Disclaimer

- The views expressed in this presentation are the personal views of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or of its committees or working parties.

Freedom of Information – Recent History

- In the EU the widest possible public access to European Parliament, Council and Commission documents is addressed in a 2001 regulation (1049/2001).
- In the UK the FOI act (2000) came into full force in 2005
  - Provides general right of access to information from local and central government and publicly owned companies – exceptions commercial sensitivity, national security.
- Other EU countries have equivalent national legislation
- These acts reflect a change of paradigm in public perception concerning information.
  - FROM: Why SHOULD we give access to information?
  - TO: Why should we NOT give access to information?

Re-evaluation of data access at EMA

- Requests by Nordic Cochrane Centre in 2007 for access to study reports on weight loss drugs led to EMA reassessment of procedures in light of ruling by European Ombudsman
- The ruling helped to define criteria for release of such reports and the thresholds were clearly lower than applied by EMA in 2007
- In addition, the question of exactly what information could be supplied to external researchers became a more pressing concern. In particular the question of individual patient data – not routinely supplied to EMA but not necessarily excluded – had to be addressed.

Implementation at EMA

On 10 April 2012 the European Medicines Agency (EMA) announced that it would proactively publish clinical trial data and enable access to full data sets by interested parties.

OPEN ACCESS Freely available online

PLoS MEDICINE

Perspective

Open Clinical Trial Data for All? A View from Regulators

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Advantages of FOI to clinical trials data

- Accountability
- Improve public trust
- Openness about what information are available
- Allow additional analyses to promote public health

What are the concerns about FOI to clinical trials?

- Identification of patients
- Commercial opportunism
- Multiplicity
- Regulators errors open to scrutiny

This should be seen as an advantage!

Draft Policy 70: Publication and access to clinical-trial data.

On 24 June 2013 the European Medicines Agency published for consultation its policy concerned with making available information from clinical trials. In particular, it covers release of data in an analysable form.

Some factors for further discussion:

- Enabling public scrutiny and secondary analysis of CTs
- Protection of personal data
- Respect for the boundaries of patients' informed consent
- Ensuring future investment in bio-pharmaceutical research and development
- Addressing the consequences of inappropriate secondary data analysis
- Protecting the Agency's and the European Commission's deliberations and decision making process

EMA Public Consultation

Prior to the draft policy, in early 2013, the EMA undertook an open consultation regarding 5 key areas related to data access

- Protecting patient confidentiality
- Clinical trial data formats
- Rules of engagement
- Good analysis practice
- Legal aspects

The objective was not to reach consensus but to sound out a wide range of stakeholders concerning areas of contention. However, when consensus existed this was also of interest.

Opinions received specifically concerning patient level data

- Fully de-identified patient-level data may compromise analytical validity
- Access to patient-level data should be allowed under pre-defined rules
- Consultation with MAH before data disclosure
- Divergent opinions on need for identification of requesters
- Agreement to respect personal data protection
- Agreement to refrain from unintended commercial use
- Preparation of a protocol before analysis by the data requester
- What guidelines should be followed, e.g. CHMP guidelines
- Relevant expertise in requester team, e.g. statistician or epidemiologist
- Modifications to data or code should be made public

FDA committed to similar consultation on when sponsors should release data

- **FDA should convene a group of internal and external stakeholders to discuss the possible uses of non-summary safety and effectiveness data from product applications, the circumstances under which it would be appropriate for sponsors to disclose non-summary safety and effectiveness data from applications submitted to FDA, and if appropriate, the format and the method by which disclosure should occur.**

Draft proposal 17 of Phase II transparency report May 2010

FDA Rationale

***Reasoning*:** A different balance may be struck with respect to the disclosure of non-summary safety and effectiveness information. A blanket policy against disclosure of this type of information may not be justified because there are significant public health benefits associated with the disclosure of this information, including reducing the costs and increasing the efficiency of research.

But given the nature of the information, other factors may weigh more strongly here. For example, the timing of any disclosure, the potential uses for this information, the means by which disclosure would occur, and the impact disclosure may have on innovation, may lead to a different balance regarding the disclosure of non-summary safety and effectiveness data.

Briefly return to contrasting features of reports and patient level data

1. Making clinical trial reports public
    - Basis for current licensing decisions
    - Selected information
    - Safeguards against post-hoc analyses
2. Giving access to machine readable datasets
    - Not yet routinely collected in Europe
    - Appreciably more information
    - Concerns over inappropriate use

What is an RCT report?

1. A report contains the results of a series of calculations carried out on the raw data.
   - View 1: Hones in on important messages and eliminates noise
   - View 2: Only examines selected aspects and hides uncomfortable truths
2. A more balanced view is that RCTs are generally analysed with the intention of providing useful information to aid treatment and licensing decisions BUT that large amounts of information contained in the original data are excluded.

