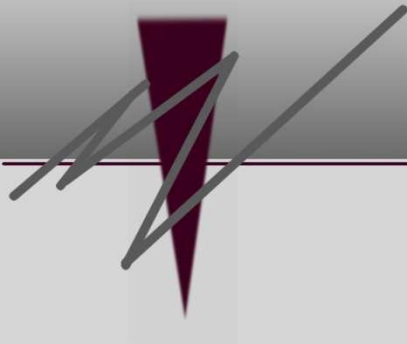


*EuroBio 2009, Lille*

# Regulation of Biomarkers

*A European (EMEA) perspective*



**Bruno FLAMION, MD, PhD**

Chair, Scientific Advice Working Party (**SAWP**), CHMP-EMEA

Member of **CAT** (Committee for Advanced Therapies) and Vice-Chair of  
**PGWP** (Pharmacogenomics Working Party), EMEA

Federal Agency for Medicinal and Health Products (**FAMHP**), Belgium

Professor of Pharmacology, University of Namur, Belgium



My presentation might not be the view of the CHMP/SAWP, the EMEA, or the FAMHP.

My presentation is a personal viewpoint and binds in no way the organisations mentioned above.





## BM's are used at all stages of drug development

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- In the R&D process
- In preclinical trials
- In clinical trials
  - *At baseline:* for screening, diagnosis, stratification
  - *During a study:* target binding, mechanism of action, PD, interactions, efficacy (outcome), safety
  - *During a Ph II-III study:* primary or secondary surrogate endpoints
  - *After a study:* response signatures (“**retroactive fishing**”) → but retrospective cutoffs or subgroup analyses are difficult to use





## EMEA experience with innovative BMs

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- During marketing authorisation applications
  - e.g. maraviroc (Celsentri) and CCR5
- Post-marketing
  - e.g. abacavir (Ziagen) and HLA-B\*5701
- Exploratory stages, early development
  - in PGWP Briefing Meetings, in many Scientific Advices
- Qualification of Novel Methodologies (new)
  - pilot case (preclinical nephrotoxicity markers - PSTC)
  - ongoing procedures



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- **Biomarkers for drug development**
  - Biomarkers for regulatory decision-making
  - EMEA Briefing Meetings (Pharmacogenomics Working Group) - FDA/EMEA Joint VGDS
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  - The new EMEA (FDA) Qualification Process
  - The need for collaboration




- Have not prevented the high attrition rate in Phase II-III
- Probably because many of them lack predictive power
- Should be refocused towards **clinical success**
- Should be used to improve the learn phase and to design better **dose-response studies** \*\*

\*\* More often cited as a solution by regulatory agencies than by industry



- Should be *qualified* in collaboration with regulatory authorities **at an early stage**
- New technologies (genomics, imaging) as well as Modelling and Simulation create great hopes



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## Biomarkers for marketing authorisations

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- Have a long history (BP, HbA1c, LDL-cholesterol, CD4 cell counts & HIV viral load \*\* ...)
- Have accelerated drug approval (once they were accepted as surrogates)
- Must remain under continuous scrutiny

\*\* Increased sensitivity and decreased variance compared with morbidity endpoints





Even the best surrogates may fail...

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## ***Examples***

- Rosiglitazone and HbA1c (?)
- CETP inhibitors (torcetrapib)
  - CIMT not the best surrogate for atherosclerosis
  - Decrease in plasma lipid levels not always the best surrogate for survival
  - Off-target pharmacological effects (blood pressure)





## Biomarkers for regulatory decisions

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- In the future, could be used more often for
  - enrichment approaches (high risk patients and/or likely responders)
  - staggered approvals (rather than **conditional approvals**) (e.g. imatinib-Gleevec®)
  - safety monitoring
  - personalised medicine





