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Regulation of Biomarkers

A European (EMA) perspective

Irish Biomarker Network - Inaugural Workshop; 4th Nov 2010

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Pre-clinical Assessor & CAT Alternate,
Irish Medicines Board

Current Uncertainties with Drug Development

- Large majority (>80%) of compounds entering clinical trials fails because of toxicity or unsatisfactory efficacy.
  (50% phase III fail for safety/efficacy reasons)
  - Risk of pipeline draught
  - ~30% failure of MAAs in the centralised (EMA) procedure
- Significant labelling restriction at the time of approval and within the first two years after launch
- Two or more valuable medicines per year withdrawn because of serious ADRs
- Current mortality and morbidity due to ADRs or insufficient efficacy
  - Impact on individual patients, public health, industry

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Biomarker Potential

- Greater understanding of patho-physiology and subtypes of diseases
- More efficient science-based drug design, prediction of efficacy and management of toxicity in drug development
  - Better target identification and improved selection of candidate compounds
  - Higher potential for compounds in the pipeline
- More appropriate drug and dose selection in a better defined population or individuals
  - Improved benefit/risks balance
  - Less treatment failures and withdrawals
- More vigorous and productive industry

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The use of Biomarkers is not new!

Drug	Biomarkers	Clinical endpoint
Anti HTA	Blood pressure	Stroke, Heart failure
LDL cholesterol lowering	Blood cholesterol	Coronary heart disease, infarction mortality
Anti-retrovirals	Viral RNA load	Survival
Anti-diabetics	HbA1c, glycaemia	Diabetic neuro/ nephropathy
Anti-Osteoporosis	BMD	Fracture rate
Anti-Cancer agents	Imaging of tumor size	Survival

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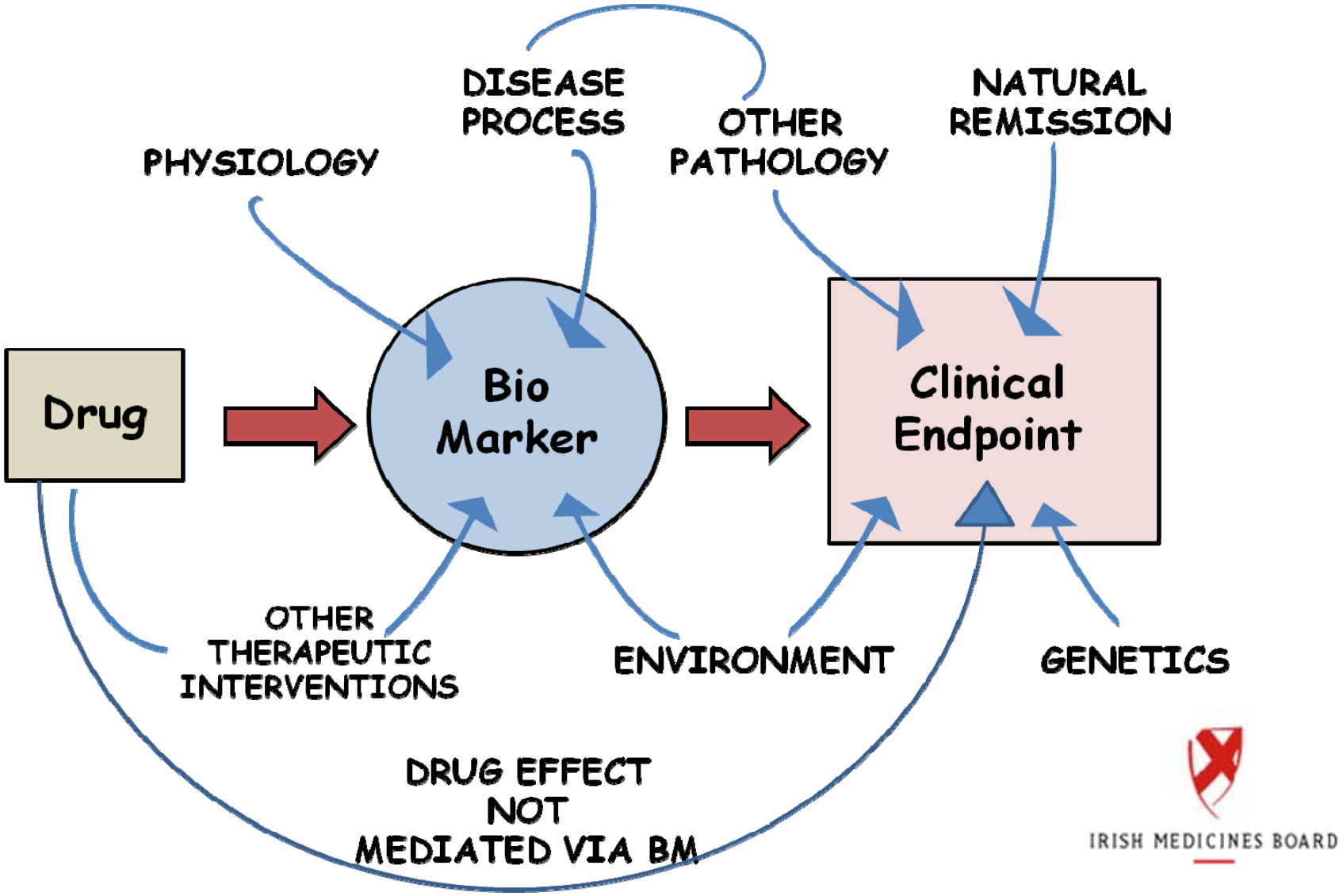

