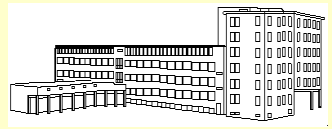


Practical experience from a reviewer

What do I expect?

Giovanni Apolone

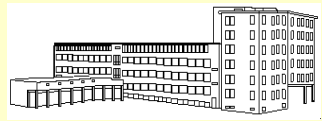
Istituto di Ricerche Farmacologiche

"Mario Negri", Milan - Italy

DIA-ERIQA Workshop

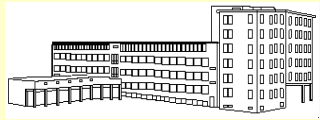
Paris, May 10 2004

Overview



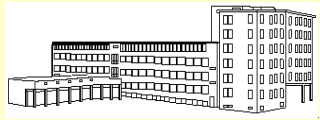
- The speaker
- The context (FDA, EMEA and Italy)
- Requirements for authorization of anti-cancer drugs
- Some empirical data (from FDA, EMEA, an Italian EC)
- Comments and proposals

G. Apolone



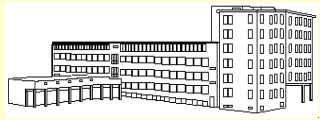
- MD (1982), post doctoral degrees in internal medicine (1987) and clinical pharmacology (1992)
- At IRFMN since 1987
- Training period in U.S.A. (1989-1990)
- Head of Translational and Outcome Research Lab. (LaTOR)
- Expert at EMEA on anti-cancer drugs and HR-QoL (2000-)
- Member (vice-president) of the REC at IEO (1998-)

My experience as reviewer



- Expert in ad-hoc (EWP) groups to prepare/revise NfG (anti-cancer drugs and PRO measures)
- Dossier assessor (anti-cancer drugs)
- EMEA GCP Inspector (in USA)
- Member of an Italian REC (IEO, Milan, Italy)
- Reviewer and Board member for several Scientific Journals

My Conflicts of interests



Research support

- Italian and international Drugs Industries (from A to... Z)
- Public or non-profit organizations (60%)

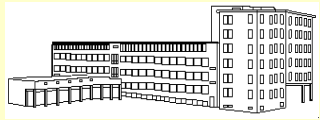
Financial interests

- None

Individual interests

- Paid Consultant for GSK (post-marketing projects)
- Speaker fees from Amgen and NHS Health Authorities

European Drug market (1)



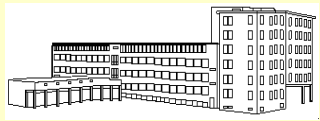
- Ten years ago EU was the pharmaceutical industry bigger market: now USA explains 60% of drugs makers' profit
- A European Agency for regulatory activities since 1995 (EMEA)
- In most countries, governments are cutting drugs prices (Italy):

  7% price cut, maximum reimbursement level, monitoring prescriptions

  5.3% fall in 2003 of state spending on drugs (32.7% rise in 2001)

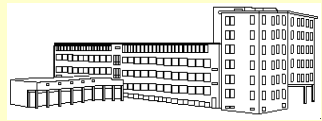
  drugs now accounts for 13.8% of overall healthcare spending (16.3% in 2001)

European Drug Market (2)



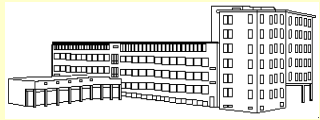
	USA	EUROPE
Share of global market	46%	22%
Health system/coverage	Non universal, mixed (most private)	Universal, state sponsored
DTC advertising	Yes	Banned (only some OTC)
D-to-Physician Ads	Yes(regulated)	Yes (restricted)
Drug price policy/control	None	State controlled

Drugs Approval in Europe



- 1995: creation of the new European Agency (EMEA)
- Since then 2 different possibilities to submit an application
  - » **Centralized procedure (EMEA)**
  - » **Mutual recognition (decentralized)**
- EMEA: scientific evaluation (quality, safety and efficacy)
- European Commission: single market authorization
- At national level: cost, pricing, reimbursement,…

Drugs Approval in Italy



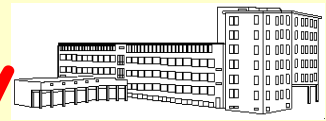
- Before 2002: a dedicated Department at Min. of Health that worked together with other (Government) Institutions

- 2003: creation of a new National Agency for Drug Evaluation

- National ADE: approval, reimbursement, monitoring, interactions with Europe and Regions (that have fully accountability of regional drug market)

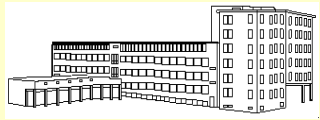
- Poor impact of EMEA on Italy: in 2001, 80% of out of

Research Ethics Committees in Italy



- 1998: **decentralization** of protocols evaluations (from central to local REC)
- 1998-2000: Publication of **new guidelines** for REC mission, structure, and functioning
- Activities: RECs **review and evaluate protocols**, educate health professionals, provide consultation for individual cases, provide ethical input for hospitals policy
- Now, about **280 RECs** !