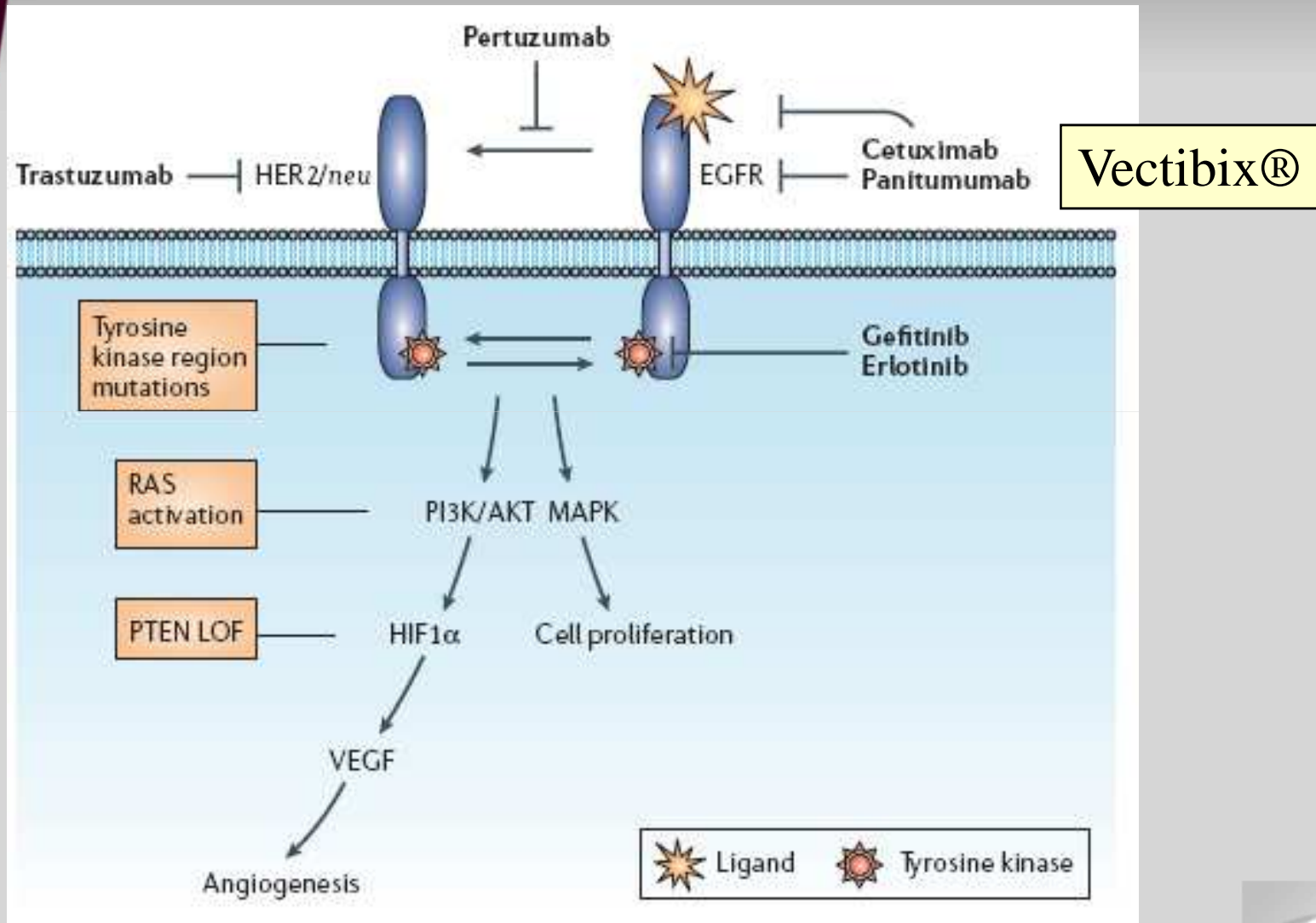
## Biomarkers to define subpopulations - 1

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- May be decided **early on** (if data are available on natural history of disease and its treatment) or **once the studies are completed** (if there is a strong hypothesis that treatment effects and B/R balance differ between subpopulations)
- Statistical approaches exist (including adaptive designs) to analyse BM-defined patient groups as **co-primary populations in clinical trials**
- A **prospective/retrospective approach** (prospective for collection, retrospective for analysis) is considered more and more acceptable (FDA, CHMP)



# Biomarkers to define subpopulations - 2



EGFR+, wild-type k-ras Colorectal Cancer





## Biomarkers to define subpopulations - 3

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*(from the December 16, 2008 FDA Oncologic Drugs Advisory Committee Meeting on kras)*

[...] FDA also recognizes that there may be legitimate reasons for failure to prospectively consider early in drug development the impact of genomic biomarkers, primarily due to advances in the scientific knowledge of a drug or disease that occur while drug development is ongoing. In the latter situation, [...] the levels of evidence needed may differ depending on the claim being sought. For example, **restriction of drug use to patient subsets** to improve safe use of the drug **might not require the same level of scientific rigor** as claims for specific drug benefits.