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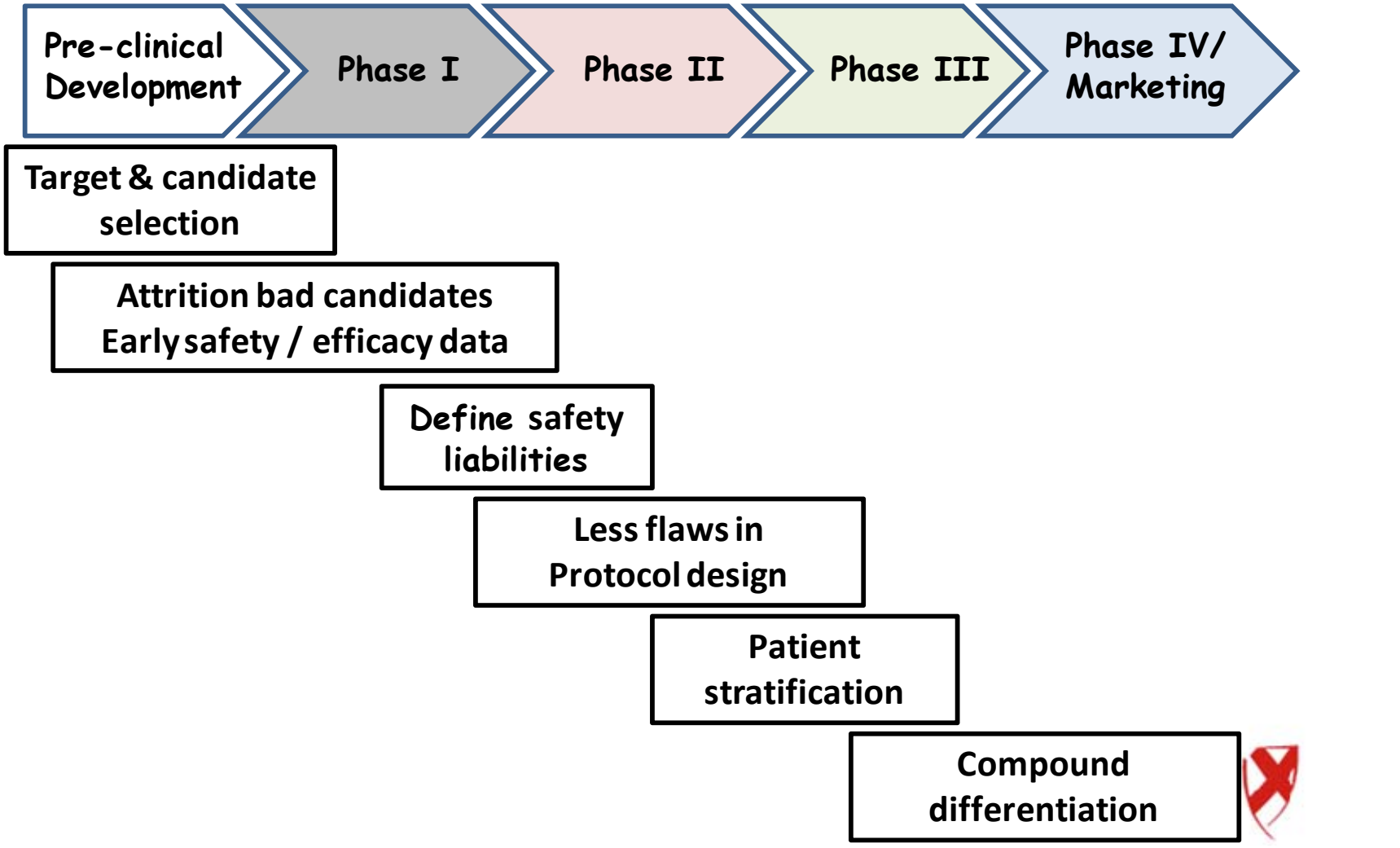
Biomarker Application during Drug Development



