EFPIA POSITION PAPER

THE EFPIA SURROGATE ENDPOINT INITIATIVE

EMEA/EFPIA Workshop on Biomarkers
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Topics for discussion

1. Current situation
2. Agencies perspective and expectations
3. EFPIA Surrogate Endpoint Initiative
4. Industry perspective and expectations
5. EFPIA position paper
6. Examples - similarities & divergences between Europe and the USA
7. Next steps

Current situation

- Biomarkers (BM) are useful in early drug development but less well accepted as surrogate endpoints (SE) for Phase III studies

- Speed up drug development and thereby add to patient benefit by facilitating access to innovative medicines is an issue

When surrogate endpoints are useful,
it is because they are fully validated!

AGENCIES PERSPECTIVE AND EXPECTATIONS

- **In the US, use of SE is an acceptable concept**
  - US regulation enables FDA to grant accelerated MA for certain therapeutic areas
- **In 2004, FDA created the Critical Path initiative**
  - is now playing a pivotal coordinating role in various activities (e.g. National Cancer Institute - use of FDG-PET scan to screen molecules in early Clinical Trials)

AGENCIES PERSPECTIVE AND EXPECTATIONS

- **EU regulation (EC 726/2004) is giving special emphasis**
  - Scientific Advice with its new enlarged framework
  - Conditional Approval offering complex challenging opportunities

- **In December 2005, EMEA has also started consultation**
  - **Contributing to academic meetings (e.g. European Society of Cardiology – imaging biomarkers in atherosclerosis)**

Regulation EC 726/2004

Conditional Approval - Art. 14(7) & Art. 4(c)

"…following consultation with the Applicant an authorisation may be granted subject to certain **specific obligations**, to be reviewed annually… The list of these obligations shall be made publicly accessible (within the SmPC)"

Required clinical criteria to grant conditional approval:

Demonstration of product public health interest, including **unmet medical need**

- ➔ **Presumed positive B/R balance**
- ➔ **Specific Obligations, further studies**
- ➔ **If obligations are not fulfilled, MA will be withdrawn**

THE EFPIA SURROGATE CLINICAL ENDPOINT INITIATIVE

- STRPC Objective for the EFPIA Efficacy AHG
- Nov. 05: questionnaire to survey companies' views
- EPARS survey
- Questionnaire (10 items)
  - 24 responses
  - 20 companies are actively participating
  - Responses analysed and key messages identified
  - To better address needs and way forward

EFPIA Position Paper released in April 2006

EFPIA Position Paper: Some remarks

- BM are useful for drug development and risk estimation, but not as endpoint in the pivotal studies
- SE are primarily important for efficacy reasons
- Position Paper's focus is on SE of efficacy for Marketing Approvals
- Proposals could also apply to other topics, e.g. SE for safety (non-clinical or clinical)

INDUSTRIES PERSPECTIVE AND EXPECTATIONS

- Innovative Medicines Initiative – Strategic Research Agenda
- Companies are ready to actively support EMEA initiatives
- Companies are also expecting a global strategy that is still missing, to better enhance drug market access for patients
- Companies are working on projects with the expectation that BM/SE will be included in MAA

In which areas?

- Diabetes *
- Atherosclerosis
- COPD
- Alzheimer's Disease (brain disorders *)
- Oncology *
- Multiple sclerosis
- Osteoarthritis/Rheumatoid Arthritis (inflammation *)
- Osteoporosis
- HCV infections (antibiotic-resistant Infections*)
- Vaccines

* IMI priorities

➔ High unmet medical need, affecting millions of EU citizens

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

Diabetic retinopathy

- Is an excellent example of the idea that BM and SE are arbitrary points along the same continuum
  - Laser treatment is the only approved therapy
  - Several endpoints could be considered:
    - Retina changes using a scoring system for disease progression
    - Prevention of laser treatment
    - Progression to blindness

  ➔Which is the SE and which is the true endpoint?

- Sustained moderate visual loss - agreed by both EU and US, although not a single approval yet

SOME SUCCESSES

Since 1997, 7 HIV products (Crixivan, Epivir, Norvir, Invirase, Fortovase, Viramune) have been approved using SE data

- **Collaboration between companies and with authorities, was active and useful**
- **Changes in CD4 cell count, viral RNA have been shown to be relevant SE for clinical efficacy**
  - even for combos, prior single ingredient data
  - initially, pending availability of clinical endpoints data, in the context of Exceptional Circumstances approvals
- **Full approval was achieved based on SE data alone, with no requirements for clinical endpoint data**

SOME SUCCESSES

In oncology,

- **FDA and EU have been willing to accept SE (e.g. tumour progression) as alternative to survival outcome, but dependant on the type of cancer**
- **Both agencies in refractory cases expect survival data to be generated ongoing, and have requested studies to be powered for eventual evaluation of survival**

FURTHER EXAMPLES OF EU-US COMMON OPINION

- **Colorectal cancer:** 3-year DFS could replace 5-year OS for adjuvant treatment

- **Breast cancer:** Herceptin - in HER2neu+ patients where evidences that the BM was dividing the population into responders and non responders was quite useful, even if after a few years and still now there is not a major guideline on which type of test to prefer

- **Multiple Sclerosis:** MRI not considered acceptable as SE for efficacy as correlation with clinical endpoint not fully demonstrated

EXAMPLES OF DIVERGENT OPINION

- **Type 2 Diabetes and nephropathy**
  - "Hard" outcomes (death, ESRD or doubling of serum creatinine) in the US while progression to macroalbuminuria can be used in EU *as per* the guideline
  - Irbesartan/nephroprotection - SE accepted by EU and not by FDA

- **Type 2 Diabetes and retinopathy**
  - Use of an anatomic grading scale (Early Treatment of Diabetic Retinopathy-ESRD) as a SE is in the EU guideline while visual acuity is requested by FDA for approval

FURTHER EXAMPLES OF DIVERGENT OPINION

- **For new CV drugs**
  - Imaging might be acceptable (2 complementary studies in 2 vascular beds) by FDA with post-approval commitment for outcomes but unacceptable in EU
  - Five lipid-lowering drugs have a US indication to alter the progression of atherosclerosis as measured with vascular imaging technologies (carotid ultrasound)

CAN WE CLOSE THE GAP BETWEEN EUROPE AND THE US?

- **Recognized differences between US and EU, including aspects of drug regulation and clinical practices**
  - **CHMP have always wanted to see larger response rates to justify the acceptance of SE**
- **FDA/EMEA bilaterals intended to provide transparency and understanding of each Agency's viewpoint**
  - But not intended to mandate unanimity of regulatory decisions

NEXT STEPS

- Developing the use of SE has the potential change the way clinical development and approval assessments are performed
- A challenge for all concerned
- Industry is ready to engage in open and constructive discussion with all stakeholders, to allay regulatory concerns while ensuring high scientific standards
- EFPIA proposals to be discussed further…