### 4.1 Therapeutic indications

CELSENTRI, in combination with other antiretroviral medicinal products, is indicated for treatment-experienced adult patients infected with only CCR5-tropic HIV-1 detectable (see section 4.2).

Before taking CELSENTRI it has to be confirmed that only CCR5-tropic HIV-1 is detectable (i.e. CXCR4 or dual/mixed tropic virus not detected) using an adequately validated and sensitive detection method on a newly drawn blood sample. **The Monogram Trofile assay was used in the clinical studies** of CELSENTRI (see sections 4.4 and 5.1). Other phenotypic and genotypic assays are currently being evaluated. The viral tropism cannot be safely predicted by treatment history and assessment of stored samples.



Biomarker

Label Context

# FDA Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels


Examples of  
other Drugs  
Associated with  
this Biomarker

References  
(PubMed ID)

Biomarker	Representative Label	Drug	References (PubMed ID)
<b>C-KIT expression</b>	<b>Gastrointestinal stromal tumor <i>c-Kit</i> expression</b> “ <i>In vitro</i> , imatinib inhibits proliferation and induces apoptosis in gastro-intestinal stromal tumor (GIST) cells, which express an activating c-kit mutation.” “Gleevec is also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).”	<a href="#">Imatinib mesylate</a>	<a href="#">12851888</a> <a href="#">16226710</a> <a href="#">16294026</a>
<b>CCR5 - Chemokine C-C motif receptor</b>	CCR5 is a receptor site on the human T-cell that HIV uses to bind to the cell allowing it to enter and begin replication. “SELZENTRY, in combination with other antiretroviral agents, is indicated for treatment experienced adult patients infected with only CCR5-tropic HIV-1 detectable, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.” “SELZENTRY blocks a specific receptor called CCR5 that CCR5-tropic HIV-1 uses to enter CD4 or T-cells in your blood. Your doctor will do a blood test to see if you have been infected with CCR5-tropic HIV-1 before prescribing SELZENTRY for you.” <b>Pharmacogenomics</b> The impact of CCR5 promoter and coding sequence polymorphisms on the efficacy of maraviroc is being evaluated.”	<a href="#">Maraviroc</a>	<a href="#">17933726</a> <a href="#">17933725</a> <a href="#">17933724</a> <a href="#">17933723</a> <a href="#">17933722</a>
<b>CYP2C19 Variants</b>	<b>CYP2C19 poor metabolizer status</b> is associated with diminished response to Clopidogrel. The optimal dose regimen for poor metabolizers has yet to be determined. (Dosage and Administration-Pharmacogenetics) Based on Literature data, patients with genetically reduced CYP2C19 function have lower systemic exposure to the active metabolite of clopidogrel and diminished antiplatelet responses and generally exhibit higher cardiovascular event rates following myocardial infraction than do patients with normal CYP2C19 function. (Precautions-Pharmacogenetics) CYP2C19 is involved in the formation of both the active metabolite and the 2-oxo-clopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokinetic and antiplatelet effects as measured by <i>ex vivo</i> platelet aggregation assays, differ according to CYP2C19 genotypes. The prevalence of CYP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differs according to race/ethnicity. (Clinical Pharmacology-Pharmacogenetics)	<a href="#">Clopidogrel</a>	





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## Examples of recent discussion meetings

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- Link between genetic markers (e.g., HLA-B1\*501) and severe cutaneous reactions
- Biomarker PCR development programme (pivotal + exploratory) for a new product for metastatic melanoma
- Early exploratory clinical trials of a new Mab intended for the treatment of SLE





U.S. Food and Drug Administration




European Commission



European Medicines Agency

**Guiding principles**  
**Processing Joint FDA EMEA Voluntary Genomic Data Submissions**  
**(VGDSs)**  
**within the framework of the Confidentiality Arrangement**

