatory success:

- *Company strategy*: Strong science based decision making, early clarity of labeling goals; and a focus on products which satisfy unmet medical or show superior efficacy and safety
- *Technical data*: Well thought out clinical programmes to support the desired label, with clearly defined, measurable, validated endpoints in well powered studies;
- *Communication*: Early and open dialogue with agencies, good contacts, frequent interactions resulting in continuity and consistency of regulatory advice.

The subject of communication with agencies was followed-up in the current survey and companies were asked about their plans for arranging meetings with the authorities, during drug development. Data on the early development stages (preclinical to Phase IIa) indicated about 50% of the companies plan on having some kind of meeting with the authorities. In the US, the majority are held to discuss preclinical development, whilst, for Japan, the planned meetings were distributed evenly between preclinical, Phase I and Phase IIa. Asked about plans for meetings later in development (end of Phase II to pre-submission) 16 of the 17 companies indicated that would have meetings with FDA at the end of Phase II and at the pre-submission stage. A similar pattern was found for Europe (centralised procedure) and Japan, with 12-14 of the 17 companies seeking meetings at these stages.

When companies were asked whether they had experienced significantly different advice from agencies 14 out of 16 respondents (86%) indicated that they had. This was analysed further and the responses indicated that the three areas where differences in scientific advice arise most frequently were in relation to clinical endpoints, use of comparators and dose levels.

Barriers to global development

Looking at barriers to global drug development companies were asked to give their view on whether regulators in the US, EU and Japan were imposing requirements that are additional to those agreed under the ICH guidelines and are therefore, in turn, an impediment to global development. Of the 16 companies who responded, nine felt that this was true in the US and eight for the EU but the response for Japan indicated that 14 companies were of the view that Japan asked for data that went beyond the ICH norms. In the US, the issues often related to clinical safety and CMC data and in Europe there were often problems in respect of the different interpretations by member states and issues related to specific comparator data. Not surprisingly, the concerns in Japan were over the implementation of the ICH E5 guideline on acceptance of foreign data and there were also issues related specifically to the use of Asian data generated in the countries around Japan.

When asked about bridging studies, the majority of companies (11/15) expressed the view that these had reduced the lag time between submission in the West and Japan. A similar majority, however, believed that bridging should be regarded as a temporary measure until Japan can be integrated fully into global drug development. When asked how long such integration would take the median of the responses was 5.5 years but the actual responses ranged from zero to ten years.

Other key constraints to global drug development were covered in the survey and the five major barriers that emerged were differences in medical practice, cost of patient recruitment, clinical trial infrastructure, regulatory hurdles and patient availability. Whilst the data indicated that these problems arose predominantly in Japan, Professor Walker emphasised that this was a snapshot of the situation as perceived today and he was

³ The changing regulatory environment: Reality and Perception, JAN McAuslane & C Anderson, December 2003, Ref: CMR03 - 221R

confident that many of these issues would be resolved with the establishment of the new PMDA.

Future perspectives

The survey had also asked companies to identify factors that may have an impact on progress towards global development in future. The response indicated that the key factors to enhance global development are; increased dialogue between agencies (14/15); use of the CTD dossier (14/16); integration of risk management plans into development (11/16); increased use of conditional approvals (10/16); and use of pharmacogenetics (8/15).

Professor Walker concluded by looking at the regulatory landscape over the next ten years. In response to an open-ended question in the survey, companies had indicated that they would be looking for predictability and consistency, partnerships and, possibly a paradigm shift to reshape and rethink regulatory processes. Predictability in the timing and outcome of regulatory decisions across regions is the key to successful global drug development. Partnership is a word that is now frequently used in relation to working closely with the agencies and industry is now looking towards strengthened tripartite agreements to facilitate exchange of information and coordination of regulatory advice. Finally, it appears that industry would welcome the opening up of discussions on a fundamental paradigm shift to move away from the 'traditional' approaches to drug development and review. This might include the use of risk management plans to reduce Phase III studies and establishment of a global, coordinated safety database. The ultimate aim, however, is to have the quality measures in place that will allow a move towards joint reviews and decision-making.

WHAT ARE THE KEY QUESTIONS THAT NEED TO BE ADDRESSED IN A GLOBAL DEVELOPMENT PLAN TO UTILISE A SINGLE PROTOCOL?

Dr Christine Cioffe

Vice President Project Management, Merck and Company Inc.

Dr Christine Cioffe provided an overview of the factors to be addressed in order to achieve the goal of a single protocol for global drug development. Although the intent was to present an industry view, she acknowledged the influence of the perspective of her own company. She was, however, sure there were themes and issues common to all the pharmaceutical industry, when designing research programmes and dealing with regulatory agencies

The initial design for a global programme and associated studies will be driven by the defined objectives, in particular the hypotheses to be proved when working in a new therapeutic areas. The goal is to create a label that optimises the product in the marketplace. There may also be critical, related issues to be taken into account in respect of the scientific, pre-clinical and other technical issues.

The clinical challenges to be addressed include the need to take account of different medical practices across the globe and such factors as the epidemiology and prevalence of the disease. Again, this is particularly relevant for new therapeutic areas and where the disease prevalence may not be consistent worldwide. Clinical endpoints can also vary significantly and Dr Cioffe cited diabetes and obesity as examples. Another clinical issue is the on-going debate about the use of placebo *versus* active comparator in the design of trials. Regulatory challenges include identifying registrable endpoints as well as the ability to extrapolate data or bridge between different ethnic populations.

When addressing differences in medical culture and standards of care, many companies have found it useful to work through local subsidiary companies or CROs with appropriate expertise, especially in new, emerging markets. This is also a factor in dealing with the issues around patient recruitment including logistics and infrastructure that may not exist when moving into new markets or new countries.

As the strategy for a global Phase I and II clinical data package is developed, with a view to extrapolation or bridging into other ethnic populations, studies on dose response and studies

in special patient populations become particularly important. With respect to efficacy, studies on pharmacokinetics and pharmacodynamics are critical to the decision on the best way to extrapolate data to meet the regulatory requirements of a new region.

Use of the ICH E5 Guideline

Dr Cioffe discussed the ICH E5 Guideline on Ethnic Factors in the Acceptability of Foreign Clinical Data, which sets out the concept of bridging studies as a means of extrapolating data from one population or region to another. She suggested that use of the guideline should be considered as an *interim* measure in ensuring a successful global programme and timely registration in the major markets, until the time when fully integrated global development is achieved.

Data extrapolation can be possible if the drug is insensitive to intrinsic factors (genetic or physiological) and if extrinsic factors (cultural and environmental) are sufficiently similar between regions that they are not a cause for concern. One of the critical factors, referred to earlier, is making sure that differences in medical practices between the regions, particularly disease definition and diagnosis, have been taken into account. The key to success in extrapolating data, Dr Cioffe suggested, is finding a common primary efficacy endpoint that will provide common thread across all the regions.

The guidelines on the application of the E5 guideline encourage discussion between sponsor and regulatory authorities before conducting a bridging study and Dr Cioffe strongly advised early engagement with the regulatory authorities in order to determine that the proposed approach is acceptable.

Success with bridging studies

Using data from the MHLW, Dr Cioffe discussed the status of bridging studies in Japan. The number of pre-NDA consultations with the former Organisation for Pharmaceutical Safety and Research (KIKO) had been charted for 1997 to 2000, showing a steep rise from 101 to 279. Alongside these was the number of consultations that specifically addressed the subject of bridging studies, which showed only 24 such consultations in 1997 rising to 98 in 1999. Data, also from MHLW, on 27 successful new drug approvals, between 1999 and 2002 that were based on a foreign clinical data package showed that 22 of the approvals had included extrapolation using bridging studies.

Dr Cioffe also cited specific examples, where companies have used bridging data to bring about successful registration and reduce the review times (see Box).