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Regulatory considerations/guidance

- What does the EMA offer to discuss the regulatory impact of Biomarkers in drug development
  - Informal Briefing meeting (PGWP)
  - Scientific Advice – Protocol assistance
    - Biomarker qualification
    - Pre-filing meetings
  - MAA evaluation
  - New genomics information for products on the market
  - Guidelines

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EMA Pharmacogenomics Working Party (PgWP)

- The PgWP provides recommendations to the CHMP on all matters relating directly or indirectly to Pharmacogenomics
- Core group of 14 experts nominated by the CHMP
- Pg Working Party structure
  - Multidisciplinary group
    - 50% academia scientists
    - 50% regulatory scientists
    - EMA therapeutic group leaders
    - + “area” specialists invited for PG briefing and drafting groups

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PgWP Tasks

- Share experience on issues arising from the integration of pharmacogenomics in drug development, assessment and information
- Prepare, review and update guidelines
- Support dossier evaluation and contribute to scientific advice
- Advise on Pharmacogenomic related issues the European Commission
- Liaise with interested parties
- Support European and international cooperation

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PG Briefing Meetings

- An informal dialogue among Regulators, Academia and Industry scientists on emerging science
- Aim of meeting is to highlight technical, scientific and regulatory issues
- Submissions are voluntary and strictly confidential
- Sponsors provide background information
- Regulators do not provide formal advice – informal!

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Guideline on PG briefing meetings

European Medicines Agency

London, 27 April 2006
Doc. Ref. EMEA/CHMP/PGxWP/20227/2004

COMMITTEE FOR HUMAN MEDICINAL PRODUCTS

GUIDELINE ON PHARMACOGENETICS BRIEFING MEETINGS

DRAFT AGREED BY PHARMACOGENETICS WORKING PARTY	28th February 2005
ADOPTION BY CHMPFOR RELEASE FOR CONSULTATION	31st March 2005
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30th September 2005
AGREED BY PHARMACOGENETICS WORKING PARTY	5th April 2006
ADOPTION BY CHMP	27th April 2006
DATE FOR COMING INTO EFFECT	30th November 2006

KEYWORDS	*Pharmacogenetics, pharmacogenomics, genes, alleles, single nucleotide polymorphisms, genome sequencing, microarrays, mRNA, DNA*

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Examples scenarios discussed at PG briefing meetings

- Genomic expression signature as a biomarker bridging proof-of-concept from animal model to man
- Data from pre-collected samples. Potential regulatory value in conducting retrospective PG biomarkers analyses and impact on existing and new drugs
- Genomic markers in prospective studies. Methodological options.
- Determination of the PG clinical utility (clinical magnitude of the differential response, benefit in clinical outcomes using the PG test) and labelling implications