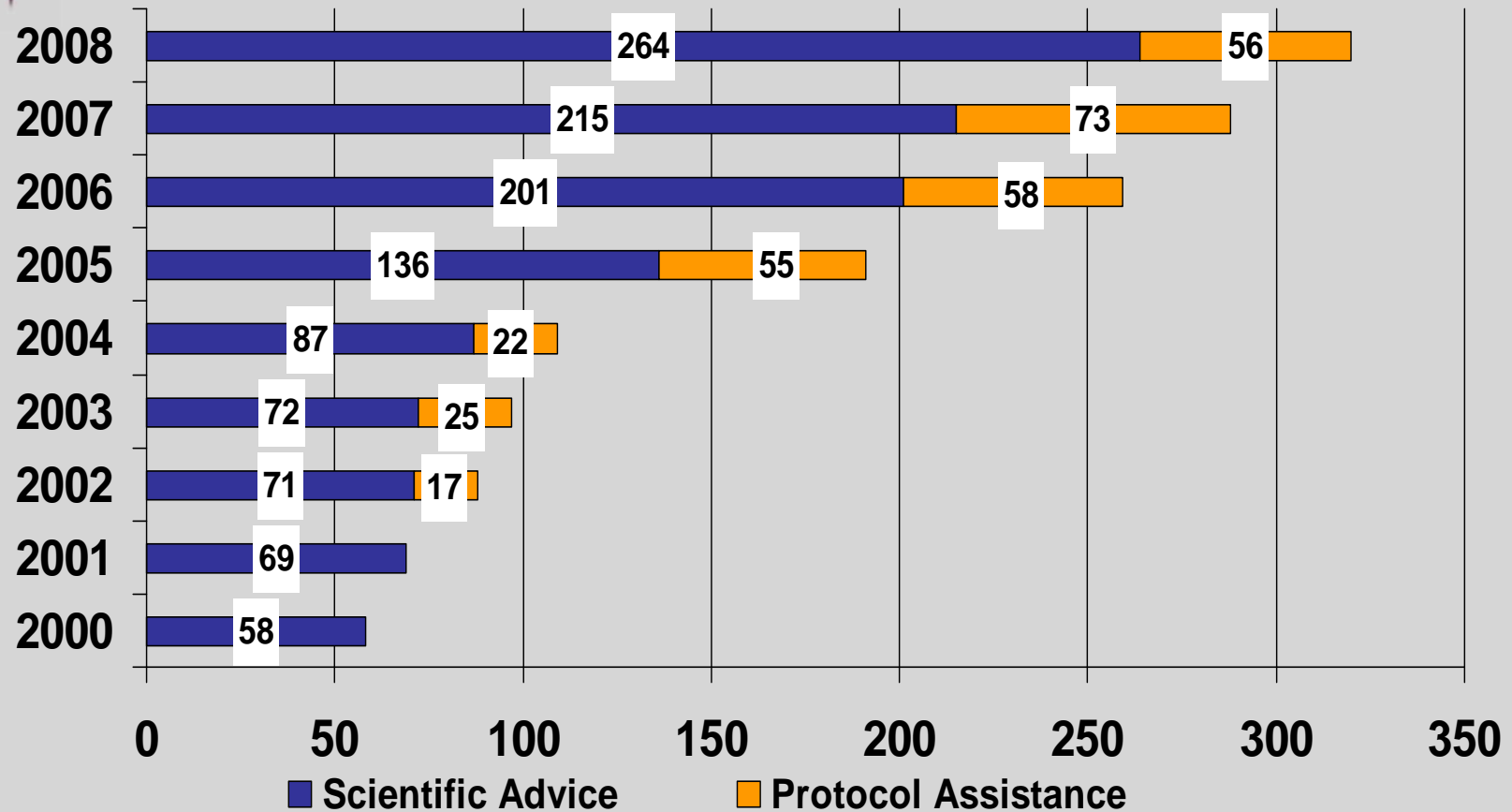


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## Scientific Advice and Protocol Assistance



\* Protocol Assistance = Scientific Advice for Orphan Medicinal Products





## MRI in Ph II study in Multiple Sclerosis

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- Question. Is it acceptable to use % subjects with no new Gd-enhanced lesions on T1 MRI at 3 months (adaptive design to minimise number of patients exposed) as primary endpoint in **Phase II**?
- Answer. Acceptable.