Examples of Bridging Studies

- **fexofenadine** : randomized placebo-controlled double-blind dose -finding study (Allergic Rhinitis n=310), 14 months
- **oseltamivir** : randomized placebo-controlled double-blind phase III study (n=316), 4.7 months
- **anastrozole** : randomized phase II study (n=31) clinical pharmacological study (healthy n=48), 13.3 months
- **sumatriptan** : randomized placebo-controlled double-blind dose -finding study (n=274), 10.7 months
- **zolmitriptan** : randomized placebo-controlled double-blind dose-finding study (n=289), 15.5 months
- **palivizumab** : single arm open trial (n=31), 12.9 months

Challenges for clinical research

Dr Cioffe outlined some of the challenges faced by clinical researchers in a global regulatory environment:

- *Justification of bridging studies*: Whether it is possible to 'generalise' this or whether decisions will continue to be made on a case-by-case basis;
- *Global clinical trials*: To what extent multi-centre trials using the same protocol are feasible in practice and the stage at which they can obviate the need for bridging studies;

- *Registrable endpoints*: The need to identify these from the outset and trend to move away from traditional, clinical-based endpoints towards the application of new technologies such as pharmacogenomics and, increasingly the use of biomarkers;
- *Accommodating change*: The need to keep abreast of changes brought about by continuing harmonisation of regulatory requirements and take account of the implications of the evolution and definition of agencies' structures, as exemplified by the recent changes in Japan and establishment of the PMDA.

She suggested that the keys to successfully streamlining the development of drugs for international use lay in:

- Early alignment with all functional areas during the study development process, ensuring universal implementation of GCP and transparent, standardised communications across the globe;
- Designing, during Phase I - II, an integrated Study Development Process that meets global regulatory requirements and determines appropriate endpoints and specific factors for inclusion;
- Defining the final market image at an early stage as this can complicate drug development programmes.

Development options

Reviewing the development options for a global programme, Dr Cioffe noted that, at Merck, they are trying to move away from sequential development in which development in selected areas would wait for the worldwide programme to be well advanced before Phase I is started. The majority of development programmes are currently 'Phase shifted' with development Phases being no more than 12 months apart in US, EU and Japan. Parallel development is, however, considered the optimal goal, with simultaneous development worldwide and filing at the same time in all the regions.

With this in mind, Global Product Teams have been established at Merck and Dr Cioffe outlined the guiding principles for their operation. These include transparency, the elimination of redundancy in the development process and clarity on 'ownership' of decisions. Oversight committees are responsible for ensuring that documented regulatory requirements in Japan, EU and the US are taken into account when reviewing and approving protocols and regulatory submissions.

The Global Product Teams are responsible for driving early decisions on the global programme for the US EU Japan or emerging markets and integrated review bodies particularly for R&D, marketing and manufacturing also help to formulate the final strategic and commercial decisions. A key element in the development, however, is that decisions for one region should not slow down the worldwide programme

In conclusion Dr Cioffe predicted that, although current experience of bridging studies (E5 guideline) and global integration is limited and varied, in the next five years the company will be thinking in terms of a single development programme with simultaneous data development and a single regulatory submission.

DISCUSSION

Hurdles to global drug development: Dr Cioffe was asked to identify the most significant hurdles to be overcome, from a corporate perspective, in order to achieve the goal of a single development programme within the next five years. She replied that the answer lay in making a conscious decision that all products will be developed on a global basis and no longer deciding on a product-by-product basis. The policy will, however, need to be pursued proactively.

Parallel programmes and true integration: The comment was made that there is a big difference between having parallel development through synchronised regional programmes and having an integrated global programme that may require some extra regional pieces.

Dr Cioffe acknowledged that Merck is carrying out staggered or parallel development, in many cases but that there may not be the choice of a fully integrated global programme, at this time, especially in certain therapeutic areas. Nonetheless the optimal goal remains to true global programme.

A further comment suggested that the real issue was whether parallel launch could be achieved. A target of, for example, launch in Japan not more than six months after launch in the US could be a measure of whether global development had been achieved. Dr Cioffe agreed that this would be a good approach as there is a tendency to focus on simultaneous submission as the target, whereas the true endpoint is the launch. Global development has not achieved its goal if there is still a delay in making the product available to the patient and physician.

Pre-clinical and CMC: It was noted that the focus of presentations had been almost entirely on achieving global clinical development and Dr Cioffe was asked to comment on whether global development had been achieved with respect to the CMC (chemical and manufacturing controls) and pre-clinical work. Speaking for Merck & Co., Dr Cioffe felt that coordination of development in these areas, between Japan and the Western countries was at a far more advanced stage and had benefited from a good relationship, over many years, between the research laboratories based in the US and those in Japan. There were fewer differences in requirements for pre-clinical testing and the lead has, predominantly, been taken by the US headquarters. CMC has been a more difficult area but has not, to date, proved rate limiting in the submission process. Time will tell whether this situation will remain as a larger number of simultaneous submissions is achieved.

DIALOGUE WITH REGULATORS DURING GLOBAL DEVELOPMENT: WHEN, WHY AND HOW?

Dr Stewart Geary

*Deputy Director, Corporate Regulatory Compliance and Quality Assurance Headquarters,
Eisai Co Ltd, Japan, Eisai Co Ltd, Japan*

In his presentation, Dr Stewart Geary focused on consultations with regulators for formal scientific advice, how it differs in different parts of the World and how that influences the way the advice is used.

Formal advice

If we all agree that 'advice is good' suggested Dr Geary, then it follows that 'more advice is better'. Frequent contacts between companies and regulators during the development programme are useful and can set the stage for development strategies or help solve problems in the critical path for development. The need for advice, he believed, is greatest when the indication or the drug are innovative and he added that advice is more important for a smallish company, such as his own, that is new to a particular market and regulatory environment. The request for advice may also have different purposes, for example this may be to ask whether a study can be performed at all and whether the safety issues have been adequately addressed. Alternatively, the purpose may be to ask if the development programme is appropriate to support the desired indications or simply whether the data is adequate for the country which, in Japan, can lead on to bridging discussions.

Time lines

Dr Geary pointed out that the procedures for obtaining advice, especially in relation to timelines differ between the regions.

FDA

There are clear FDA guidelines for different categories of advice and how quickly it can be obtained, Dr Geary explained (see *Box*). In his own company's experience, meetings can normally be scheduled earlier than is stated in the guidance documents and official minutes are issued from the review division after the meeting. Fees are not charged for consultations with FDA.

EMA

Advice from the EMA is obtained via the CPMP and its Scientific Advice Working Group (SAWG). Unlike the FDA system, the advice is not binding but Dr Geary suggested that, in practice, no advice from regulators can really be held to be binding as new safety issues may arise as new data are collected.

Fees of €34,8000 to €69,600 are charged for the initial consultation and €11,600 to €34,800 for follow-up advice but this is small if considered in relation to the overall cost of clinical development. Dr Geary pointed to the timing of the advice procedure as being the main concern, especially when compared with the FDA process. In order to start the CPMP advice procedure one must inform the Secretariat one month in advance of the date of making the formal submission. The documentation is then validated before the coordinators' reports are discussed at SAWG and it can be a 40-, 70-, or 100-day procedure, or longer before the outcome is known, depending on the type of advice being sought.

Dr Geary contrasted this with experience of seeking advice at national level in the EU where advice can often be obtained more quickly and easily. He cited the UK Medicines and Health products Regulatory Agency (MHRA) where it is possible to submit materials for the consultation 10 days before a meeting and formal minutes are received 30 days afterwards.

Japan

For Japan, Dr Geary could only speak from experience of the previous system under MHLW and KIKO, before the establishment of PMDA. There are many different categories of consultations that are possible and the fees can range from ¥170,000 to ¥3,300,000 (US\$ 28-29,000). Advice can, however, be obtained on a very short timeline with material needing to be submitted only 3 weeks before the meeting.

Actual use of advice

Dr Geary pointed out that advice from different agencies might be requested and used differently because of the company's regulatory goals in various territories. The advice received is normally very useful and if it is not, he suggested, it often reflects problems with the way the questions are posed and the extent to which the development plan has been considered within the company. If the request for advice is made appropriately the response should be helpful although the company may not always agree with the advice and it may not, in fact, change the development plan significantly. At Eisai, the goal of obtaining advice is not only to obtain approval more rapidly but also to protect trial subjects and they have found it useful to obtain advice at several points in a single programme.

Turning to the use of advice in Japan, Dr Geary noted that his company not only develops products that it has discovered but also license-in products from outside and the most common advice that is sought relates to adapting the existing development programme to Japan. This mainly relates to questions on the extent to which data can be bridged into Japan and which studies need to be repeated in a Japanese population.

The tone of the consultation tends to be defining in terms of how Japanese patients or clinical practice are different, for the purposes of the programme and what therefore needs to be done in order to make the package applicable to Japan. Even when the KIKO consultation

FDA timelines for obtaining advice**Type A** (Critical Path)

Scheduled within 30 days of request

Type B (Pre-IND, End of Phase 1, End of Phase 2/pre-Phase 3, pre-NDA)

Scheduled within 60 days of request

Type C (others)

Scheduled within 75 days of request

Review division issues official minutes

comes at the beginning of the global development programme their advice does not usually guide the development programme, or give scientific advice that is applicable outside Japan.