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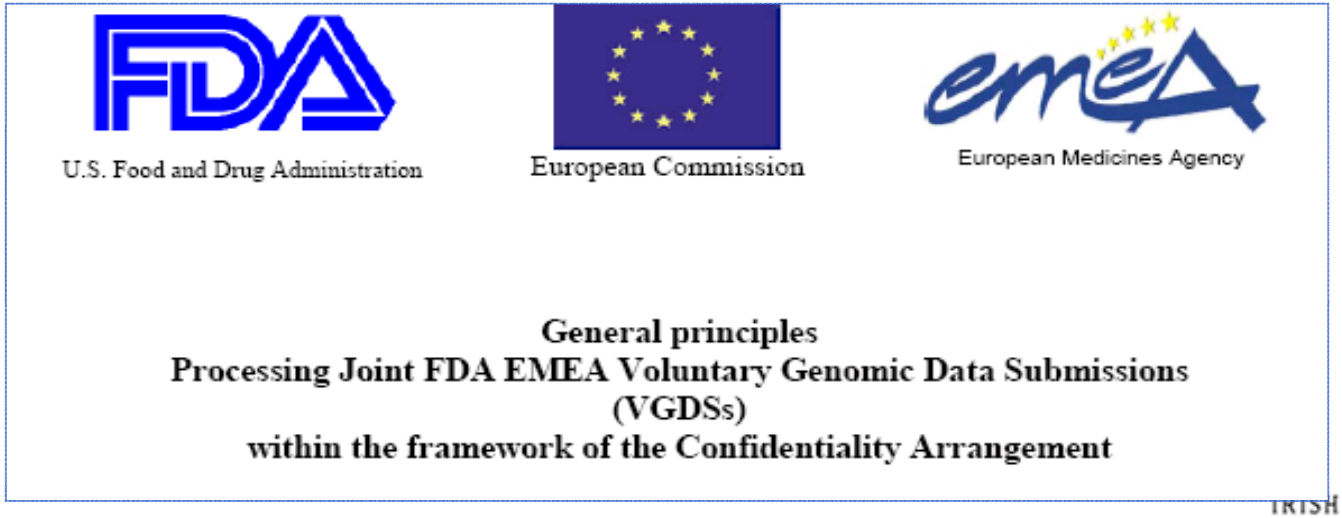
Joint FDA-EMA Briefing Meeting

- Joint FDA-EMA voluntary genomic data submission (VGDS) briefing meetings (and PMDA)
  - Sponsor submits data and questions for review by FDA-EMA
  - Help agencies gain understanding of genomic data
  - Are not part of the regulatory decision making process
  - Document explains how sponsor requests for briefing meetings are received, processed and reviewed by the Agencies.



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PgWP Adopted Guidelines & Concept Papers

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 25 May 2007
EMEA/128517/2006

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

REFLECTION PAPER ON THE USE OF PHARMACOGENETICS IN THE PHARMACOKINETIC EVALUATION OF MEDICINAL PRODUCTS

DRAFT RELEASED FOR CONSULTATION	July 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	October 2006
AGREED BY PHARMACOGENETICS WORKING PARTY AND EFFICACY WORKING PARTY	April 2007
ADOPTION BY CHMP	May 2007

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PgWP Adopted Guidelines & Concept Papers

European Medicines Agency

London, 15 November 2007
Doc. Ref. EMEA/CHMP/PGxWP/201914/2006

COMMITTEE FOR HUMAN MEDICINAL PRODUCTS
(CHMP)

REFLECTION PAPER ON
PHARMACOGENOMIC SAMPLES, TESTING AND DATA HANDLING

DRAFT AGREED BY THE PGWP WORKING PARTY	October 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	November 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	February 2007
AGREED BY THE PGWP WORKING PARTY	October 2007
ADOPTION BY CHMP	November 2007

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PgWP Adopted Guidelines & Concept Papers

