EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Harmonization across regions

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Agenda

- Review of Clinical Trial legislation in EU
- Harmonization across regions
  - Early Approval Mechanisms
  - International cooperation
- EU-USA Differences: Examples
- Choice of Primary Endpoints
  - The role of PFS
- Conclusions

Clinical trials in EU

- Protocol design
  - Scientific Advice from EMA optional
  - Advice non-binding on Agency or companies
- Authorisation to conduct trials in EU
  - Requires different national authorisations, approvals
  - No EU-wide approval is available
- All clinical trials submitted must be in agreement with GCP

Implementation of quality systems for clinical trials

- Current manner of implementation is costly and time-consuming
- Major challenge for trials with limited resources
- Reluctance to change current practice for fear of adverse regulatory consequences
- Regulatory environment may be over-interpreted, or misunderstood

EMA Reflection paper on risk based quality management in clinical trials (4 August 2011) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500110059.pdf (Draft)

Over-interpreting The Regulatory Environment

- Excessive data collection for unimportant aspects
- Poor risk identification and poor risk mitigation
- Lack of proportionality (one size fits all)
- Lack of understanding of regulatory guidelines and their flexibility
- Poor design (too complicated, too many objectives)

EMA Reflection paper on risk based quality management in clinical trials (4 August 2011) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500110059.pdf (Draft)

Way forward

- Review of "Clinical Trials" legislation (EU)
  - Risk-based approach
- Optimising the scientific advice process
  - Earlier and more continuous dialogue
  - Involve co-operative groups/academia
  - Parallel advice with FDA
  - Involve payers

Harmonisation Across Regions

The productivity deficit: What can be done?

Reduce development time ?

Reduce cost ?

Reduce attrition ?

Reduce "heterogeneity" of regulatory standards?

What is the root cause of the divergent evidentiary standards? A multi-factorial issue

True biologic differences*
PK (metab. enzyme heterogeneity
PD (beta-receptor responsiveness)

Differences in health-care environment* (disease definition, co-meds)

Political, cultural, traditional "approaches" Value judgements

* ICH E5: Intrinsic, extrinsic factors

Early Approval Mechanisms in EU and US

EU Conditional Marketing Authorisation	U.S. Accelerated Approval
Serious or life-threatening disease, orphan drug, emergency threats	Serious or life-threatening disease
Positive benefit-risk balance but clinical data not complete	Surrogate endpoint likely to predict clinical benefit
Requires confirmation of benefit in post-marketing	Requires confirmation of benefit in post-marketing
Unmet medical needs will be fulfilled	New agent has to be better than “available therapy”

Processes in place to harmonise standards between FDA and EMA

FDA and EMA/EC confidentiality arrangements (since 2004):

- based on the understanding that both agencies share the same fundamental public health mission,
- aim at improving dialogue between us
- have resulted in a range of regular and ad hoc activities ("clusters")

Positive Example: Guidelines

- EMA (2006, 2012). Guideline On The Evaluation Of Anticancer Medicinal Products In Man. Available from: http://www.ema.europa.eu ;
- FDA (2007). Guidance for Industry, Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. Available from: http://www.fda.gov.

Even the best intentions and processes in place will not guarantee full harmonisation

Negative examples:

- **Vorinostat** for cutaneous T-cell lymphomas
  - Primary endpoint: "the response rate of.. "
  - Result: ".. response in approx. 30% of patients"
  - FDA approves Vorinostat
  - EMA/CHMP opinion: "no data on overall survival has been submitted"…"…not considered sufficient to provide evidence to support [approval]"
- Other CTCL/PTCL examples: romidepsin, pralatrexate

Even the best intentions and processes in place will not guarantee full harmonisation

- December 2010: FDA plans to revoke the approval of bevacizumab for breast cancer because new studies did not show improvement in OS or PFS
  - Hearing took place June 28-29, 2011

- December 2010: EMA has confirmed that the benefits of bevacizumab in combination with paclitaxel (but not docetaxel) outweigh its risks
- On 14 April 2011 EMA recommended approval of bevacizumab in combination with capecitabine

- FDA approves ixabepilone for MBC based on PFS improvement (2007)

- EMA refuses to recommend approval of ixabepilone for MBC (2009): benefit-risk balance not positive

EU-USA Differences That Have An Impact On Clinical Practice

Anticancer drugs approved by EMA between 1995 and 2008 (N=100 indications):

- 47/100 different indications EU *v*. USA
  - 19/47 approved only in one of the two regions
  - 28/47 different types of restrictions
    - 15/28 different combinations/lines of therapy
    - 13/28 different target populations
- 69 approved first in the USA (but time lag reducing)

Trotta *et al*. Evaluation of Oncology Drugs at the European Medicines Agency and US Food and Drug Administration: When Differences Have an Impact on Clinical Practice. J Clin Oncol2011 Jun 1;29(16):2266-72.

PFS as primary endpoint in confirmatory trials

Choice of primary endpoint in pivotal confirmatory trials per 5-year period (EMA)

		1995-2000	2001-2005	2006-2010	Total
Endpoint	OS	3 (11%)	10 (19%)	23 (24%)	36 (21%)
	PFS	**6 (21%)**	**14 (26%)**	**46 (49%)**	**66 (38%)**
	ORR	16 (57%)	24 (45%)	19 (20%)	59 (34%)
	Other	3 (11%)	5 (9%)	6 (6%)	14 (8%)
Total		28 (100%)	53 (100%)	94 (100%)	175 (100%)

Recent new drug approvals for cytotoxic/cytostatic agents and new indications for already approved prooducts (source: EMA Scientific Memory Database, I. Gravanis, WIP)

Issues with PFS

OS remains most clinically relevant and convincing endpoint for confirmatory trials

- Use OS when PFS ≈ OS, or major differences in toxicity
- Use PFS when further lines of therapy modify OS

PFS acceptable if it measures clinical benefit (not as surrogate for OS)

- Clinical relevance of PD based on RECIST criteria?
- What is the smallest clinically relevant and convincing effect in terms of PFS?
- Many methodological issues to avoid bias
- **Local evaluation *v.* Blinded Independent Central Review**
- **How much supportive OS data? One-way cross-over after progression**

Conclusions

- Cross-Atlantic synergies through communication, collaboration and cooperation
  - Discussion on guidance and drug evaluation
  - Increased understanding of different viewpoints and regulatory requirements
  - Scientific advice, early approval
- Different outcomes possible in situations where uncertainty is high
  - Value judgements
  - Accelerated *versus* conditional approval
- PFS clinical benefit *versus* likely surrogate

Thank you!

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