Dr Geary referred to his company's flourishing pipeline at Phase I but also the increasing attrition rate as products move towards Phase III and therefore their greater experience, in relation to FDA consultations, in obtaining pre-IND and other early development advice. In his experience, it is often sufficient to obtain written answers to the questions asked, without needing a formal meeting. Since the company tends to start its development programmes in the US and Europe, and frequently obtains advice from the FDA first, they find that this guides the development programme internationally, as well as in the US. When consultations are held they will often be attended by the company's experts from Europe and Japan, as well as the US. This is in contrast to meetings with KIKO that are usually only attended by Japanese experts.

In the EU, the time taken to obtain advice via the CPMP means that the company is more likely to seek advice from a national authority, even recognising that applications are more likely to go through the centralised than the mutual recognition process. They are also aware of data suggesting that programmes that have benefited from a CPMP consultation are more likely to have a successful outcome but, nonetheless, time is a more significant consideration. Again, the advice received in Europe, where development programmes frequently begin, is often found to be useful for guiding programmes in the US and Japan and company experts from all three regions attend the consultations.

Examples

Dr Geary gave the example of a new chemical entity where the company has some questions on pre-clinical safety. In his experience no single consultation will speak for other regulators and his company's tendency is to obtain advice from the FDA or an EU national authority, depending on the site where Phase I studies will start.

A situation that was not necessarily envisaged when the guidelines were developed is the case of in-license candidates with data available through Phase III. The company will wish to have a better sense of whether this data will be considered adequate for the EU and US, but time is of the essence. A three- to five-month delay to consult the CPMP is a major deterrent, and even the 60 days to arrange a pre-NDA meeting with FDA may be too long. An informal meeting with an agency such as MHRA may often be seen as an acceptable option.

In the case of the protocol for a major, pivotal multinational study including Japan, however, Dr Geary recognised that advice is needed from all the regulatory agencies involved where studies are to be performed and submitted for product registration.

Is simultaneous development the goal?

Finally, Dr Geary posed the question 'Do we necessarily want to perform development simultaneously in all three regions? There are cases, he suggested, where one needs to concentrate resources to develop the product quickly in one region, either until a significant Phase I barrier (e.g., bioavailability) is passed or until proof of concept is achieved. This tends to be Eisai's policy. It means that data obtained from the early stages of development in one region may affect the evaluation and/or advice that are given by other regions and regulators.

Reconciliation

If different advice is obtained from two regulators on a single protocol there is no mechanism to reconcile that advice, formally, and certainly no rapid mechanism. Dr Geary noted that, when advice differs substantially, it can result in development programmes being duplicated. In his experience this tends to happen as a result of the different philosophies over the use of placebo versus active comparator in the US and Europe, but this is not the only example where it has not been possible to reconcile advice.

A possible solution, he suggested, could be the endorsement, by one regulator, of scientific advice received from another. If this could be achieved outside (i.e., faster than) the

timelines set for formal advice it would be a major step forward. Other solutions might lie in the current pilot scheme for trans-Atlantic advice under the EMEA-FDA confidentiality agreement and the possibility of similar pilots for trans-pacific advice.

DISCUSSION

Conflicting Advice: Dr Geary was asked further about his experience of contradictory advice and how this is managed and rationalised. He replied that it is not an unusual experience to receive conflicting advice and, in extreme cases it may mean that the company sees no alternative but to duplicate the programme using different protocols.

A member of the audience commented on the benefits of ensuring that advice from one agency is shared in an open manner when consulting the next. This can be extremely helpful in reconciling advice. A comment from a regulator agreed that it would be extremely helpful, at pre-submission meetings, to have a background summary of the reasons for adopting the development strategy, including the input received from consultations with other regulatory agencies.

Advice in Europe: Dr David Jefferys referred to the comparisons made by Dr Geary between the timelines for obtaining advice from the EMEA compared with individual Member States and suggested that this may not be comparing like with like. Scientific advice obtained via the EMEA is a composite view from 15, and shortly 25, Member States. Two *Rapporteurs* are assigned and account needs to be taken of the fact that it may be necessary to reconcile different starting positions. In some cases, in fact, companies turn to the central advice procedure because there has been different advice from individual Member States.

Dr Geary acknowledged that it was a little unfair to compare the CPMP advice procedure with individual national procedure, because of the depth of consultation needed, but he nonetheless emphasised that timelines are extremely important and there are many instances where waiting 4-5 months for advice is not a viable option, however important that advice may be.

Joint advice: Asked if he believed that joint scientific advice between FDA and the EU, under the confidentiality agreement signed in 2003, would help to speed up drug development, Dr Geary expressed general confidence that it would but also raised the possibility that joint advice could also mean adopting the most onerous position and rigorous requirements. There is the danger that attempts to reach consensus might lead to the adoption of a much more conservative regulatory position.

A member of the audience noted that at least one successful pilot, involving an orphan drug product, had already taken place under the joint confidentiality agreement and hoped that the procedure would also be tested on other products of more commercial interest. One of the concerns is whether companies would be allowed to attend the joint advisory meetings and whether the interactive approach to discussion adopted by FDA would be permitted.

Consequences of disregarding advice: A question was addressed not only to the speaker but the audience on whether companies are prepared to go against the advice received from regulatory authorities. One participant responded for the European system, saying that, if Scientific Advice from the EMEA has not been accepted, an explanation should be included in the application giving the reasons. A regulatory member of the audience suggested that there are times when advice should be challenged and that this is one way that regulators will also learn. Examples could be cited where companies have not taken all the advice given and were right to do so. Dr Geary acknowledged this but pointed out that, in practice, it was a very hard –and potentially dangerous – decision for company personnel to take and that management might take a lot of persuading.

THE REGULATORS; ROLE IN ENHANCING MEDICAL SCIENCE INNOVATION

Dr Murray Lumpkin

Principal Associate Commissioner, FDA, USA

Dr Mac Lumpkin referred to the title of his presentation and hoped that the idea of regulators actually enhancing innovation would not be considered 'an oxymoron'. He recognised that there is a lot of justifiable concern within the industry over the state of the research pipeline and the amount that is being invested with an apparently diminishing output. Industry should, however, be heartened by the positive view of pharmaceutical innovation taken by the immediate past FDA Commissioner, Dr Mark McClellan. He characterised 'innovation' as the ability to take knowledge and transform it into something that was of value to the community. On this basis, Dr McClellan had expressed the view that biomedical technology had probably had a more beneficial impact on the community, in the 20th century, than all of the other more obvious, and better appreciated, technological advances. He referred not only to the public health benefits of treating victims of heart attacks diabetes HIV and cancer, but also to the 'trillions of dollars' of economic benefit to the community through better health and productivity.

Dr Lumpkin suggested that the innovations yet to come through genomics, proteomics, nanotechnology and biomedical information technology gave cause for equal optimism over prospects for the 21st century. The expectations are for more effective, more targeted and 'individualised' medical therapies but there are questions about their commercial viability, given the heavy investment required for a development process that is becoming increasingly lengthy, costly and risky. Add to this regulatory processes that can seem impenetrable and unresponsive and a marketplace where payment and reimbursement issues are becoming an ever-greater issue, and the result is a growing belief that the time has come to discuss a new research and review paradigm.

Many believe that the way new medicines have been developed from scientific discovery to the marketplace, in the past, will not work for the new generation of medicines.

From basic to applied science

Dr Lumpkin referred to the annual open discussion forum held between FDA and industry which provides a platform for discussing the wider issues surrounding the science of medicines research and development. At the recent meeting the discussions had focused on basic and applied science and how to move from a new scientific discovery to a tangible, innovative product. Dr Elias Zerhouni, Director of the National Institutes of Health, had referred to the large investment that is made in basic science but pointed out that this can only benefit the community at large if similar resources and effort are invested in the applied sciences. He had been charged by Congress to foster the development of the applied sciences through greater support and funding.

At the same meeting, Joshua Lederberg (Nobel Prize winner 1958) drew the analogy between the elucidation of the structure of DNA, in 1953 and the unravelling of the human genome at the turn of 21st century. Some 35 years elapsed before the first medicinal product was developed that could be directly traced back to the basic scientific knowledge of the DNA double-helix structure. Today we have an enormous investment in the basic science of genomics and proteomics, but we cannot wait another 30 years before realising the practical applications of these scientific discoveries.

