

# A New Paradigm for Clinical Research

Report of the Workshop organised by the  
**CMR International Institute for Regulatory Science**

at the

**Mandarin Oriental Hotel, Washington D.C.**

**2-3 October 2005**

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**Institute for Regulatory Science**



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## A NEW PARADIGM FOR CLINICAL RESEARCH

### CMR INTERNATIONAL INSTITUTE WORKSHOP

3-4 October 2005

### WORKSHOP REPORT

Margaret Cone and Neil McAuslane

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## OVERVIEW

*The definition of insanity is doing the same thing over and over again and expecting the different result*

*Albert Einstein<sup>1</sup>*

### The current paradox

- The pharmaceutical industry's investment in R&D is rising inexorably but success rates are falling, judged by the number of new molecular entities reaching the market in recent years.
- New medicines discovered using 'new century' science are being developed under a clinical trial paradigm from the middle of the last century<sup>a</sup>.
- New technologies hold a promise of novel and innovative therapies to address unmet medical needs but the current research, regulatory and commercial environment could make them too expensive for health care providers to deliver.

### The future paradigm

Against this background, participants at the CMR International Institute Workshop on 'A New Paradigm for Clinical Research' were unanimous in agreeing that change is essential and urgent. There was, however, less unanimity on the question of whether such change should represent an 'evolution' of the current paradigm to accommodate scientific advances, or whether a more radical 'revolutionary' approach is required.

There were far-ranging discussions on ways to improve the efficiency of clinical trials and on possible new business models designed to bring new medicines to the market more rapidly and cost-effectively.

### Farewell to the four 'Phases'?

There was general agreement that the classic clinical development paradigm defined in terms of 'Phases I to IV' had served well but needs to be replaced with a more flexible model that takes advantage of new techniques, including disease modelling, adaptive clinical trial designs, biomarkers and Bayesian-style statistical approaches.

A simplified model was discussed that divides clinical development into two basic stages: 'learn' (from discovery to 'proof of concept') and 'confirm' (from PoC to marketing submission).

### Early marketing for a wider range of products?

There was renewed discussion of adapting the model to allow early release for marketing for products that are innovative and therapeutically significant, but do not meet the strict criteria that currently allow, for example, oncology and HIV drugs to be released after Phase II, under special conditions, in the EU, US and Japan.

The model envisages that the early clinical development (the 'learn' stage) would provide more information, especially on safety, that the current Phase II and that the 'confirm' stage, would be based on data and feedback from treatment of 'real world' patient populations that meet the conditions of the authorisation.

### Where the costs lie

There were arguments that priority for reducing research costs lies in early identification and attrition of unsuccessful products rather than reducing the cost of late-stage clinical programmes for products that are destined to succeed. The optimal solution, however, would be to address saving at both ends of the development spectrum.

In order to take the discussions forward, it was recommended that studies should be carried out:

- To investigate retrospective data on failed compounds to assess whether novel trial methodology (adaptive designs, new statistical approaches), etc might have resulted in earlier attrition and cost-saving
- To identify recently marketed products that might have been eligible for early release, allowing patients to benefit from faster availability of new therapies;
- To develop a model to test the commercial viability of early release with monitored follow-up for products that do not meet current requirements for accelerated review and conditional approval.

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<sup>1</sup> Quoted at the Workshop by Dr Peter Corr, Chairman of Sessions 1 and 2

## Other recommendations from the Workshop

A wide-ranging discussion in the Syndicate Session of the Workshop gave rise to many further recommendations for the next steps that are needed to bring about change. These included:

**Biomarkers and surrogate endpoints:** Public-private partnerships (PPPs) could be involved in pre-competitive validation of markers where this meets public health needs;

**Scientific Advice:** Initiatives to improve inter-agency cooperation on scientific advice should be stepped up and extended;

**Patient involvement:** Mechanisms are needed to ensure that patients' views and needs are taken into consideration at an early stage when designing a clinical programme.

**Education and awareness:** Any moves to change the current paradigm will require a major campaign to reassure the public and political bodies and, in particular, health care providers, that safety standards will not be compromised.

Evidence will be needed to support arguments that the changes will result in more effective, efficient and economic product development with new medicines being made available to patients more rapidly.

## A snapshot from the presentations

An exceptional team of speakers looked at many different aspects of the 'New Paradigm' debate:

- Future visions for the role of the agencies in supporting and encouraging innovative research were provided by Dr Janet Woodcock, FDA, Dr Osamu Doi, PMDA, Japan and Dr Outi Maki-Ikola from the EMEA.

- The economics of clinical research and the importance of early attrition of unpromising products were discussed by D Peter Corr, Pfizer and Dr Eiry Roberts, Eli Lilly.

- The development and validation of new technologies, biomarkers and computer modelling were featured in presentations by Thomas Metcalfe, F Hoffmann-La Roche, Professor Gunnar Alván, MPA, Sweden, and Dr Mikhail Gishizky, Entelos inc.