## Major molecular response in CML

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- Question. Major molecular response as surrogate for survival data for CML (Phase III) for a product with a similar mechanism of action as imatinib?
- Answer. Agreed, but the company should keep in mind that this prognostic surrogate endpoint **needs further validation by the secondary endpoint “overall survival”** especially in patients with chronic phase CML. The sample size should be large enough to have 95%CI for response rates that exclude values <20% cytogenetic response in chronic CML and <25%, 15% and 10% in accelerated, blastic CML and Ph+ ALL respectively.





## New product for PET for diagnostic purposes

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- Answer. The Company will have to decide, whether the primary objective is to establish a biomarker that yields information on the pathological staging and whether this should be restricted to de novo patients only, and/or if the clinical relevance of this information will be studied, e.g. to describe the progression of this disorder.







## Some controversial/difficult issues - 1

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- Biomarkers as safety endpoints (e.g. hepatic, renal, vascular injuries)
  - Benchmarking against an infrequent clinical outcome is difficult (high rate of false positives)

Call topic code:	<b>IMI_Call_2008_1_05</b>
Topic title:	<b>Qualification of Translational Safety Biomarkers</b>
Project acronym:	<b>SAFE-T</b>
Project title:	<b>Clinical biomarker qualification via SAFER and FASTER EVIDENCE-BASED TRANSLATION</b>


Call topic code:	<b>IMI_Call_2008_1_08</b>
Topic title:	<b>Surrogate Markers for Vascular Endpoints</b>
Project acronym:	<b>SUMMIT</b>
Project title:	<b>Surrogate markers for Micro- and Macro-vascular hard endpoints for Innovative diabetes Tools</b>

Biomarkers should not be used to:

- Seek a broadened or “personalised” indication in a field where many products are approved

Biomarkers should be used to innovate



- 
- 
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European Medicines Agency  
*Human - Pre Authorisation Evaluation*