In order to advance the applied sciences in the field of new medicines, Dr Lumpkin suggested that regulators and industry will need to work together to first define, and then decide, how to 'get comfortable' with a new paradigm for drug development. Specific issues he identified were:

- Biomarkers and surrogate endpoints;
- Risk-benefit assessment;

- Statistical modelling and other kinds of computer modelling;
- Innovative study trial design.

He referred to the discussions on critical paths for the way forward in the FDA white paper *Innovation or Stagnation: Challenge and opportunity on the critical path to new medical products*¹ and urged companies and fellow regulators to become involved in the debate on the issues raised in this paper.

The FDA critical path discussions do not only address the need for change in the realm of clinical development but also in the manufacturing realm, where there are equally important issues to be addressed.

Role of Regulators

Turning to specific areas where regulators can have a positive impact on innovation, Dr Lumpkin referred to issues that are driving the public policy debates that are currently going on within FDA. The political leadership and senior management are issuing the challenge that, although there are problems that FDA cannot solve alone, it can become part of the solution. Four main areas have been identified where the 'traditional' role of regulators needs to be strengthened in order to promote and support innovation: Confidence building; Market protection; Marketing incentives; and Regulatory oversight.

Assuring confidence

A fundamental role of the regulator is to provide assurance to the broader community that products coming on to the market meet appropriate criteria and standards and are truly innovative. The different parties include:

- *Patients and practitioners who require* assurance of a quality product that has been demonstrated to have a positive benefit-risk profile;
- *The paying community*, whether private or public who are looking for good value for their money;
- *The companies* who require confidence in a fair, level playing field for market entry;
- *The general community* who need assurance that the claims that products are innovative is valid and not simply exploitation.

These assurances have, traditionally, been provided by setting and enforcing science-based standards for pre-clinical and clinical development and manufacturing that are transparent to the industry and public alike. The challenge will be to develop standards for the new generation of 21st century products that will continue to provide these assurances without inhibiting innovation.

Appropriate market protection

An area where government and regulators have a clear and appropriate role in facilitating innovation is by enforcing meaningful and appropriate marketing protection. Given the risks, innovators need to know that successful development will result in a reasonable period in which to recoup a return on investment. Although this is a top priority with companies, Dr Lumpkin pointed out that there are other areas where regulators have a role to play. One is to ensure that the community can have confidence in generic products put on the market, once the patent has expired on the innovator product. A second is the issue of counterfeit medicines. This is a rapidly growing problem that has to be addressed by both the innovative and generic industry, working together with the regulators. Again, Dr Lumpkin stressed, it is important that the larger community realise that the market is one that is protected and one in which they can have confidence.

Creating incentives when the marketplace does not

Dr Lumpkin referred to the responsibility of government and regulatory bodies to recognise that there are times when the marketplace does not create incentives to develop the kinds of product that are required, from a public policy perspective. This has been addressed by

special regulatory procedures to facilitate the development of orphan medicines and regulators have also taken a role in measures to encourage research into paediatric medicines and paediatric dosage of medicines. More recently, the question of how to deal with countermeasures to terrorism has arisen and a Bill on *Bioshields* recently passed by the Senate, which includes a provision for emergency-use authorisation. This will be another tool for looking at ways to expedite procedures for making new products available.

Assurance that regulatory oversight makes sense

One aspect of the regulators' role that is continually under scrutiny by political leadership and senior management is the question of the standards for processes and the need to ensure that they facilitate, and are not impediments to, quality products.

The regulators must establish transparent and science-based procedures for the development of standards in collaboration with others within the international community. Internal processes for regulatory oversight must be predictable and accountable with the capacity to work with manufacturers throughout the lifecycle of the product, again bearing in mind the impact on the community at large from a public health and economic perspective.

Critical Paths in an international context

Taking up themes that had been discussed earlier in the Workshop, Dr Lumpkin referred to areas of *convergence* (Confidentiality agreements Parallel scientific advice and leveraging resources) and *divergence* (Different goals and timing of development programs, Different positioning of products) in the critical paths to improving the research, development and review of innovative products.

He referred to the signing of confidentiality agreements between FDA and its counterparts in the EU, Switzerland, Canada, Australia and, in the near future, Singapore. FDA is particularly keen to set up processes that allow parties to talk in real-time, and talk about real issues, in ways that have not been possible in the past. The confidentiality agreements have enabled the agencies to look at the concept of parallel scientific advice, and this has been started with the EU on an agreed *ad hoc* basis in 2004. Some five such consultations have taken place to date and there will shortly be a meeting to review the experience and determine how to proceed.

One of the major issues has been the logistics. Time difference and videoconferencing do not pose particular difficulties but there is a problem with timing. Historically, FDA has tried to have a very flexible approach to meetings with industry, explained Dr Lumpkin, and in 2003, CDER held approximately 1600 meetings with companies – anywhere between 3 to 4 meetings on any given day. Trying to time the FDA meetings with a company to coincide with the timing that the EMEA can offer has been 'challenging' he said. From a company perspective they need to be able to consult both agencies on a specific issue at a time that makes sense, within their development programme.

Binding advice

Although it is often stated that scientific advice in the US is 'binding', Dr Lumpkin suggested that, in the main, it should only be regarded as advisory. There are, however, three types of advice that are legally binding, unless there are fundamental changes in the science and those relate to the design of carcinogenicity studies, stability testing and pivotal efficacy trials. Even in these areas, however, there is a protocol for dealing with changes in requirements to meet the needs of innovation.

He stressed the importance of questioning advice that does not make sense to the company, and of coming back for iterative discussions to address areas of concern. Some companies have asked for a broader discussion in an Advisory Committee or to take the matter up in closed session. Companies should certainly not hold back from questioning the advice they are given for fear that it would be held against them for future INDs and NDA if they have the temerity to challenge the FDA.

DISCUSSION

Preventative medicine: Referring to the 'critical path' document, a participant noted that it mentions the move towards preventative medicine but does not discuss development issues, in particular the type of database that might be needed and the potentially large numbers of subjects to be included in outcomes studies.

In replying, Dr Lumpkin noted that some vaccines, products for anti-microbial prophylaxis and preventative approaches had been developed successfully within the present context but he agreed that this was an area that brings up a new set of issues. The products are given, predominantly, to healthy individuals to prevent illness in that person or in the community and this requires a different perspective on the risk-benefit calculation. He felt that this was one of the areas where there was an opportunity, under the critical path document, to examine the kind of applied research that is necessary to arrive at methodology for such products.

Economic factors: Concerns were expressed that, particularly in relation to preventive medicines, the grounds for approval were moving from purely technical issues to economic factors. The chairman (Dr Robert Peterson) observed that future debates on this aspect would need to involve more than just the regulators and industry as it was moving into the territory of the payers and would raise issues on the availability of medicines, for example, their listing in formularies.

Dr Lumpkin agreed that this would soon become a very real issue in the US where the government is soon likely to become one of the industry's biggest purchasers, through CMS (Center for Medicare & Medicaid Services), which is now headed by ex-FDA Commissioner, Dr Mark McClellan. The question is to know where the information that is needed by potential purchasers fits into the overall development plan and into the data required for the regulatory submission. Companies will obviously need to know what additional data they are expected to generate during the IND stage and not learn about this after launch.

Liability and media reaction: Dr Lumpkin was asked, by a participant from Japan, about the legal responsibilities in the US in the event of serious harm coming to patients as a result of using medicines that have been approved by FDA. In Japan not only is MHLW heavily criticised in the press if a registered medicine causes serious adverse events but it can result in prosecution. There is also a compensation scheme that arose out of the thalidomide and SMON tragedies and the more recent HIV contamination in blood products.

Dr Lumpkin replied that, historically, the US government does not pay compensation and the system is very different from that in Japan. The exception is a vaccine compensation programme, the reason being that their use is mandated by the government; children have to be vaccinated in order to go to school.

With regard to media reaction there is little difference between the US and Japan, in that FDA is likely to be blamed in the press when something goes wrong. However, one of the challenges over the years has been to try to educate not only the news media but more importantly the patient groups involved with the products. Here there has been some success with the HIV/AIDS advocacy groups, who have accepted that serious but rare adverse events are, statistically, not going to be detected in a normal clinical development programme and that demands for a greater level of assurance will result in unacceptable delays in new products reaching the market.

CONSTRUCTION OF A GLOBAL DOSSIER: WHAT NEEDS TO BE CONSIDERED, AND WHAT ARE SEEN AS THE CRITICAL SUCCESS FACTORS?