Efficacy measures in CT

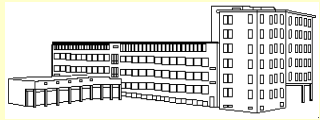


- (Regular) Marketing approval requires substantial evidence about safety and efficay

- Efficacy= Clinical benefit= Life prolongation or Life improvement

- The true/final endpoints are: Survival and/or better (quality of) life

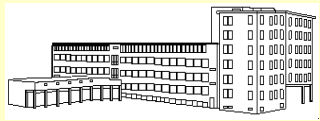
Differences between US and EU



- Minimal until 1992-1997: at least 2 RCTs (III) showing an extension of life and/or better life

- Major since 1997: "…FDA has changed its philosophy about how much and what information is needed…"

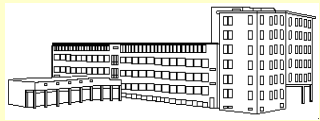
Difference between FDA and EMEA



- FDA: Possibility of fast track, priority review, and accelerated approval (in certain circumstances)
  - use of surrogate endpoints and SAT (with further confirmative studies)

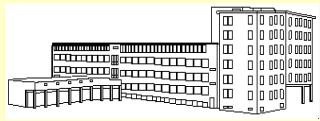
- EMEA: Less explicit regulations on "quick procedures" with a more conservative attitude (need of phase III RCT)
  - expedited "approval" and SAT (surrogate endpoints) only in exceptional circumstances

EMEA Requirements for authorization



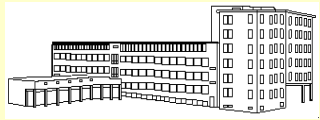
- In general, Phase III randomised comparative studies are required
- In exceptional circumstances, when full comprehensive data are not available,...
- ...Phase II (SAT) studies may be considered,...
- **Anti-cancer drugs: In previously treated patients, no existing established regimen,** only in very specific circumstances

Efficacy measures in oncology (anti-cancer drugs)



- Biologic activity in Phase II CT (Response rate, quality and duration of response)
- Survival or improvement in patients' symptoms in Phase III RCT
- DFS in adjuvant setting
- In specific circumstances: impressive/outstanding tumor-related outcomes (complete response with reasonable duration)
- **(HR)-QoL to support tumor shrinking or toxicity or symptoms**
  (EMEA: either in Phase II/III as primary endpoint, but justified case per case)

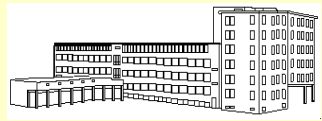
FDA and EMEA: an evaluation



- FDA: *JR Johnson et al*, JCO 2003; 7: 1404-1411

- EMEA: *S. Garattini, V. Bertelè*, BMJ 2002; 325:269-271

Approval of Oncology drugs: FDA

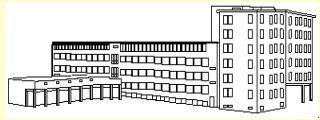


- Evaluation of endpoints used by FDA over the last 13 years
- 71 oncology drug applications (1990-2002)
- Tumor response endpoints in 26/57 (46%) RA applications
- Tumor response endpoints in 12/14 (86%) AA applications

- **Overall, SAT (Phase II) 24/71 (34%) of cases!**

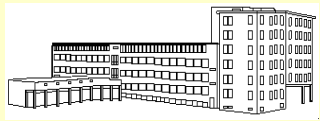
- **No approvals were based on HRQOL measures...!**

Approval of Oncology drugs: EMEA



- Evaluation of endpoints used by EMEA over the last 6 years
- 14 "new" oncology drug applications (1995-2000)
- Most of the first applications in second/third lines
- Tumor response endpoints in 6/14 (43%) applications
- **Overall, SAT (Phase II) 6/14 (43%) of cases !**
- **No approvals were based on HRQOL measures...!**