European Medicines Agency

London, 15 November 2007
EMEA/CHMP/PGxWP/278789/2006

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

REFLECTION PAPER ON THE USE OF GENOMICS IN CARDIOVASCULAR CLINICAL INTERVENTION TRIALS

DRAFT AGREED BY THE PGWP WORKING PARTY	October 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	December 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	March 2007
AGREED BY THE PGWP WORKING PARTY	October 2007
ADOPTION BY CHMP	November 2007

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Guidelines/Reflection Papers in Draft

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 April 2010
EMA/CHMP/37646/2009
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products

Draft

Draft Agreed by Pharmacogenomics Working Party and EWP- PK	March 2010
Adoption by CHMP for release for consultation	22 April 2010
End of consultation (deadline for comments)	31 October 2010

This guideline replaces the Reflection Paper on the use of Pharmacogenetics in the Pharmacokinetic Evaluation of Medicinal Products (EMEA/128517/2006)

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Guidelines/Reflection Papers in Draft

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 June 2010
EMA/CHMP/641298/2008
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on co-development of pharmacogenomic biomarkers and Assays in the context of drug development

Draft

Draft Agreed by Pharmacogenomics Working Party	June 2010
Adoption by CHMP for release for consultation	24 June 2010
End of consultation (deadline for comments)	30 November 2010

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EMA Scientific Advice Working Party (SAWP)

- SAWP is a multidisciplinary group established by CHMP
  - comprises 26 Members & 1 Chair
- Expertise includes
  - Non-clinical safety
  - Pharmacokinetics
  - Methodology and Statistics
  - Therapeutic fields for which there are frequent requests and/or defined in the Annex of Regulation (EC) No 726/2004, e.g. cardiology, oncology, diabetes, neurodegenerative disorders, and infectious diseases including HIV infection.
- Sole remit of providing Scientific Advice and Protocol Assistance to applicants

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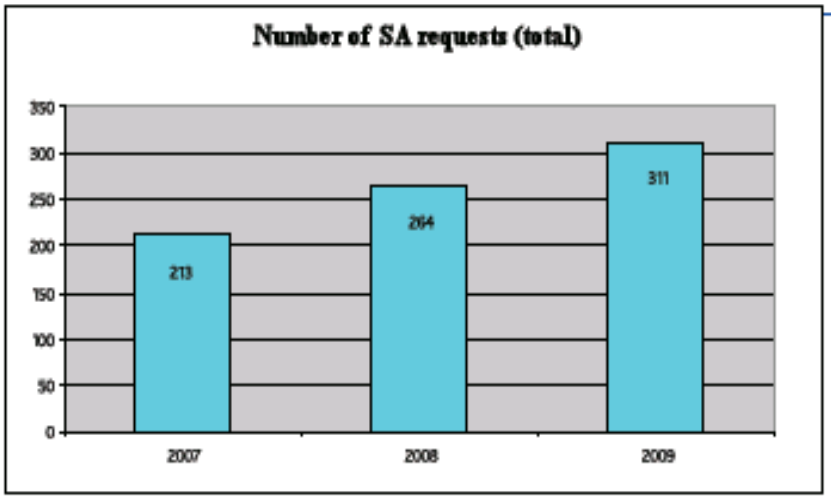
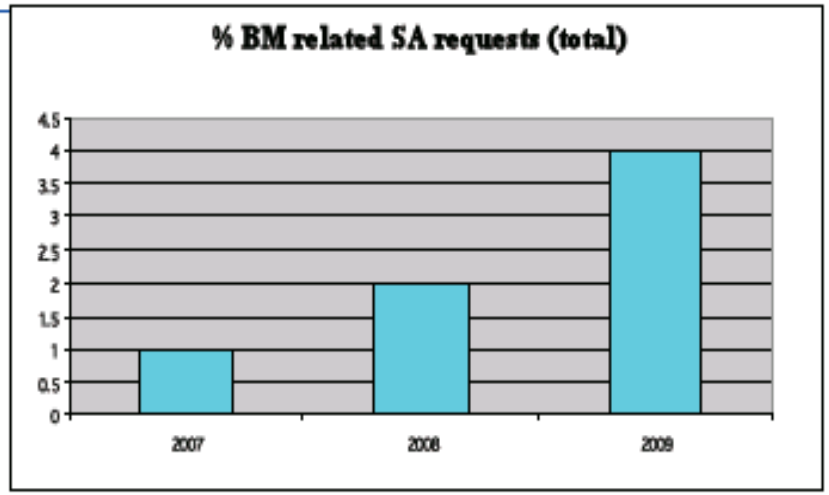
Scientific Advice