Dr Tim Franson

Vice President, Global Regulatory Affairs, Eli Lilly & Company Limited, USA

Dr Tim Franson introduced his presentation by emphasising that a 'global dossier' is a dynamic rather than a static document, and that he would be discussing how it fits into the overall context of international drug development. He noted that having the same data in the same format was only a vehicle for conveying information and that there was no guarantee that regulatory agencies would reach the same conclusion, particularly in relation to the risks and benefits of a medicine, given geographic differences in medical practice and related considerations in utilisation.

His theme would be the role of the global dossier, within a global plan, as a vehicle to present the commonality of data, in particular the safety data. Whilst the global dossier can facilitate near simultaneous submission, the stage has not yet been reached where there are simultaneous timelines for the review and approval processes and differences in medical practice and culture are still significant issues. The dossier is, however, the critical bridge between the development plan for a new medicine and the utilisation of information about it, in practice. The critical success factors for constructing that bridge lay in adopting good practices and avoiding 'deconstruction' through sub-optimal practices. Dr Franson elaborated this concept later in his presentation.

Objectives of the CTD

Although he would not be providing a detailed review of the logistics of how a global dossier is constructed and formatted, Dr Franson referred to the importance of the 'road map' provided by the ICH Common Technical Document (CTD). He cautioned, however, that the format must be seen as a dynamic and not a rigid vehicle in order to accommodate changes in drug development, for example the increasing focus on pharmacodynamics and genomics. The potential benefits of the CTD (derived from ICH publications) are that it should:

- Provide a logical order with a sequential pathway for review;
- Increase efficiency for authorities and industry;
- Minimise review time and resources;
- Facilitate exchange of regulatory information, joint reviews and mutual recognition;
- Make responding to queries and deficiency letters easier;
- Facilitate electronic submissions (e-CTD);
- Provide agreement on defined terms;
- Reduce anticipated obstacles, e.g., increasing aggregated requirements and country specific requirements.

Change drivers in the development of a dossier

Dr Franson provided an overview of some of the critical factors influencing the final dossier on a new medicine as it progresses from the discovery and preclinical stages, through the clinical development Phases to the 'datalock' point and dossier preparation. These included the identification of biomarkers and investigation of pharmacogenomics, in the early clinical phases and the use of comparators for the pivotal studies (placebo or active comparator). A critical factor in the preparation of the dossier is drawing up proposals for a risk management plan. Dr Franson noted that this is a rapidly changing field where the dossier requirements are evolving, and he cited developments in Japan and changes expected in the US as part of the implementation of the third iteration of PDUFA.

Dr Franson pointed out that whilst the point at which the dossier is submitted might be considered definitive but it is, in fact, only a 'snapshot' of one point in time in the evolution of that product and its documentation, as there are usually ongoing clinical studies throughout the product's lifespan. This is particularly true with respect to the accumulation of new safety data. After approval and launch the database on the product continues to evolve and is particularly important in relation to an on-going evaluation of the risk-benefit of the medicine and its place in medical practice.

In some cases, changes in the product database might result in supplementary applications and changes to the product labeling (SPC), during the active life of the product. He noted the tremendous challenge involved in condensing 100,000 pages of a dossier into a one-page package insert that met the needs of the practitioner and patient.

Critical Success Factors

In defining the critical success factors for a dossier, Dr Franson suggested that content should be judged on its completeness (versus conciseness) and clarity, whilst the key factors for the process are consistency and timing.

In looking at the CMC data for drugs there is normally little room for discussion or disparity in the type of data required except, perhaps, in relation to stability, transport and storage of medicines in countries with climatic extremes of temperature and humidity. The most vexing challenges, Dr Franson suggested, are the clinical issues, particularly related to diseases, such as Alzheimer's, that do not have defined endpoints for treatment in one medical culture, let alone in different geographies.

Another aspect to be addressed is that the ultimate utility of the dossier is to provide, through the product information, advice to practitioners on the care of their patients. The dossier is about communicating first with regulators and later with practitioners and the question is whether it meets the expectations of all of the recipients concurrently, or if differing studies are required to meet such divergent needs, over time. There are pitfalls in preparing a dossier that meets these expectations, Dr Franson suggested, and he advocated 'minding the gaps'.

GAPs

The 'GAPs' that Dr Franson described were not to be confused with the 'Japan Gap' discussed in earlier presentations. These were acronyms for Good practices in the preparation and review of the global dossier:

- **Good Analysis Practices** – the sponsor's responsibility in making the transition from raw data to the evaluated information presented in the dossier;
- **Good Assessment Practices** – the regulator's responsibility in the transition from 'information' about a product to 'knowledge' that enables a decision to be made;
- **Good Approval/Acceptance Practices** that allow the transition to be made from the data in the dossier to the communication that will facilitate the product's use by practitioners.

In discussing this concept, Dr Franson emphasised that 'Good' means exactly what it says – neither 'perfect' nor 'bad'. Seeking perfection, he suggested, can be the 'enemy of the good' as it consumes an inordinate amount of time. 'Practices' is also an important word as it conveys a situation that is evolving.

Conversely, he suggested that there were 'suboptimal' practices (SAPs) leading to the 'deconstruction' of the objectives of the dossier:

Suboptimal Analysis Practices: failure to assess critical covariances;

Suboptimal Assessment Practices: drift in endpoint agreements;

Suboptimal Approval Practices: the same dossier leading to different outcomes and regionally divergent labels

Overview of the CTD

Dr Franson presented an overview of the five Modules of the ICH CTD and highlighted certain aspects of each:

Module 1 enables administrative and procedural information to be provided on a regional basis and is described as not being part of the CTD. There is provision, for example, to include the special certification (e.g., financial disclosure) required in the US and to document the patent situation. Labeling (SPC) is included in this Module as it may differ between countries and regions. One of the greatest challenges, suggested Dr Franson, is to find labeling that is comparable, internationally, but is also compatible with different medical practices.

Module 2 provides summaries and overviews of the quality data, nonclinical investigations and clinical work. The content of the clinical summary, in particular, is critical as it forms the basis of the product label.

Module 3 gives the supporting evidence for the quality statements in the summary and includes elements that ultimately translate into label statements, for example on storage and handling.

Module 4 includes detailed reports of the pre-clinical investigations and other nonclinical work. Dr Franson singled out, in particular, the way in which evolving information on QT prolongation has been handled in the data presented in this section and suggested that there had been a lost opportunity to seek common standards at an early stage.

Module 5 is the repository for the individual clinical study reports where the main issues is the level of detail that is desirable to provide the required transparency and clarity as the data is translated into the summaries and, ultimately, the label.

Whilst acknowledging the benefits of the CTD as a harmonised format, Dr Franson suggested that there was also some drawbacks. The particular weaknesses he highlighted were that it is not a good vehicle for discussing benefit-risk arguments and that the structure did not provide enough flexibility to accommodate divergences between different therapeutic classes. It is also difficult to do justice to a discussion of the development programme within the format of the CTD.

The dossier as a contract

Dr Franson suggested that the global dossier and its development should be viewed as a 'contractual' arrangement between the company and the regulators in which there should be pre-submission agreements, communication during submission and review and a time for examining the 'lessons learned' in the post-action stage. At the heart of this contract is the target labeling for the product which should be defined at an early stage in development and discussed with the regulators during the consultation stages as the link from the development plan to the communication with practitioners. The different types of 'contract' needed for drug development to accommodate the different balances of benefit-risk expected in life-saving drugs, life-altering medicines and so-called 'lifestyle' drugs and the global dossier should be sufficiently flexible to accommodate such differences.

The ways forward to achieving a better sense of partnership between industry and regulators include establishing patient-focused outcomes (utility and clarity) and establishing common approaches to key issues such as risk management programmes, surrogate markers and endpoint agreements. One of the most important elements, however, was the development of more dynamic global safety dossier to form the basis for appropriate discussions and shared learning, over time.

DISCUSSION

Concept of a 'contract' with regulators: The Chairman, Dr Jefferys asked Dr Franson to comment further on the scope for more interaction with regulators during development, as a step towards global assessment. He responded by noting the positive experience with FDA in developing agreements during the development stage, and stressed the importance of adhering to such agreements with vigour. As an example of the 'drift' in expectations that can occur, he cited the industry practice of submitting additional clinical reports, not specifically related to the main indications in the rather vague hope 'that something might happen' to yield additional label claims. He felt that such practices lacked the integrity that is required in interactions with regulators. The 'contract' with regulators should create an understanding or framework for understanding that should be applied with an appropriate standard of rigour, bi-directionally.