- Dr Robert R. Ruffolo Jr, Wyeth Research discussed revolutionary developments within his company to 're-engineer' research procedures and Dr James Shannon, Novartis Pharma AG discussed a research model to allow earlier access to therapeutically important new medicines.

- Ways to ensure that clinical trial design 'evolves' by retaining the best of the old whilst embracing new ideas were examined by Professor Sir Michael Rawlins, National Institute for Clinical Excellence, UK and Dr Robert Temple, FDA

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<sup>a</sup>"In many cases, developers have no choice but to use the tools and concepts of the last century to assess this century's candidates. As a result, the vast majority of investigational products that enter clinical trials fail". Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products, US DHHS and FDA, March 2004, [www.fda.gov](http://www.fda.gov)

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## CMR INTERNATIONAL INSTITUTE FOR REGULATORY SCIENCE

The CMR International Institute for Regulatory Science has been established 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.

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## Workshop Organisation

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

**A NEW PARADIGM FOR CLINICAL RESEARCH**  
**CMR International Institute Workshop, 3-4 October 2005**  
**Workshop Report**

**SUMMARY AND OUTCOME**

**INTRODUCTION**

Regulatory experts from government agencies, pharmaceutical companies and academia contributed to the discussions at this Workshop that set out to:

- Explore the assertion that the clinical development and regulation of new medicines, as practiced today, is not sustainable;
- Discuss alternative scenarios that build on and develop current thinking and technologies as well as radical alternative approaches;
- Identify key initiatives that could form the next steps in bringing about change

The presentations and speakers are listed in the Annex.

**The need for change**

With the cost of developing new medicines moving relentlessly upward many healthcare providers, both governments and private parties, will soon be unable to afford the novel therapeutic agents that new research technologies have the potential to deliver.

There was general consensus, at the Workshop, that the current trend for larger, longer, and more costly development programmes is not sustainable but there was recognition that the problems could not all be attributed to an increased burden of regulatory requirements. A major factor in the much-quoted investment of \$881 million for each new medicinal product that reaches the market is the cost of the products that fail during development. These can account for as much as \$665 million<sup>2</sup> of the total R&D expenditure.

Metrics on new drug development show higher late-stage attrition rates and fewer products reaching the stage of regulatory submission although the development pipeline remains relatively full. This underlines the need to improve predictive capabilities by using new technological tools to identify the 'winners' sooner, and eliminate, at a much earlier stage in the development process, products that are destined to fail.

In seeking a 'new paradigm', the speakers explored:

- The new technologies being developed for biomedical research and their role in translating potential targets into innovative medicines as well as improving predictions of safety and efficacy;
- Innovative approaches to clinical trial design that create richer data sets and accelerate clinical development.

They also initiated the discussions, which were continued in the Syndicate sessions, on adapting the regulatory model to allow a departure from the established model of 'Phase I, II and III' clinical development and to accommodate a more flexible approach to the design of clinical testing programmes.

**SCOPE OF THE WORKSHOP**

The following provides a selection of the many topics that were discussed by the Workshop speakers (see *Annex*) and which formed a backdrop to the Syndicate discussions in Session 3:

***Translational medicine***

Bridging the gap between pre-clinical and clinical studies and also feeding back from clinical experience to the 'laboratory bench'.

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<sup>2</sup> Presentation by Dr Peter Corr

- Providing better molecular understanding of drug metabolism and toxicology enables better extrapolation to man
- Improving understanding of targets, signalling pathways, metabolism and mechanisms of toxicity and action allows better interpretation of biomarker data
- Facilitating more cost-effective determination of efficacy and safety through identification of appropriate biomarkers

#### **Development and validation of biomarkers**

- Role in translating potential new targets into innovative medicines
- Use to assess medical utility, predict safety, and identify responders
- Value in developing more predictive preclinical safety assays—both *in vitro* and using animal biomarkers
- Role of genetics, genomics, proteomics and imaging techniques in developing new markers
- Use of ‘response’ markers to enable smaller/shorter trials that are enriched for potential responders

**Biomarker** is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological response.

**Clinical endpoint** is a characteristic that reflects how a patient feels, functions or survives

**Surrogate endpoint** is a biomarker intended to substitute for a clinical endpoint. Predicts clinical benefit on e.g. epidemiological, therapeutic, pathophysiological or other scientific evidence.

*EMA Biomarkers Definitions Working Group 2001*

#### **Modelling and simulation**

- Development of rigorous disease and drug-effect computer models prior to the initiation of clinical trials
- Mechanistic bio-simulation - ‘in silico’ research platforms that mathematically represent human physiology and allow hypotheses to be tested in ‘virtual patients’

#### **Adaptive clinical trial design**

The use of adaptive clinical trial designs and Bayesian approaches can create richer data sets and accelerate clinical development.