What information is only available from the raw data?

1. Much of the information about distribution of variables and, in particular, outliers.
2. The correlation structure of the variables
3. The set of values relating to an individual (de-identified) patient

Does this matter?

- Do we hope for personalised medicine?
- Do we believe that we should try to handle adverse drug reactions at an individual level?
  - Predictability – allows appropriate monitoring of patients
  - Potential for restrictions to use by subgroups rather than withdrawal
- If the answer to these questions is yes then knowing information at the level of the individual is important.

Some thought on multiplicity

Wider access to RCT data will encourage more analyses. But:

- Data collected under controlled conditions
- Everyone has the same data
- Recommendations of Good Analysis Practice
- Preparation of a protocol before analysis by the data requester
- Guidelines should be followed, e.g. CHMP guidelines
- Relevant expertise in requester team, e.g. statistician or epidemiologist
- Modifications to data or code should be made public

Everyday in Pharmacovigilance

- Multiple sources of data – of different types and sometimes of low quality
- Multiple study designs
- Multiple analysis methods
- Multiple outcome variables
- Multiple covariate adjustments
- Often no protocols!
- BUT
- The effort of evaluating these is the price paid for looking for unpredictable safety problems

Multiplicity is a fact of life in drug safety regulation. We can live with a bit more!

- These are not new data. They are already available to the MAH. Competent analysts have already spent many hours examining the data and hence ‘surprise’ results should be less likely here than in Electronic Health Records or ADR reports.
- They should be the highest quality data
- High transparency will promote rational debate

- Overall we expect a positive effect BUT monitoring and evaluation are essential.

Conclusions

- Release of data has the potential to make a positive contribution to public health
- It allows analyses that cannot be performed from study reports
- It allows access to high quality controlled safety data that can set findings from less reliable data sources in context
- It permits individual patient meta-analyses
- Concerns exist the impact of which is difficult to quantify but these should be evaluated against the public health benefits.

THE END

Good Analysis Practice -Status

1. Agency will document and disseminate expectations concerning GAP
2. Chief component is complete transparency. Eg:
   - Any omissions or changes to data
   - Definitions of variables
   - Pre-specified analyses and associated computer code
3. Agency cannot enforce adherence but:-
4. Failure to follow GAP recommendations or justify departures will undermine credibility of research

Article 8 of Directive 2001/83/EC

3. The application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I:

(i) Results of:

- pharmaceutical (physico-chemical,

biological or microbiological) tests,

- pre-clinical (toxicological and

pharmacological) tests,

- clinical trials.

What are the 'Results' of a clinical trial?

MODULE 5 of Annex 1

Reports of Efficacy and Safety Studies

— Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

— Study Reports of Uncontrolled Clinical Studies

— Reports of Analyses of Data from More than One Study including any formal integrated analyses, meta-analyses and bridging analyses

— Other Study Reports

— *Reports of Post-marketing Experience*

a) The clinical particulars to be provided pursuant to Articles 8 (3) (i) and 10 (1) must enable a sufficiently well-founded and scientifically valid opinion to be formed as to whether the medicinal product satisfies the criteria governing the granting of a marketing authorisation.

Consequently, an essential requirement is that the results of all clinical trials should be communicated, both favourable and unfavourable.

John Castellani, president and chief executive officer, Pharmaceutical Research and Manufacturers of America (PhRMA)

- Dumping millions of pages of clinical trial information into the public domain without providing appropriate scientific and clinical context or guidelines for meta-analysis could lead to second guessing* of the expert decisions of national regulators worldwide, undermining patient trust and confidence in the safety and effectiveness of approved medicines.

- Mandatory public disclosure of intellectual property, confidential commercial information, and proprietary scientific methods found in clinical trials could stifle discovery and open the possibility of competitors or unscrupulous actors using the information for their own products in other markets or countries. Without appropriate protection for intellectual property to incentivize the enormous investment risk involved, biopharmaceutical companies will be discouraged from investing in the next generation of new medicines, leading to patients and physicians being deprived of innovative therapies to tackle the serious and life threatening diseases of the 21st century.

* to use hindsight in criticizing or correcting.

Ben Goldacre

- When discussing transparency it is important to be clear on what is being requested, as obfuscation is sometimes used to avoid discussing simple fixes. At stake are four levels of information about trials: (1) knowledge that a trial has been conducted, from a clinical trials register; (2) a brief summary of a trial's results, in an academic journal article or regulatory summary; (3) longer details about the trial's methods and results, from a clinical study report where available; (4) individual patient data. The AllTrials campaign calls only for the first three to be published.