Dr Jefferys added that this reflects points made earlier in the meeting about shared involvement and greater partnership with regulators in order to identify the issues at an early stage in the dialogue.

SAME DOSSIER, SAME DATA: BUT THREE REVIEWS IN THREE REGIONS: IS THIS A VALUABLE EXERCISE OR WASTED RESOURCE?

Dr George Butler

*Vice President and Head, Worldwide Regulatory Affairs,
AstraZeneca Pharmaceuticals, USA*

Having been asked to speak about the review of the same data in the same dossier in the different regions, Dr George Butler started with some assumptions as the framework for his deliberations. First, he assumed that regulatory systems in question would be in the US, Canada, EU (centralised procedure) Japan and Australia, and that the application had been made within the same week, in paper and electronic format. The product would be in the same formulation from the same manufacturing site and all countries would have participated in the clinical programme. Furthermore, there would have been dialogue with regulators throughout the development process and this, in the scenario developed later by Dr Butler, would not only be a dialogue about development plans but would include a continual data review. Dr Butler also added the assumption that the prescribing information, sought in the application, would be the same in all countries.

Based on AstraZeneca practices, the structure for delivering the global dossier is essentially a company product team with core members from the regulatory affairs clinical and commercial areas. There are also members, from the same three disciplines, located in the individual countries, who act as the interface with the authorities. The dialogue that occurs during development will include not only the core members of the global team but also the local contacts and in that way the team receives feed-back from its customers at local level.

Companies' strategies

The strategy for a product is something that is created years in advance, and is not 'instantaneous', Dr Butler noted, nor can it be easily changed, although it can be affected by significant technical, political or economic changes in the external environment. An example he cited was the recent decision to allow statins to be sold without prescription, in the UK.

Another item in the strategy is the position on labeling (SPC). In Dr Butler's view, there is currently an industry tendency to start out with an extremely ambitious label, particularly in the indications section, that is not necessarily supported or validated by the clinical

development plan. Realism needs to be introduced to avoid a situation where the label attempts to be 'all things to all people'.

Dr Butler took the position that the full prescribing information for a product should be written at 'Phase 0' as if the product was to be marketed the next day. Assumptions can be made and a position taken on safety, based on animal data and knowledge of the therapeutic area. Each line of the text can then be tested in the design of the clinical programme and the results thereof.

Questions from regulators

The stage when questions start to come in from regulators is one of the most stressful for the product development teams and can lead those involved to question the merits of parallel submission of dossiers! In theory, questions should be answered pragmatically, as they are received. In practice deficiency letters may be coming in from all quarters and, as Dr Butler commented, 'It is a question of which aeroplane you get on'.

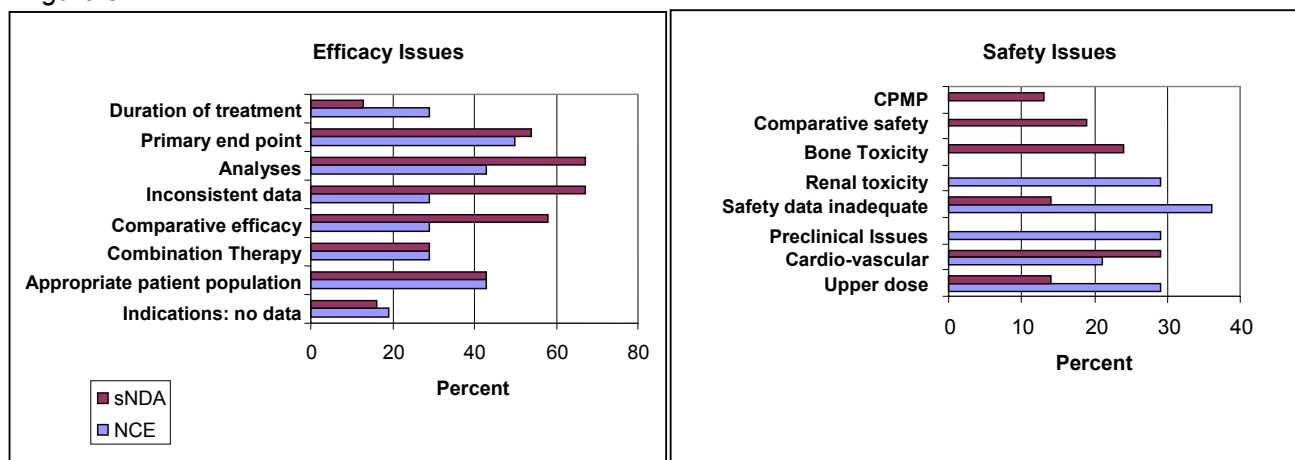
There is also the frustration, for example with some FDA divisions, of having to wait through an eight-month silence before receiving a letter itemising the reasons why the product is not approvable, when many issues could be resolved by the assessor having picked up the phone and clarified the matter on a one-to-one basis with his or her counterpart in the company. Dr Butler regretted the trend towards only talking to committees and questioned whether we are being supported by, or hiding behind, team decisions.

Analysis of deficiency letters

Dr Butler described an exercise that had been undertaken by his company to look at the deficiency letters they received, as an indicator of the quality of the dossier. This involved looking at the last five new active substances that were submitted in 16 dossiers to the US, Canada, EU Japan and Australia, although dossiers for individual substances were not all submitted simultaneously to the agencies. The questions from authorities were analysed to look at trends from a company, and from an authority, perspective.

Dr Butler outlined the results from questions received in relation to three areas; pharmacokinetic/pharmacodynamic (PK/PD) issues, efficacy issues and safety issues (see Figure 5). The approach to listing a topic from a question was inclusive, however minor the question. Information was also presented on the sources of the questions which indicated, in the countries covered, that the majority of questions arose from the CPMP, with the FDA being the second most frequent.

Figure 5



The potential weaknesses in data that were signalled by the trends and analyses are being validated and investigated further within the company. Examples include: drug interactions; PK in special populations; inconsistencies in, and analyses of, the clinical data. Dr Butler noted that many of the questions on the clinical data that related to analyses and primary endpoints came from FDA who carry out their own analyses of the data.

Commenting on the nature of the questions, Dr Butler noted that the points raised by the different authorities are often very similar although they may have a different 'flavour' or emphasis. The result, however, is that experts from the global project teams spend their time travelling from one country to another to provide the answers and ensure they are put into context. This represents an enormous consumption of time and effort which, from a company perspective, is a poor use of critical resources. The company experts have also found that the learning curve for health authorities can be quite high which can be a problem when the company is under a time pressure. The company's scientists also have to learn, however, that questions from regulators may be influenced by considerations outside the purely scientific realm as politics and other factors in the external environment can affect their decisions.

New regulatory scenarios

Having discussed some of the issues associated with the current review of a global dossier at the end of the development process, Dr Butler put forward the proposition that this 'terminal' regulatory review process is not the right way to continue and does not benefit the early availability of new therapies to patients. He believed that the dossier should be a dynamic document that is subject to a rolling review process. Furthermore, the major part of that review could take place at the end of Phase II thus enabling the review at the end of Phase III to be a much smaller exercise with agreement being achieved much more rapidly. He also suggested that companies are willing for different authorities to discuss their applications in joint meetings, as companies are looking for a single development programme and one interpretation of the data. At present, the assessment may start with a single set of safety data, but the end result can be that the product is put on the market with different safety information in different countries. Dr Butler wondered why there could not be a single safety database that is shared between the company and the authorities. This would provide a much larger database from which to read the signals and the opportunity to have shared opinions across multiple health authorities. The main concern about consultations between authorities is to ensure that there is no 'political' agenda or undue influence of economic factors and that the company does not end up with the lowest common denominator of indications (and the highest common multiple of warning notices).

Dr Butler also expressed concerns that the World appears to be moving more and more towards risk avoidance rather than risk management.

Resources

Finally, Dr Butler looked at the question of resources and expressed the view that companies and health authorities have very few experienced reviewers with the appropriate competencies. He recognised that it is hard to recruit experts into regulatory agencies and that the agencies complain that this is exacerbated by the higher rates of pay in industry. With the current figures indicating that only 20-25 new active substances per year are being submitted for marketing approval, however, Dr Butler felt that there should not be a problem to assign sufficiently experienced individuals to ensure that the review is carried out in a timely fashion.