- Adaptive trials use information collected during a trial to perform mid-trial design modifications
- Changes are pre-specified in the protocol
- Possible adaptations include:
  - Sample size, and sample size allocation to treatments
  - Treatment arms (delete, add, change)
  - Population (e.g., inclusion/exclusion criteria, subgroups)
  - Hypotheses (non-inferiority vs superiority)

#### **Clinical trial enrichment**

Use of enrichment (through biomarkers or other methods) to identify subpopulations of patients who are most likely to be responders, so that modest effects can be seen faster

#### **Biostatistics, bioinformatics, electronic data capture**

- Enhancing the ability to collect, store and interpret more data
- Adoption of Bayesian statistical models which incorporate prior knowledge and accumulated experience of probability density into determinations:
  - Optimising the value of the Bayesian approach for interventional studies (allowing multiple examinations of the data) and for high impact trials.

### **Electronic Health Records**

- Use of linked EHR databases for better post-approval safety reporting and management
- Allowing the evaluation of safety in a 'real-world' population

### **Public-Private Partnerships (PPPs)**

PPPs were identified, particularly, as having a role in pre-competitive collaborative research:

- Qualifying biomarkers and developing standards
- Standardising clinical trial infrastructure
- Developing standard disease models, outcome measures and trial designs

### **Putting the patient at the centre**

This is pivotal to the Strategic Research Agenda of the EU Commission's *Innovative Medicines Agenda* (Innomed).

- Identifying patient-oriented risk benefit, rather than that designated by the authorities
- Involving the patient and health care providers at an early stage in considering the optimal outcome of a clinical research programme

### **Regulatory initiatives**

Several speakers referred to key reference documents from government agencies:

- Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products<sup>3</sup>
- NIH Roadmap for Medical Research in the 21<sup>st</sup> Century<sup>4</sup>
- The European Medicines Agency Road Map to 2010: Preparing the Ground for the Future<sup>5</sup>

'A new product development toolkit – containing powerful new scientific and technical methods such as animal or computer-based predictive models, biomarkers for safety and effectiveness,..... - is urgently needed to improve predictability and efficiency along the critical path from laboratory concept to commercial product'.  
*FDA Critical path*

## **NEW MODELS FOR CLINICAL DEVELOPMENT**

Two models for clinical development (that are not mutually exclusive) were presented during the Workshop and are represented, schematically, on the following page.

### **Model 1: 'Learn and confirm'**

This model (presented by Dr Robert Ruffolo) represents a transition from the current 'phased' approach for clinical development to an integrated process moving seamlessly from proof of concept (learn) to expansion to global clinical trials (confirm). The design of the early studies is characterised by:

- Accelerated testing in patients vs. healthy volunteers
- Use of adaptive methodologies in trial design
- Elimination or decreased use of blinding and continuous assessment of data