London, 13 January 2009

Doc. Ref. EMEA/CHMP/SAWP/72894/2008

**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE  
(CHMP)**

**DRAFT**

**QUALIFICATION OF NOVEL METHODOLOGIES FOR DRUG DEVELOPMENT:  
GUIDANCE TO APPLICANTS**





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

London, 15 December 2008  
Doc. Ref. EMEA/679719/2008 Rev. 1

**COMMITTEE FOR HUMAN MEDICINAL PRODUCTS**

**FINAL CONCLUSIONS ON THE PILOT JOINT EMEA/FDA VXDS EXPERIENCE ON  
QUALIFICATION OF NEPHROTOXICITY BIOMARKERS.**

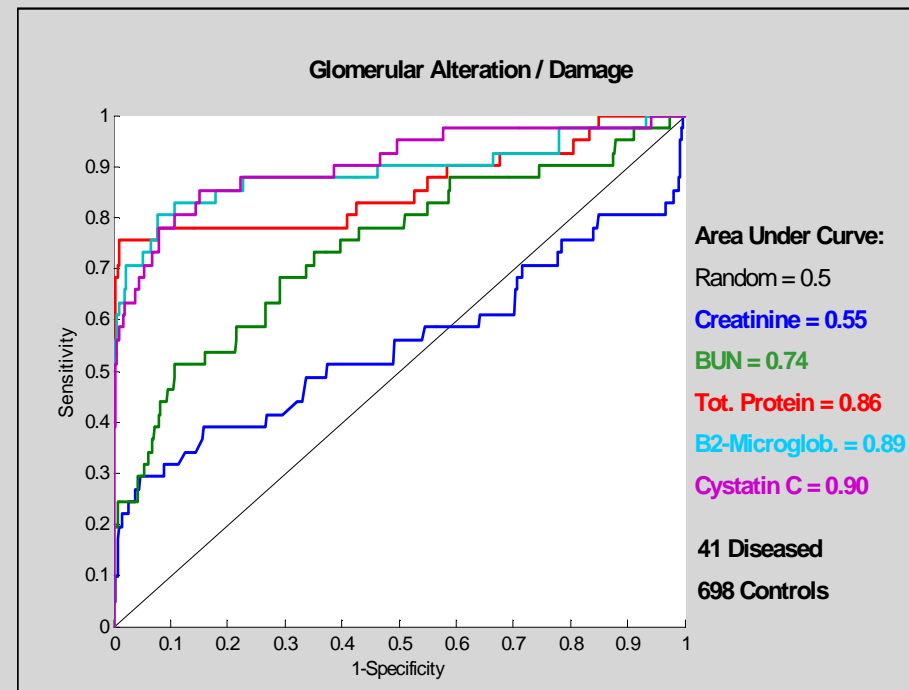
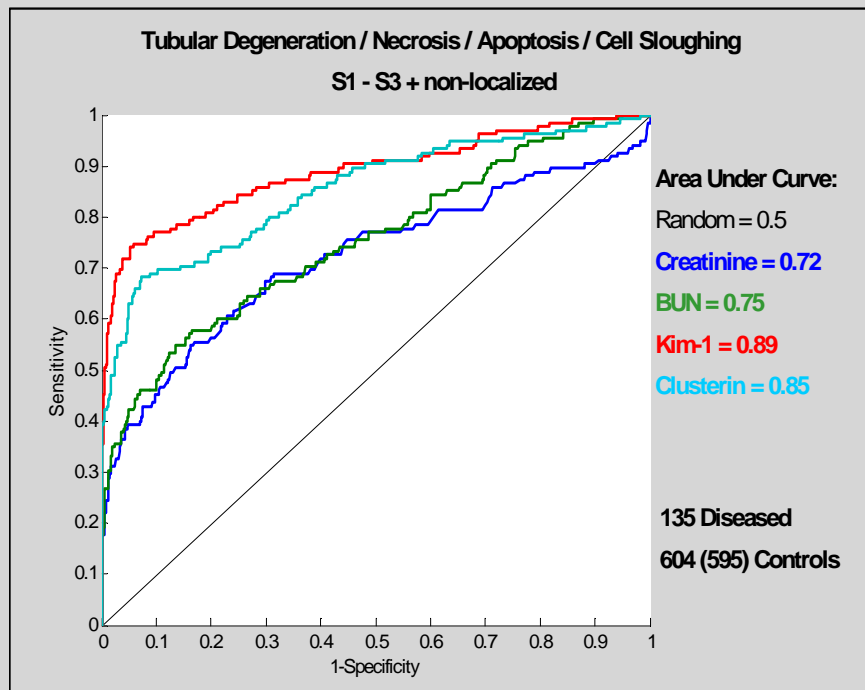
<b>ADOPTION BY CHMP</b>	April 2008
<b>FOR RELEASE FOR CONSULTATION</b>	May 2008
<b>END OF CONSULTATION (DEADLINE FOR COMMENTS)</b>	Extended to July 2008
<b>FINAL DOCUMENT</b>	December 2008



# What is needed for qualification

## Performance of new preclinical urinary biomarkers of nephrotoxicity (PSTC data)

### ROC curves



# Joint FDA/EMA qualification of NTox BM

## Conclusions

### *Non-clinical context:*

- The urinary kidney BMs (Kim-1, Albumin, Total Protein,  $\beta$ 2-Microglobulin, urinary clusterin, Urinary Trefoil Factor 3 and urinary Cystatin C) are considered acceptable in the context of non-clinical drug development for the detection of acute drug-induced nephrotoxicity, either tubular or glomerular with associated tubular involvement.
- They provide additional and complementary information to BUN and serum creatinine to correlate with histo-pathological alterations considered to be the gold standard.
- Additional data on the correlation between the BMs and the evolution and reversibility, of acute kidney injury are needed. Also, further knowledge on species-specificity is required.

### *Clinical context:*

- It is recognised that it is worthwhile to further explore, in early clinical trials, the potential of Kim-1, Albumin, Total Protein,  $\beta$ 2-Microglobulin, Urinary clusterin, Urinary Trefoil Factor 3 and urinary Cystatin C as clinical BMs for acute drug-induced kidney injury. Until further data are available to correlate the BMs with the evolution of the nephrotoxic alterations, and their reversibility, their general use for monitoring nephrotoxicity in clinical setting cannot be qualified.
- The use of these renal biomarkers in clinical trials may 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.