What is happening in companies is that the best people are being taken from anywhere in the company and are being put on the most important brands and biggest potential new products. At present, this is, perhaps, not being undertaken at a sufficiently early stage in development, when new surrogate markers and new endpoints are being investigated. There is a strong case, he suggested, for putting those who have the most experience on a compound at the beginning and not at the end of its life.

Similarly, he questioned whether health authorities are actually putting their best experienced people on these 20 to 25 new chemical entities or whether they are constrained by inflexible organisational structures.

In conclusion, Dr Butler suggested that both industry and health authorities should drive forward initiatives for joint, rather than duplicate reviews, particularly in respect of human safety data, in order to maximise the best usage of experienced resources.

DISCUSSION

Answering regulators' questions: Robert Peterson, Health Canada, expressed concern that, when trying to resolve a local issue by asking a question about a company's global database for a product, there could be a considerable delay before receiving a response. He asked whether this indicated that the global database did not exist until asked for, or whether this might reflect corporate strategy. Dr Butler suggested that there may be several reasons, one of which reflected the 'dominance' of the US position. Having filed parallel submissions, companies may wish to await the FDA questions before answering those of the smaller agencies, as a strategy to ensure that the final label did not differ significantly from country to country.

Another explanation could be that the particular question required a substantial, new statistical analysis of the database and the delay might simply reflect a lack of available expertise to carry out the work quickly, with a result that the question has to wait its turn in a queue.

Speaking for his own company, Dr Butler said that they tried to answer questions within 30 days but this was becoming increasingly stressful as the number of countries to which parallel submissions are made is increasing. He re-iterated his call for the review to start earlier in the development process in order that many of the questions could be answered at an earlier stage.

Delay in receiving questions: Dr Mac Lumpkin, FDA, referred to comments about the delay before questions were raised on a dossier and suggested that, under the FDA system, the routine time for a discussion of the data was during development and that, once the application was filed, the review must proceed uninterrupted. There was a danger, he suggested, that mixing the two could lead to a return to the 'pre-PDUFA' days when there were no clear timelines for the review. If major deficiencies are pointed out during the review that result in major new data sets being submitted it would be difficult to maintain accountability and the 'review clock' that had led to the much improved review under PDUFA. Dr Butler agreed that the addition of substantial new data during the review would be untenable but he, nonetheless, felt that there were many occasions where minor matters and points of clarification could be resolved by a simple telephone conversation between the reviewer and company expert. Dr. Lumpkin agreed with this assessment of minor matters that could be cleared up with a telephone call with the Agency.

End-of-Phase II assessment and rolling reviews: A participant commented that the idea of an end-of-Phase II assessment followed by rolling review was attractive as a modular approach could conserve resources. The challenge, however, would be the current Phase III attrition rate of some 50%, which would be a significant deterrent to regulators who might see the early review as a potential waste of time and effort. Dr Butler responded that the primary responsibility lay with the company for determining, once the pivotal Phase II studies against placebo or active comparator were complete, whether the expected 'p-values' had been achieved. He also added that the problem of incentives for early review could be overcome by companies paying a fee for the service.

A related question asked if there had been studies to determine how many of the questions raised at the NDA stage could have been answered at the end of Phase II. If the proportion was significant, it would support the arguments for an end-of-Phase II review. Dr Butler

replied that he was unaware of such a study but it was a subject that CMR International might wish to take up.

Consequences for Phase III: The Chairman, Dr Jefferys, asked for clarification of whether the end-of-Phase II review could be definitive, and how this would impact on Phase III development. Dr Butler responded that Phase III could be conducted as at present, with a much simpler final review. He envisaged, however, that this could be taken a step further with studies being conducted in a much larger patient population, by having studies carried out in a 'real world' situation involving not only companies and regulators, but also the purchasers of medicines. The trials would not necessarily be more complex but the database generated, especially with respect to safety would be much more robust.

Resources: Dr Lumpkin, FDA, commented on Dr Butler's concerns about the resources assigned by regulatory agencies to the review of new (i.e., NCE) drugs. He suggested that the perception of companies that NCEs are the main issue is somewhat different from the regulatory viewpoint. At FDA, only about a quarter to a third of NCEs qualify for priority review on the grounds that they add value from a public health perspective. Many are 'me-too follow-on' products and assigning additional resources to these is hard to justify from a health perspective, although he recognised that corporate priorities were different.

Joint reviews and decisions: Referring to the prospects for joint decision-making by regulatory agencies, the Chairman, Dr Jefferys, suggested that there was hope to be gained from the situation in the EU. Fifteen years ago it would have been impossible to believe that the, then, 12 members of the EU could work together on parallel submissions and arrive at consensus but we are now looking at the prospect of the centralised procedure applying in the 25 countries of the expanded Union. Dr Butler agreed, and added that he believed that the system, particularly in relation to Scientific Advice, would benefit from the establishment of therapeutic assessment groups. He hoped that the confidentiality agreement between FDA and the EU would, similarly, lead to coordinated consultations during development but he believed that such a system would work better if the formality could be minimised and two or three experts could discuss the issues. In the EU, it would be necessary for changes to be made that would allow EMEA to assign individuals to new compounds at an early stage in their development rather than assigning Rapporteurs at the dossier stage.

Dr Lumpkin, FDA, questioned whether companies were really seeking one dossier and one assessment and whether it was realistic with the differences in laws and attitudes to benefit and risk in different parts of the World. To expect a unified decision-making might not, he suggested, be realistic or in the best interest of public health. Dr Butler replied that, whilst a single regulatory decision might be a 'dream scenario', progress was being made in achieving unified labeling throughout the World, as transparency increases and products move across national boundaries.

Risk Management: The Chairman, Dr Jefferys, noted that differences in risk management had been cited as one of the hurdles in global development and review, and suggested that this was frequently related to differences in healthcare delivery systems. Dr Butler agreed, and suggested that, in view of the stress being placed on developing a single, integrated clinical development programme, perhaps it was time to focus on developing a single risk management plan for the three ICH regions.

A further comment from the audience suggested that this would be facilitated by the suggestions about a single global safety database. What was also needed, however, was international agreement on the related topic of benefit-risk assessment.

GLOBAL COOPERATION IN DRUG DEVELOPMENT: A EUROPEAN VIEWPOINT

Mr Thomas Lönngren

Executive Director, European Medicines Agency, (EMA).

In addressing the European perspective on global drug development, Mr Thomas Lönngren explained that he would first be talking about regional cooperation within the European Union before discussing the priority being given by the EU to global cooperation. He regretted not being able to be present at the Workshop, in person, to discuss these important issues.

The changing environment in the EU

Mr Lönngren referred to two events that are currently bringing about some dramatic changes in the regulatory environment in Europe; the enlargement of the EU from 15 to 25 Member States (MS) and the implementation of new and revised pharmaceutical legislation.

The accession of ten new Member States on 1 May 2004 means that there are now 43 national competent authorities working together in the regulatory network. Although this is a dramatic change for Europe, he said, the EMA has, for several years, been making preparations in order to bring in the new regulatory authorities in the regulatory system of the European Union. A very successful training programme has been in operation to inform new members how the European system operates and, although time will be needed to see how the accession countries settle in, Mr Lönngren expressed his confidence that the integration would go well.

The new pharmaceutical legislation for the EU was published on 30 April 2004 and will enter into force in two stages. Some parts will enter into force immediately, in particular, those dealing with the composition of scientific committees, bringing down the number of members from two per MS to one, and altering the composition of the EMA Management Board.

The legislation also includes several new tools that will be important in order to improve the regulatory system, some of which, Mr Lönngren suggested, have implications from a global point of view. The first is that the centralised procedure will become mandatory for four therapeutic areas, which will mean that many more new chemical entities will go through the centralised procedure in the future. There are also new tools in the legislation for issuing conditional Marketing Authorisations, for a fast track procedure and for compassionate use. It also includes specific provision for EMA to support small and medium-sized companies and for strengthening the way of dealing with scientific advice to pharmaceutical companies. In addition, there will be changes in the system for pharmacovigilance and post-marketing controls in the European Union. The way in which these tools are implemented will be a major issue for EU regulators for the coming year and a half. (The implementation date is 20 November 2005).

'Road map' for Europe

Mr Lönngren referred to the discussion paper published in March 2004 *The European Medicines Agency Road Map to 2010: Preparing the Ground for the Future*². This is intended for consultation both within and outside the European Union and comments from regulatory colleagues in all parts of the World would be welcomed. It is intended that this document should be discussed during 2004 in order to formulate, at the end of the year, the work plan and goals for 2005 and 2006 for the European regulatory system. In the coming 18 months, of course, the focus for the European Union will be concentrated on the enlargement of the Union and the new tools in the legislation but the need to look beyond the regional dimension to the global dimension will not be overlooked. The need for global development and cooperation in the pharmaceutical area is recognised in the changing regulatory environment.