### **Model 2: 'Build, confirm expand'**

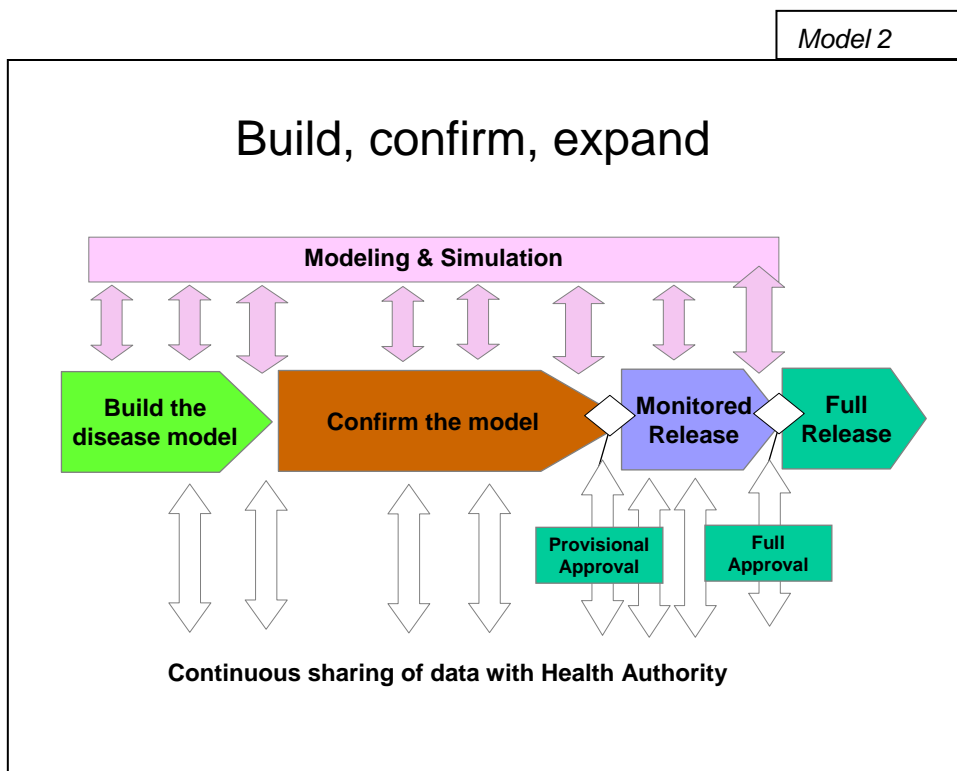
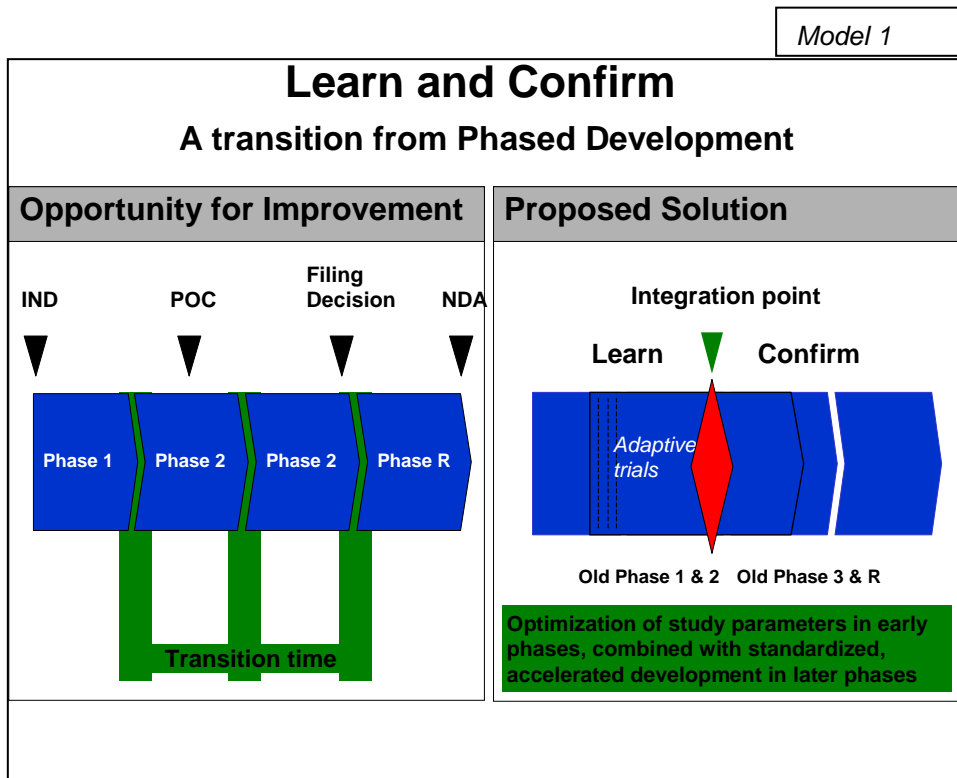
This is a three-stage model (presented by Dr James Shannon) with a similar concept of more efficient early clinical development but with late stage development carried out in a 'real world' population. .

<sup>3</sup> Published by the US Department of Health and Human Services and the FDA, March 2004, [www.fda.gov](http://www.fda.gov)

<sup>4</sup> Published by the US National Institute for Health on the website <http://nihroadmap.nih.gov>

<sup>5</sup> Published by the EMEA, March 2004, available from the EMEA website: <http://www.emea.eu.int>

- A 'disease model' of the potential safety and efficacy of the drug in the disease state is developed with increased use of biomarkers supported by epidemiology (discovery to proof of concept);
- A provisional approval phase follows with controlled early market access and strict safety management
- Full approval is achieved after updated safety assessment and clinical outcome



## SYNDICATE DISCUSSIONS

Session 4 of the Workshop, during which the syndicate discussions took place, was chaired by **Professor Robert Peterson**, *Associate Head of Pediatrics, Dept of Pediatrics, British Columbia's Children's Hospital, Canada*.

The Workshop participants formed four Syndicate groups to discuss the issues arising from the Workshop presentations and to make recommendations under the two general headings of *Re-engineering the development business model* and the *Evolution of Clinical Trials*.

The Chairpersons and Rapporteurs for the four groups were:

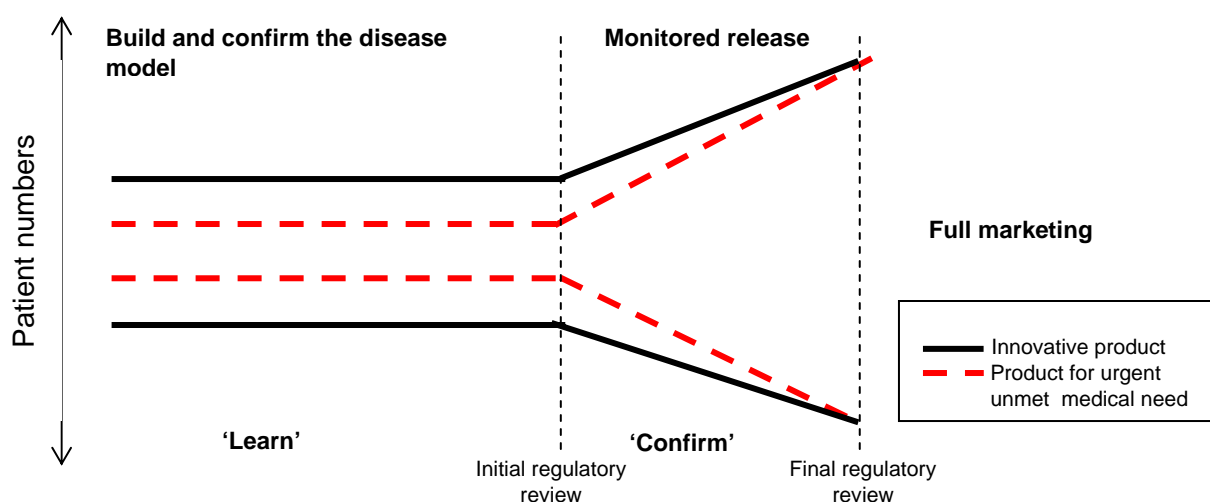
<b>Syndicate 1</b>	<i>Chair:</i>	<b>Professor Sir Alasdair Breckenridge</b> , <i>Chairman, Medicines and Healthcare Products Regulatory Agency (MHRA), UK</i>
	<i>Rapporteur:</i>	<b>Dr Ed Harrigan</b> , <i>Senior VP, Worldwide Regulatory Affairs and Quality Assurance, Pfizer Inc., USA</i>
<b>Syndicate 2</b>	<i>Chair:</i>	<b>Dr David Jefferys</b> , <i>Senior Regulatory Strategic Adviser, Eisai Europe, UK</i>
	<i>Rapporteur:</i>	<b>Dr Stephen Lucas</b> , <i>Director General of Policy and Strategic Planning Division, Health Canada</i>
<b>Syndicate 3</b>	<i>Chair:</i>	<b>Franz Schneller</b> , <i>Executive Director, Swissmedic, Switzerland</i>
	<i>Rapporteur:</i>	<b>Dr George Butler</b> , <i>Vice President, Customer Partnerships, AstraZeneca Pharmaceuticals, USA</i>
<b>Syndicate 4</b>	<i>Chair:</i>	<b>Dr Paul Huckle</b> , <i>Senior Vice President, European and International Regulatory Affairs, GlaxoSmithKline, UK</i>
	<i>Rapporteur:</i>	<b>Dr Leonie Hunt</b> , <i>Director, Drug Safety and Evaluation Branch, Therapeutic Goods Administration, Australia</i>

## SUMMARY OF RECOMMENDATIONS

### 1. NEW BUSINESS MODELS

#### Early monitored release

The model proposed in the Syndicate discussions is, in effect, a combination of Models 1 and 2 presented on page 4 and is shown here in a simplified diagram:



- The current three Phases of clinical testing would be consolidated into two stages. The sponsor could apply for a 'conditional' or 'monitored' release for marketing at the end of the first stage of testing;
- The first-stage testing (which is similar to the 'learn' stage of Model 1 and the 'build and confirm' stages of Model 2 above) would provide more information, particularly relating to dose levels and safety, than is currently available at the end of Phase II;
- The advances in clinical trial design, use of biomarkers and surrogate end points, etc., (discussed below) would be incorporated in the new design for first stage testing;
- Data for the second stage of testing would be collected either from the general patient population (when early, monitored release is agreed) or from further clinical studies. In either case, the focus would be on confirming safety and validating surrogate endpoints, where relevant;

During discussion of this model it was pointed out that many oncology drugs and products for other life-threatening conditions, under the current paradigm, are released at the end of Phase II, with specific requirements for follow-up<sup>6</sup>. Provision for urgently needed medicines to be approved on a limited data set is also shown in the diagram by the broken red line.

The current discussions, however, focused on the feasibility of applying the model to a wider range of products, on the basis of pre-release studies that extend beyond the current Phase I/Phase II requirements.

### ***Early release for a broader range of products***

As noted above companies could opt to apply for early release or to carry out the confirmatory clinical work in formal clinical trials. Scientific advice would be sought from the authorities prior to making the application.

- Criteria for accepting products for early release would need to be agreed with regulatory authorities;
- The model would be designed to encourage and reward innovation, with priority given to products that fulfil unmet medical needs or have important advantages over existing therapy;
- The overall data package at the final regulatory review would be of the same magnitude, whether or not early release was agreed, the difference being that data for the early-release products would come from patients in a 'real-world' setting rather than from formal clinical trials;
- Ideally, the data collection and patient monitoring after early release should be carried out using information from linked electronic medical record (EMR) database.