- Total number of SA requests increased from 2007- 2009
- % SA letters with questions specific to BM doubled every year from 2007- 2008 and 2008- 2009

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EMA Qualification process

- New, voluntary, scientific pathway leading to CHMP opinion or Scientific Advice on innovative drug development methods.
- **CHMP Qualification Opinion** on the acceptability of a specific use of the proposed method (e.g. use of a novel methodology or an imaging method) in a research and development (R&D) context (non-clinical or clinical studies), based on the assessment of submitted data**.**
- **CHMP Qualification Advice on future protocols and methods for further method development towards qualification**, based on the evaluation of the scientific rationale and on preliminary data submitted.
- Public consultation prior to Qualification Advice; Qualification opinion and assessment is open to the public.

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Guidance on novel methodologies for drug development

European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

London, 22 January 2009
Doc. Ref. EMEA/CHMP/SAWP/72894/2008 Corr[1]

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

QUALIFICATION OF NOVEL METHODOLOGIES FOR DRUG DEVELOPMENT: GUIDANCE TO APPLICANTS

DRAFT AGREED BY SAWP	27 February 2008
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	24 April 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 June 2008
FINAL AGREED BY CHMP	22 January 2009

KEYWORDS	*EMEA. CHMP. Novel methodology. Qualification. Scientific Advice.*

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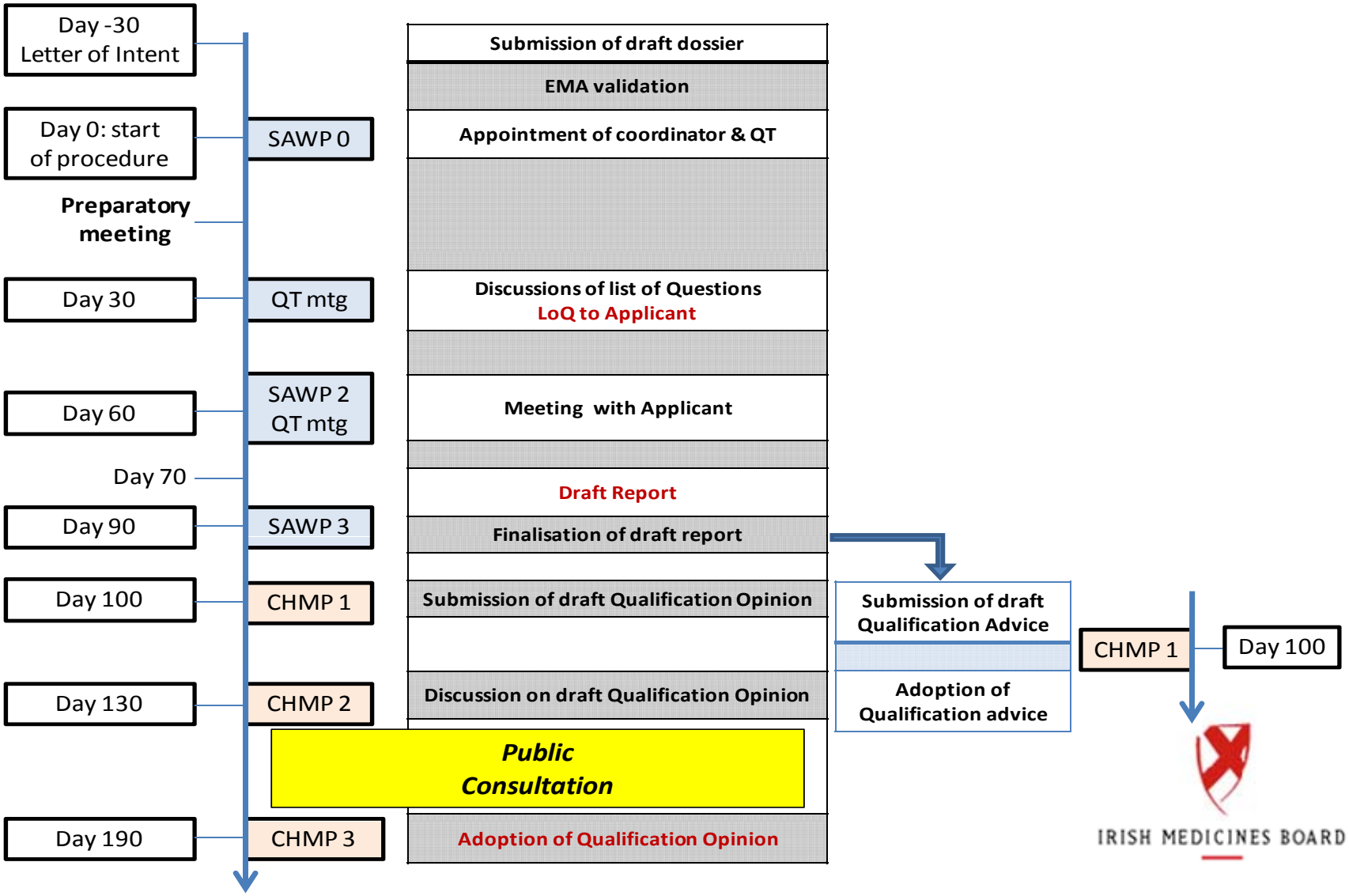
Qualification procedure at a glance