## Potential qualification examples in the CV field

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- Quantitative coronary angiography / measurement of the lumen diameter
- or Intravascular ultrasound / measurement of both lumen and plaque dimensions
  - for evaluating progression of atherosclerosis, assessing the potential incremental benefit of new therapies
- Blood parameters for stratifying the risk of CV events







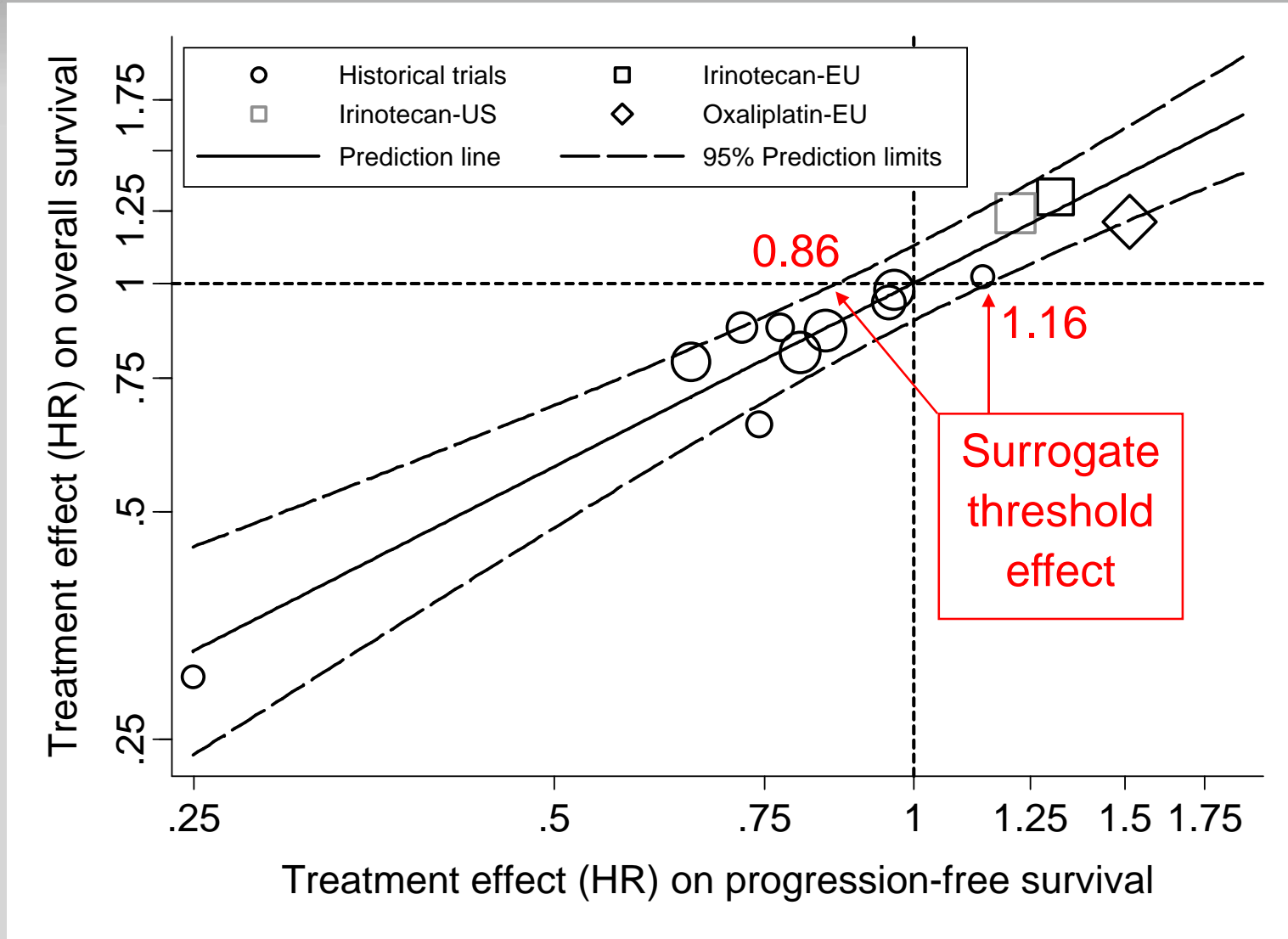
## Potential qualification examples in oncology

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- Level of expression of a certain receptor as parameter for suitability for treatment with a specific receptor antagonist
- Measurement of tumour stem cells in peripheral blood as early sign of metastasis
- *Surrogate Threshold Effect* methodology: treatment effect on the surrogate that would predict a statistically significant treatment effect on the true endpoint (clinical benefit). Examples could include imaging biomarkers (e.g. FDG-PET), histopathology biomarkers (e.g. Ki67), blood biomarkers (PSA), etc.