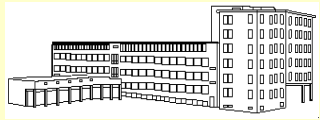
Reasons for NOT using HR-QoL



- Cumbersome and costly
- Complex methodological and statistical methods (compliance, missing, timing)
- Questionable "clinical" validity of questionnaires
- Difficult to "interpret" (meaning of findings)
- Lack of blinding/masking

PROBLEM: The alternatives are worse

Surrogate endpoints for efficacy in CT

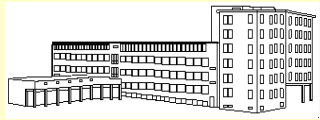


- When the objective is "to cure": RR (CR), TTP

- When the objective is "to prevent": incidence, type of recurrence (site, symptomatic status), DFS

- When the objective is "palliation": survival benefit, ad-hoc (compound) Clinical Benefit Measure (CBM), tumor response

Unrealistic survival benefits



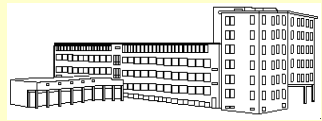
- In most phase III CT in advanced disease, survival benefit (i.e., difference between arms) is about 7-9 weeks (median)

- When asked to indicate the minimum survival benefit to accept side effects (for a 3-month survival benefit) only 22% chose chemotherapy againts BSC,* and…

- 68% chose chemotherapy if substantially reduced symtoms without prolonging life*

* In NSCLC, Silvestri et al, *BMJ*, 1998, 317: 771-775

Biased Tumor-Based Response in CT



Phase II

Most studies are SAT, non-controlled and non-masked

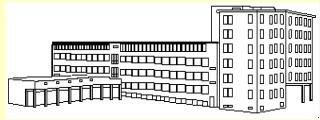
"Content and Quality of currently published phase II cancer trials" Mariani L and Marubini E. *JCO* 2000; 18: 429-436.

Phase III

Most studies have non-placebo and non-blinded design

"Does a drug do better when it is new? Fossati R, Confalonieri C, Apolone G, Cavuto S, Garattini S" *Annal Oncol* 2002; 470-473,

Unvalidated CBM measures in CT



- Composite endpoints, assembled with few variables based on patients and/or physicians subjective ratings or reports, to surrogate Quality of Life or "symptomatic" clinical benefit improvement

  - Burris et al in pancraetic cancer*, *JCO* 1997; 15: 2403-2050

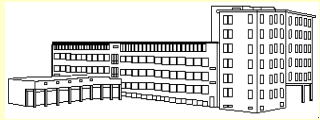
  - Vansteenkiste et al in NSCLC**, *Ann Oncol* 2001, 12: 1221-30

  - A few other examples in advanced breast cancer (hormone therapy) and prostate cancer (Skeletal Related Events)

*pain score, performance status and weight

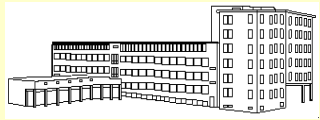
** lung cancer specific symptom score, KPS, weight

Experience at REC



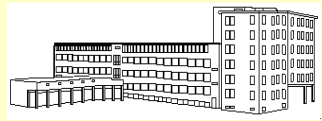
- Since 1998: 175 CTs submitted (most phase III, all on drugs)
- In most Phase III CTs, formal HRQOL measures are included as secondary/supportive endpoints
- Never as primary endpoint
- This aspect of the CTs has generally not been well conducted
- Most frequent problems: lack of blinding/masking
- But also: Lack of analytic plans prospectively detailed, power

What do I expect?



- Well defined prospective analytic plans
- Use of well-established measures
- Adequate sample size/power
- Implementation of blinding/masking
- Handling/control/discussion of missing data
- Discussion of credibility (clinical meaning) of results

What do I need?

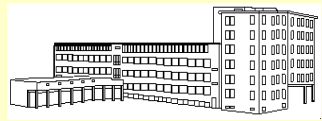


A consensus about how to do this kind of research

A guide (check-list) to evaluate/judge protocols

Training of evaluators/decision makers (regulators)

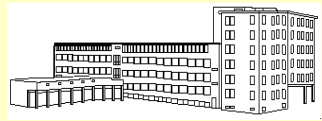
What do I have?



Several (not really different) published tools (check lists)

Forthcoming Guidelines from FDA and EMEA

Acknowledgements and Disclaimers



- This presentation was written in Dr Apolone's private capacity and the views expressed do not necessarily reflect those of IRFMN or EMEA

- Part of the slides used are from documents and reports produced in the context of a IRFMN project partially sponsored by SENDO (South Europe New Drug Organization)