### ***Involving all stakeholders***

It would be important to involve all stakeholders, including patients and health care providers in consultations on a transition to the new paradigm to:

- Provide assurances that safety standards would not be compromised and that the same regulatory standards apply regardless of the route to market;
- Ensure that the payers are prepared to include products on 'monitored release' in their programmes

### ***Constraints during the 'monitored release' stage***

In addition to the specific commitments to provide additional data on products that are subject to early release, the following were identified as possible constraints that might be attached to a conditional authorisation:

- Restriction of use to specified physicians or centres who must be able/willing to comply with feed-back and reporting requirements;

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<sup>6</sup> Discussed at the CMR International Workshop on *Post approval commitments and conditional authorisations*, May 2005. Report available on the website [www.cmr.org/institute](http://www.cmr.org/institute)

- Restriction to specific patient groups;
- An undertaking to set up a communication programme to inform physicians and patients about the conditions of release and risk management issues;
- Exclusion from direct-to-consumer (DTC) advertising provisions.

#### *Parallels with the device industry*

It was suggested that there are lessons that could be learnt from the way in which certain medical devices can only be made available to patients who agree to be included in the appropriate patient registry. This approach could be used in order to ensure feed-back and reporting of adverse events and outcomes.

#### **Advantages of the proposed paradigm**

- The initial launch of the medicine would be more contained;
- Feedback of data during the monitored release would enable problems to be identified more quickly and addressed (e.g., by dose adjustment);
- More patients would benefit from early access to important new therapies than under the current Phase III studies;
- The second review would give regulators more control over products during their early marketing.

#### **Potential problems**

- The early release of products that do not meet the current criteria for urgent and life-saving medicines would need changes to regulations and/or legislation;
- Products that are released for early marketing might be prone to off-label use, outside the conditions of the monitored release.

#### **Recommendations on the 'early marketing' model**

***It was recommended that*** a retrospective review should be carried out to identify recently marketed products that might have been eligible for early release, where patients would have benefited from the faster availability of new therapies.

#### ***The business case for early release to the market***

Questions were raised on whether the commercial sector in companies would be convinced of the benefits of early release for products with a large potential market (e.g., treatment of chronic, widespread conditions) if the market was, initially, limited.

***It was recommended that*** a study should be carried out to develop the business case and identify criteria for seeking early release with monitored follow-up for products that do not meet current requirements for accelerated review and conditional approval. This might include:

- Looking at recent cases to see whether they were potential candidates for early release;
- Examining the financial model and determining the commercial difference in being up to a year earlier onto a restricted market before full release;
- Evaluating the impact on intellectual property/data protection and any potential reduction in product life.

#### **An alternative model**

The Syndicates were also asked to discuss an alternative model<sup>7</sup> for changing the regulatory paradigm involving partial de-regulation of new product development up the stage of the pivotal Phase III trials. The latter would be subject to scrutiny by the authorities, with intensive post-marketing surveillance, preferably carried out through the use of integrated medical health record databases.

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<sup>7</sup> This was proposed as a follow-up to a model discussed at an ABPI Workshop in September 2005.

Under this model accredited companies would be licensed to carry out early research and clinical development on their own responsibility (following agreed guidelines) and subject to inspection by the authorities, but the regulatory process would only apply from Phase III onwards.

### ***Deregulation and advice from agencies***

- Companies commented that the current level of regulation during early product development was not felt to be burdensome;
- It was envisaged that obtaining accreditation would be time-consuming and onerous;
- There were concerns that opportunities to obtain advice from regulatory agencies during Phases I and II might be lost and this was felt to be a significant disadvantage;
- Although partial deregulation of clinical trials (e.g., in Australia) has been successful, there have been cases where companies, through lack of communication with the agency, have wasted time and resources on trials that are of little or no value in the final data package for registration of the product.

***It was agreed that*** deregulation was unlikely to be the key to a 'new paradigm' in the near future. On the contrary, ensuring greater rather than reduced involvement of regulatory agencies was advocated through strengthened scientific advice (see below).

### **Electronic medical records**

The use of linked electronic databases as a source of post-marketing safety data from 'real world' patient populations has significant potential for the future.

***It was agreed,*** however, that such data sources are not yet sufficiently comprehensive or reliable to provide an alternative to current systems for post-marketing surveillance. Work needs to be undertaken to compare databases and determine standards and criteria for an essential dataset.

### **Single Phase III study**

The proposal was considered that a single, well designed clinical study should suffice to fulfil the requirements of Phase III (or the 'confirm' stage of the model discussed above).

***It was agreed that*** there should be flexibility in the regulatory attitudes and that routine requirements for at least two pivotal studies were not appropriate in all cases. A single, well-designed study could provide adequate data although this would need to accommodate differing requirements for active comparators and placebos.

### ***Comparators for clinical trials***

It was noted that a major impediment to reforming clinical trial design is the on-going disparity between the US requirements for placebo-controlled trials and the EU expectations for testing against an active comparator product.

## **2. EVOLUTION OF CLINICAL TRIALS**

### **Innovative trial design: Efficacy**

Many of the current key developments have the potential for improving the way in which efficacy is determined:

- Adaptive trial design
- Pharmacogenomics
- Modelling
- Use of historical data and registries
- Adoption of Bayesian statistical approaches

It was felt that a major barrier to taking these forward is conservatism on the part of both industry and regulators. Companies may be reluctant to be the first to use methodology that might be unfamiliar to the agencies and hence cause delays in the review process.