# Surrogate Threshold Effect for CRC



Adapted from M. Buyse, IDDI, Louvain-la-Neuve, Belgium





## Potential qualification examples in CNS

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- Multiple sclerosis: MRI to correlate with clinical deterioration
- Parkinson Disease
- Alzheimer






## Other potential qualification examples

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- Measurement of a specific pathogen protein in the blood as an early signal of infections that are difficult to diagnose such as lung aspergillosis.
- Expression of interferon  $\alpha/\beta$  - inducible genes in blood to guide dose selection of immunomodulators in autoimmune diseases



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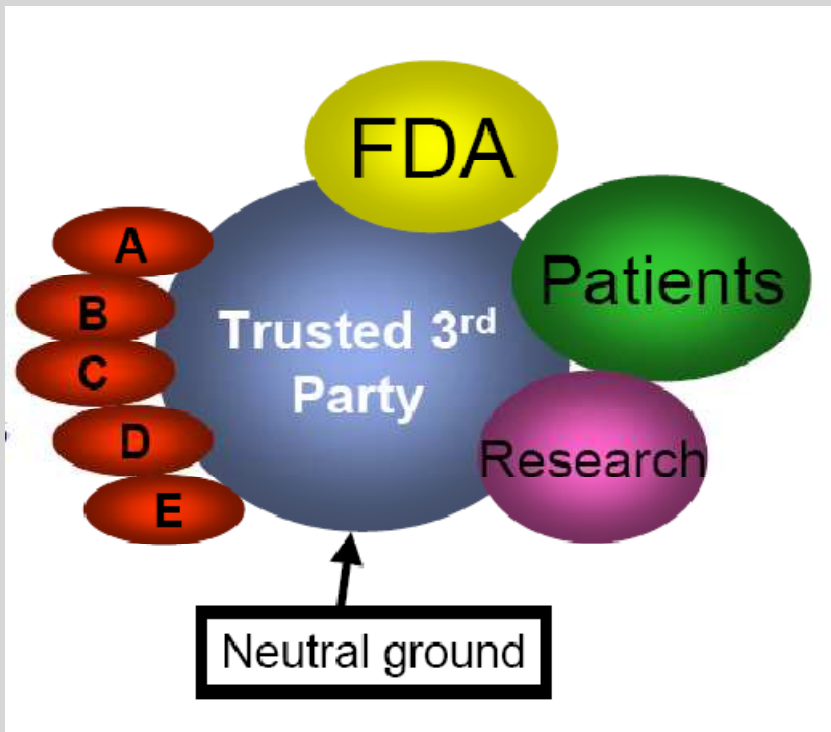


### Critical Path Opportunities List



U.S. Department of Health and Human Services  
Food and Drug Administration  
March 2006

March 2006



efpia



INNOVATIVE  
MEDICINES  
INITIATIVE  
INFORMATION DAY  
30 APRIL 2008

imi



# EMA participation in IMI projects



European Medicines Agency

London, 23 September 2009  
Doc. Ref. EMEA/585460/2009

## **The European Medicines Agency's participation in Innovative Medicines Initiative (IMI) Research projects**

### **The European Medicines Agency's position regarding participation in IMI consortia:**


The agency fully supports the overall goals of IMI, recognising its benefits for public health. We may therefore be willing and able to participate in select projects, contingent upon a number of considerations. These include:

- Resources
- Conflicts of interest
- Relevance to the consortium

[Hans-Georg.Eichler@emea.europa.eu](mailto:Hans-Georg.Eichler@emea.europa.eu)







## Collaboration – issues to resolve

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1. Confidentiality / IP / Antitrust legislation
2. Information sharing / Material transfer agreements
3. Research plan (ideally) agreed with FDA/EMEA
4. Collection and analysis of data
5. Submission for qualification

***Resources!***





# Take home messages





## Take home messages

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1. For regulators, biomarkers are more likely to be useful for enrichment and for safety than for surrogacy
2. They should be assessed, and agreed upon, on an ad hoc basis (in EU: Scientific Advice)
3. The CPI/IMI initiatives and the EMEA (FDA) process for *Qualification of Novel Methodologies* are incentives to collaborate and share data, especially pre-competitive biomarker data





Thank you very much !