The global dimension

Pharmaceuticals are no longer developed for individual countries, or on a regional basis, Mr Lönngren said, but they are increasingly being developed for the World and regulatory requirements must also be applicable to global drug development. This is even more important when considering the new medicines that will be developed in future based on new technologies and the mapping of the human genome. New therapies will be developed based on pharmacogenetics and pharmacogenomics and utilising gene therapy. The legislative requirements to regulate such new therapies cannot, he suggested, only be decided on a country or regional level, there needs to be a global approach.

Mr Lönngren referred to the problem of the apparent decline in the productivity of industry research, in terms of the number of new chemical entities (NCEs) being submitted to the regulatory agencies. There has been some recovery in 2003 and 2004, from the low point in 2002, but output is obviously at a very low level compared with data on the numbers of new medicines coming to the market in the past. This is an issue, he suggested, that is also of concern to the regulators who must ask themselves whether they have anything to do with this decline in NCEs and what action could be taken in order to facilitate drug development and allow faster access to the market of new medicines.

Platforms for global cooperation

Global cooperation is taking place through the international forum of ICH and through bilateral agreements such as the confidentiality agreement between FDA and EMEA. Mr Lönngren expressed the hope that, in the future, there would be a network of these bilateral agreements that would strengthen global cooperation among regulators. He noted, however, that there are other ways to stimulate cooperation without the need for legally binding agreements and contracts. One example is in the area of training, and the exchange of staff between the regulatory authorities is another way of increasing understanding.

Mr Lönngren suggested that some kind of platform should be established to share training between agencies. In the European Union, when training sessions and exercises are arranged, all 43 agencies are invited to participate. He saw no reason why this should not be extended to other regulatory authorities in the world in order to have a better understanding between assessors and around different scientific issues and methodology.

Another important area in which global cooperation could be stimulated is in benchmarking exercises. Within the EU there is an ongoing project, based on ISO 9000, to benchmark management systems and procedures for assessment, pharmacovigilance and inspection. Perhaps, once this has been fully established and 'stabilised', at the European level it might be appropriate to invite other parties in the world to participate in such a benchmarking exercise.

Mr Lönngren had little doubt that the Workshop would be discussing shared assessments and shared decision-making as a further step in collaboration between agencies. In his view, however, such global cooperation will be several years in the future and will require decisions at a political level that do not exist, at present. For the immediate future, increased global cooperation will, no doubt, be seen but will focus on sharing experience, within the current framework.

EMA's Priorities

Given the expected preoccupation with regional matters, over the next 18 months, the EMA has had to prioritise its actions, Mr Lönngren said, and global cooperation will mainly be concentrated in five areas:

ICH: The EMA and European Union will continue to give support to the ICH harmonisation initiatives and will be taking a position in forthcoming discussions on the future of ICH.

World Health Organization: The EMA will work more closely together with the WHO by giving additional assistance to pharmaceutical companies who want to develop products for

developing countries. EMEA has an obligation to cooperate with WHO in the evaluation of medicines that are intended entirely for use in the developing world.

Mutual Recognition Agreements (MRAs): EMEA will continue to encourage and regulate mutual recognition agreements between authorities, and Mr Lönngren was happy to announce that the MRA between the EU and Japan would come into force at the end of May 2004.

Confidentiality arrangements: The arrangement between FDA and the EMEA that was signed in 2003 will be developed further and work is currently underway to further define areas of cooperation and practical details of this collaboration.

Relations with other agencies: EMEA will give priority to maintaining the good relations established with other regulatory agencies, for example those of Japan, Canada and Australia. Programmes for visiting experts have been very successful and also for the informal sharing of information.

The new Japanese agency

In closing, Mr Lönngren congratulated the Japanese authorities on the establishment of the Pharmaceuticals and Medical Devices Agency and said the EMEA was looking forward to working with the PMDA in the future.

SYNDICATE SESSIONS ON GLOBAL DRUG DEVELOPMENT

Chairman's Introduction

Dr Hatsuo Aoki

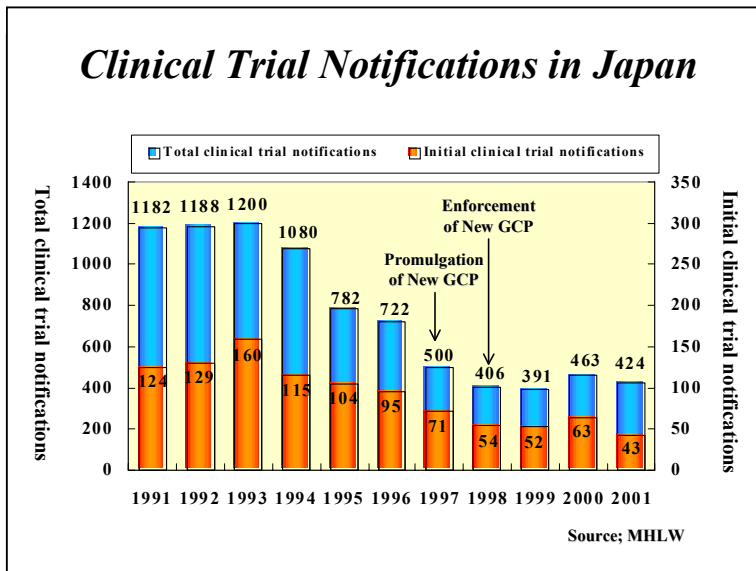
President and CEO, Fujisawa Pharmaceutical Co., Ltd, Japan

Dr Hatsuo Aoki introduced the Syndicate discussions with a brief review of some of the issues facing the Japanese industry, from his perspective as President and CEO of Fujisawa, and President of JPMA. The industry in Japan, he said, is facing many opportunities including those brought about by progress in the biomedical sciences, the ageing society and the focus on lifestyle medicines and quality of life. Most importantly were the opportunities presented by the global market and by harmonisation of scientific and regulatory requirements. On the other hand, R&D expenditure that has escalated over the three last decades is now increasing at an even greater pace in the 21st century.

One of the consequences is that multinational, multicentre clinical studies have become inevitable and parallel clinical development on a global basis, with a single worldwide protocol, is now the common process for most pharmaceutical companies. Although ICH has made substantial progress in addressing the technical hurdles to global drug development there are major issues remaining. Viewed individually, the differences among countries in medical infrastructure, medical practice and medical culture may be relatively 'trivial', Dr Aoki suggested, but these small differences cumulate to present major hurdles in the design of multinational trials. Issues include measures for diagnosis of disease, treatment procedures and methods for patient recruitment. The motivation for participating in clinical trials is also quite different, he noted, between the US, Europe and Japan.

One of the major issues for Japanese companies is the extent to which the number of clinical trials carried out in Japan has decreased over the last decade (see Figure 6). The speed of clinical studies is much slower in Japan and the clinical costs per patient are much higher which add to the hurdles when integrating Japan into clinical globalisation.

Figure 4



As a result, many Japanese countries are starting their clinical development outside Japan. This has become necessary in order to respond to the requirements of the different regulatory agencies and also in order to position the product in the global market. Global development has been facilitated by implementation of the ICH guidelines and Dr Aoki referred, in particular, to the ICH E5 guideline on acceptance of foreign clinical data and the unified format for the NDA dossier brought about by the ICH Common Technical document (CTD). There remain, however, many significant hurdles to be overcome.

Conclusions

Dr Aoki concluded by stressing the need to consider the regulatory, academic and economic factors that will create a more favourable environment for global drug development in future.

Multinational, multicentre studies will reduce the time and cost of global drug development but this kind of study is heavily dependent on the future of ICH and also on a common understanding and progress being established throughout the world. He hoped that the Syndicate discussions would provide ideas to take forward the discussion of ways to facilitate and improve the drug development process, with the ultimate goal of benefiting human health around the world.

References

1. Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products, published by the US Department of Health and Human Services and the FDA, March 2004, available from the FDA website: www.fda.gov/oc/initiatives/criticalpath/whitepaper.html
2. Discussion paper on 'The European Medicines Agency Road Map to 2010: Preparing the Ground for the Future', published by the EMEA, March 2004, available from the EMEA website: <http://www.emea.eu.int/pdfs/general/direct/directory/3416303en.pdf>