**It was recommended that** comparative studies should be carried out on 'traditional' versus 'novel' methodology, focusing, for example, on:

- The use of Bayesian statistics;
- The impact of adaptive clinical trial designs including how these affect decision-making in terms of early attrition of unsuccessful compounds.

Modelling techniques could be used to test novel approaches, using existing, currently available databases of data gathered in conventional parallel group trials, in order see whether different results could have been reached using different methodology.

It was felt that the CMR International Institute could have a coordinating role in such studies as well as in the dissemination of the findings and subsequent discussion of the lessons that could be learnt.

### **Bringing about change**

It was noted that the adoption of viable, novel clinical trial methodology would require enhanced training of all stakeholders including sponsors academics and regulatory reviewers, in the new techniques, including statistical analysis.

### **Clinical testing for Safety**

It was recognised that the introduction of more efficient efficacy testing would result in products being tested in a smaller number of patients in order to reach 'proof of concept' (end of the 'learn' stage in the model described in Section 1 above). This raised questions about the need for a new approach to safety testing.

No specific recommendations were agreed but proposals for moving forward included:

- **Separate, simplified safety trials:** Large trials that focus on determining safety in a broader population than the efficacy trials, using a simplified protocol that focuses on significant safety outcomes, rather than trying to capture a wide range of information.
- **Biomarkers for safety:** Work on the development of improved predictors of specific potential safety issues, for example markers for early detection of hepatotoxicity.
- **Societal/political attitudes to safety:** Trying to strike a balance between public expectations for 'certainty' in relation to safety and the consequent delay in making new products available to meet patients' needs.
- **Re-visiting the ICH E1 Guideline<sup>8</sup>** to determine whether regulators are likely to be satisfied by the recommended databases of 1500 patients treated for six months and 100 patients treated for one year.

### **Validation of biomarkers and surrogate end points**

Biomarkers and surrogate end points are seen as a way of streamlining research but, in the short term, savings in research costs and in the time-to-market are unlikely to be realised because of validation issues:

- Validation by individual companies can be extremely time-consuming and expensive;
- Collaborative research between companies raises problems of commercial interests and competition can arise even during the so-called 'pre-competitive' phase.

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<sup>8</sup> ICH E1: *The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions*, adopted October 1994, ICH Website: [www.ich.org](http://www.ich.org)

### **Public-private partnerships (PPPs)**

**It was recommended that** there is a role for PPPs in the validation of biomarkers and surrogate end points where public investment would be driven by public health needs:

- Pre-competitive 'basic' research on the validation of biomarkers where key research needs for the future are defined, e.g., under the FDA Critical Path Initiative or NIH Roadmap;
- Study of post-approval data (e.g., from EMRs) in relation to outcomes and the verification of surrogate markers and endpoints.

It was noted that the CMR International Institute would be holding a Workshop in 2006, which will take these discussions on biomarker validation further<sup>9</sup>.

### **Consistency of Scientific Advice**

**It was recommended that** renewed efforts be made to harmonise the scientific advice that is given, especially in relation to the direction of the clinical research programme:

- Procedures for obtaining joint advice between EMEA and FDA should be facilitated and actively implemented;
- Consistency of advice between agencies is also a major issue within the EU member states;
- Companies should report back to the agencies in cases where conflicting advice is obtained and dialogue between agencies should be encouraged.

### **Public awareness of the role of clinical trials**

**It was recommended that** CMR should participate in a campaign to emphasise the importance to the public health of maintaining and encouraging a healthy clinical trial infrastructure. This should highlight:

- The benefits to patients of participating in clinical trials and possibly receiving a higher standard of care;
- The benefit to institutions in terms of their intellectual participation in innovative research;
- The overall benefits to society in terms of speeding the availability of new medications.

It was also recommended that CMR should become involved in tracking and recording the outcome of the current UK initiative to facilitate the conduct of clinical trials under the National Health Service and to provide data that informs better clinical trial design.

### **Patient-centred models**

There was discussion of the importance of ensuring that the views of patients were taken into consideration when looking at benefit-risk perception and acceptable outcomes of clinical studies. The role of patient focus groups and disease-based patient associations were considered particularly at the stage of developing disease-specific models. It was acknowledged that there might be practical difficulties in involving such groups in the actual regulatory decision-making process.

**It was recommended that** procedures should be developed for ensuring that the patients are involved early, at the stage of developing the model for clinical trials and product development, in order to ensure that the target outcome is acceptable to the patient.

A role for the CMR International Institute was envisaged, perhaps through a future Workshop.