Global Regulation Dimension

- 2008 - EMA and FDA have concluded the first joint qualification process for biomarkers (PMDA Observers)
  - Qualification of seven biomarkers of drug-induced renal toxicity in the context of non-clinical drug development
  - the renal biomarkers submitted were acceptable in the context of non-clinical drug development for detection of acute drug-induced renal toxicity.
  - the renal biomarkers provide additional and complementary information to the currently available standards.
  - the use of renal biomarkers in clinical trials is to be considered on a case-by-case basis in order to gather further data to qualify their usefulness in monitoring drug-induced renal toxicity in man.

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Global Regulation Dimension

- 2009: ICH E15 guideline: Terminology for genomics biomarkers
- 2010: ICH E16 guideline: Context, structure and format of BM submissions
- ICH Concept paper being considered entitled the “General Principles for best practices in using biomarker in clinical trials”

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Clinical Trial Regulation

- EC Regulations, 2004 (S.I. No 190 of 2004) & Amendment 2009 (S.I. No 1 of 2009)
- Vol 10 “Notice to Applicants” Q&A document
- Non-interventional trial if –

  “no diagnostic or monitoring procedures are applied to the patients included in the study, other than those which are **ordinarily** applied in the course of current practice”

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Implications of CT regulation

- Biomarker trials are considered interventional acc. to S.I. 190/2004
- Require CA approval
- Trials must be GCP compliant
- Reports from sponsors - additional and significant administrative burden

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Implications of CT regulation

- Disharmony with application
- Recognised by EU and Member States
- No consensus on how to resolve this
- Possible clarification at the next CT directive amendment

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IMB Approach

- Pragmatic approach
  - ***"Validated*** diagnostic procedures"
  - "applied ***to the patients***"
  - Under the scope of the regulation

- No randomisation, prescribed in the usual manner in line with its MA – not clinical trial

- Must notify the IMB

  e-mail Clinical.Trials@imb.ie

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Conclusions

- The use of Biomarkers has become an integral part of modern drug development. Biomarkers can help guide drug development and use leading to enhanced efficacy and safety.
- Informal regulatory process/guidance and expert panel has been established at the EMA
- A process for the Qualification of Biomarkers and/or regulatory formal advice have been established at the EMA
- International co-operation is ongoing through joint FDA-EMA VGDS briefing meetings and joint qualification processes.
- Global ICH guidance has been published with further ICH topics being considered and drafted.
- Non validated biomarker trials not considered under the scope of the CT regulation but IMB must notified.

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Useful website

- http://www.imb.ie
- http://www.ema.europa.eu

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