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<sup>9</sup> New Technologies and Biomarker Development: the way ahead, 12-13 May 2006, Washington D.C. (details via the website [www.cmr.org/institute](http://www.cmr.org/institute) or by E-mail from [institute@cmr.org](mailto:institute@cmr.org))

### Off-label use

Enriched trial designs identify the patient population most likely to benefit from the product. Whilst the product label could restrict its use to the target population, there is a strong likelihood that, in a 'real-world' situation, product will be used in patients for whom it is not intended. There was discussion of the extent to which it is the sponsor's obligation to test the benefit-risk of a product in a broader patient population than is specified by the labelling:

- There is a trend towards requiring data on patients for whom the product is, technically speaking, 'off-label' but who are likely to be prescribed the medicine;
- This raises ethical issues in relation to testing a medicine in a patient population for whom it is not recommended or where there may be warnings against use of the medicine for that individual;
- Regulators have a duty to ensure that information is provided to the health care professional and the patient on how products should be used but this does not extend to saying how medicine should be practised.

### SUMMARY

This workshop brought together an impressive group of experts and opinion leaders to take forward discussions of a topic that is currently the subject of much debate in academic, industry and regulatory circles. It was readily acknowledged that there are no quick or unique solutions to the challenge of bringing about a paradigm shift in the way in which medicines are developed and brought to the marketplace. There was, however, consensus that the current paradigm for clinical testing is unsustainable, if the full potential for pharmaceutical innovation is to be achieved without the new products becoming unaffordable for healthcare providers.

Many of the recommendations from the Workshop focused on the need for a more flexible approach to clinical trial design and on making progress with the validation and implementation of new technologies. The priority is early detection of potentially valuable products but it is equally important, at an early stage, to identify and eliminate those that are destined to be costly failures.

The potential difficulties of introducing far-reaching changes to the clinical research paradigm were well recognised and there was emphasis on the importance of involving and 'educating' all stakeholders – patients, physicians and payers – and providing adequate assurances that safety will not be compromised.

## A NEW PARADIGM FOR CLINICAL RESEARCH

CMR International Institute Workshop, 3-4 October 2005

### PROGRAMME

#### SESSION 1: A NEW PARADIGM IS REQUIRED - WHAT ARE THE OPTIONS?

Chairman's Introduction and presentation on Realising the Promise of the Biomedical Endeavour  
D Peter Corr  
*Senior Vice President for Science and Technology, Pfizer, USA*

##### ***What is the role of the agencies in ensuring that future research into new medicines is sustainable?***

- An EMEA Viewpoint - Avenues for understanding and reacting to the challenges  
Dr Outi Maki-Ikola  
*Scientific Administrator, Safety and Efficacy Sector, Pre-Authorisation Human Unit, European Medicines Agency (EMA), UK*
  - A Japanese Viewpoint  
Dr Osamu Doi  
*Senior Executive Director, Pharmaceuticals and Medical Devices Agency (PMDA), Japan*
- Making Effective Decisions Early in the R+D Process  
- Can this approach improve the productivity of drug development?  
Dr Eiry Roberts  
*Vice President of Project/ Program Medical, Eli Lilly and Company, USA.*

#### SESSION 2: WHERE SHOULD THE EFFORT BE FOCUSED?

Chairman  
Dr Peter Corr  
***Genomics, biomarkers and surrogate endpoints: Are these the key to changing the development paradigm?***

- An Industry Viewpoint  
Thomas Metcalfe  
*Global Head of Biomarker Program, F Hoffmann-La Roche, Switzerland*
  - A Regulatory Viewpoint  
Professor Gunnar Alván  
*Director General, Medical Products Agency, Sweden*
- In patient or in silico*: Is the pharmaceutical industry realising the full potential of computer modelling and simulation?  
Dr Mikhail Gishizky  
*Chief Scientific Officer, Entelos inc, USA*

#### DAY 2 SESSION 2 (continued): WHERE SHOULD THE EFFORT BE FOCUSED?

Chair  
Professor Robert Peterson  
*Associate Head of Pediatrics, Dept of Pediatrics, British Columbia's Children's Hospital, Canada*

##### ***Are there new clinical protocol designs/statistical approaches that can revolutionise drug development?***

- A Regulatory Viewpoint: New approaches to clinical development  
Professor Sir Michael Rawlins  
*Chairman, National Institute for Clinical Excellence, UK*
  - An Industry Viewpoint: A Path to Improve Drug Development at Wyeth  
Dr Robert R. Ruffolo Jr  
*President, Wyeth Research, USA*
- A New Paradigm for Clinical Development?  
The Role of FDA's Critical Path Initiative  
Dr Janet Woodcock  
*Deputy Commissioner of Operations, Food and Drug Administration (FDA), USA*

#### SESSION 3: SYNDICATE DISCUSSIONS

#### SESSION 4: WHAT COULD THE FUTURE LOOK LIKE?

Chairman  
Professor Robert Peterson

What could the future look like? A Regulator's View  
Dr Robert Temple  
*Director Medical Policy, Food and Drug Administration (FDA), USA*

What could the future look like? An industry R&D perspective  
Dr James Shannon  
*Global Head of Clinical R&D, Novartis Pharma A.G., Switzerland*