Regulatory Requirements

CTTI Quality by Design Workshop 20-21 September 2012

Bethesda, MD

Fergus Sweeney, Head, Compliance and Inspections, European Medicines Agency

Disclaimer

The views presented in this presentation/these slides are those of the author and should not be understood or quoted as being made on behalf of the EMA and/or its scientific committees

Regulatory Requirements and guidelines for quality of design

* Directive 2001/83/EC Annex 1
* Directive 2001/20/EC and directive 2005/28/EC
* General guidelines – GCP, Statistical analysis, Clinical study report, Clinical trials in paediatric or elderly populations
* Guidelines on clinical development of medicinal products in specific therapeutic areas
* Scientific advice (non-binding) – optional possibility for sponsor to seek scientific advice on the development of a medicine - clinical, pre-clinical, pharmaceutical

Defining Quality

* Quality sufficient to support the decision making process on medicines throughout the clinical development and use post-marketing authorisation
* Collecting data, generating information, enabling decision making by:
  * Sponsors
  * Ethics Committees
  * Regulators
  * Investigators
  * Healthcare professionals
  * Study subjects
  * Patients

Ensuring:
- Subject rights, safety and welfare
- Robustness of data

Regulatory requirements

* Directive 2001/83/EC – Annex I
* " In assembling the dossier for application for marketing authorisation, applicants shall also take into account the scientific guidelines relating to the quality, safety and efficacy of medicinal products .. as adopted by .. CPMP.. and published by .. EMEA .. and the other pharmaceutical Community guidelines published by the .."

Directive 2001/83/EC – Annex I ../..

* All information, which is relevant to the evaluation of the medicinal product concerned, shall be included … whether favourable or unfavourable to the product. In particular, all … clinical test or trial relating to the medicinal product and/or completed trials concerning therapeutic indications not covered by the application.

Directive 2001/83/EC – Annex I

* All clinical trials, conducted within the [EU] must comply with the requirements of Directive 2001/20/EC …….clinical trials, conducted outside the [EU], which relate to medicinal products intended to be used in the [EU], shall be designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki.

Directive 2001/83/EC – Annex I

The particulars of each clinical trial must contain sufficient detail to allow an objective judgement to be made:

- the protocol, including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investi- gational medicinal product used
- audit certificate(s), if available
- the list of investigator(s), and each investigator shall give his name, address, appointments, qualifications and clinical duties, state where the trial was carried out and assemble the infor- mation in respect of each patient individually, including case report forms on each trial subject
- final report signed by the investigator and for multi-centre trials, by all the investigators or the co-ordinating (principal) investigator.

Details on the types of studies and content of study reports also set out.

Directive 2005/28/EC - GCP

Article 2

1. The rights, safety and well being of the trial subjects shall prevail over the interests of science and society.

2. Each individual involved in conducting a trial shall be qualified by education, training, and experience to perform his tasks.

3. Clinical trials shall be scientifically sound and guided by ethical principles in all their aspects.

4. The necessary procedures to secure the quality of every aspect of the trials shall be complied with.

../.. Directive 2005/28/EC - GCP

Article 3 The available non-clinical and clinical information on an investigational medicinal product shall be adequate to support the proposed clinical trial.

Clinical trials shall be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996).

Article 4 The protocol referred to in point (h) of Article 2 of Directive 2001/20/EC shall provide for the definition of inclusion and exclusion of subjects participating in a clinical trial, monitoring and publication policy.

The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial.

../.. Directive 2005/28/EC - GCP

"Article 5 All clinical trial information shall be recorded, handled, and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected."

PLUS Sections on Sponsor, Investigator Brochure, Trial Master File and Archiving, Manufacturing and Import, Inspection.

But all are similar high level. Detail is in guidance and the guidance allows significant flexibility.

Regulatory requirements for clinical trial design

Legislation is general – broad principles.

More information is in guidance – offers considerable flexibility, and reasonable departures, better alternatives can be justified case by case.

An awful lot of detail is in established practice, perceived requirements, "the oral and written culture" which is very open to change. Many of the issues lie in this "cultural" category as do the obstacles to change.

Current Developments

Current developments – helping to make that flexibility clear and put into practice

- EU GCP IWG/CTFG Reflection paper on risk based quality management
- OECD Draft Recommendation on risk based approach endorsed – work on final text in progress
- FDA Draft guidance on monitoring
- EU GCP IWG / CHMP draft "Points to consider on GCP inspection findings and the benefit-risk balance"
- EU Draft regulation on clinical trials published

Draft "Points to consider on GCP inspection findings and the benefit-risk balance"

- Agreed by GCP IWG, for discussion/adoption by CHMP October 2012. Publication once adopted.
- Discussion paper on key GCP inspection issues impacting risk / benefit considerations by CHMP.
- Objective - to assist inspectors and assessors in evaluating the consequences of inspection findings in relation to the benefit-risk balance. Building prioritisation and risk assessment into conclusions and decisions based on inspection.
- Three categories are used:
  - Inspection findings which are likely to influence the benefit-risk evaluation
  - Inspection findings which may influence the benefit-risk evaluation
  - Inspection findings which are less likely to influence the benefit-risk evaluation

Introduction

- Many non-compliances may result in increased variability/reduced precision
- May blur real differences between treatment groups
- For superiority studies , if superiority has been established, non-compliances which increase variability, but not introducing bias favouring one treatment over the other are relatively unproblematic
- For non-inferiority studies. Increased variability may disguise a real difference between products. On the other hand, increased variability tends to widen the confidence interval for the mean difference/ratio between the test and comparator making the non-inferiority claim more difficult to obtain.
- Non-compliance in the intermediate and low-impact category may not affect the benefit-risk assessment looked upon in isolation,
- Following slides indicate common findings or findings that are considered illustrative, not an exhaustive list.

Ethics

* The European legislation requires not only valid clinical data for the scientific evaluation of the benefit-risk balance, but also ethical conduct of the clinical development programme in order to ensure that the rights, safety and well being of the trial subjects are protected.
* Major ethical flaws should have an impact on the final conclusions about approvability of an application. Consequently, ethical misconduct could result in rejection of the application.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 4 August 2011
2 EMA/INS/GCP/394194/2011
3 Compliance and Inspection

4 Reflection paper on risk based quality management in 5 clinical trials

6 Draft

7

Draft Agreed by the CTFG[1] for release for consultation	31 May 2011
Draft Adopted by the GCP Inspectors Working Group for consultation	14 June 2011
End of Consultation (Deadline for Comments)	15 February 2012

FEEDBACK RECEIVED – VERY WELCOME -

Focus more on trial protocol design and clinical implications.

Sponsored trials - more attention should be paid to academic trials

Describe central monitoring…

Encourage use of technological advances

Standardise/harmonise risk based monitoring approaches put forward by EMA and FDA

Need for standardization, protocols, data collection tools, reporting formats…

Examples of tolerance limits, windows.. Protocol specific and general approaches.

There are also risks linked to data analysis and reporting receive too little attention.

- First Stakeholder Workshop May 2012
- Finalize and publish Q1 2013
- Establish and share experience – Case Study Workshop – Q1 2013

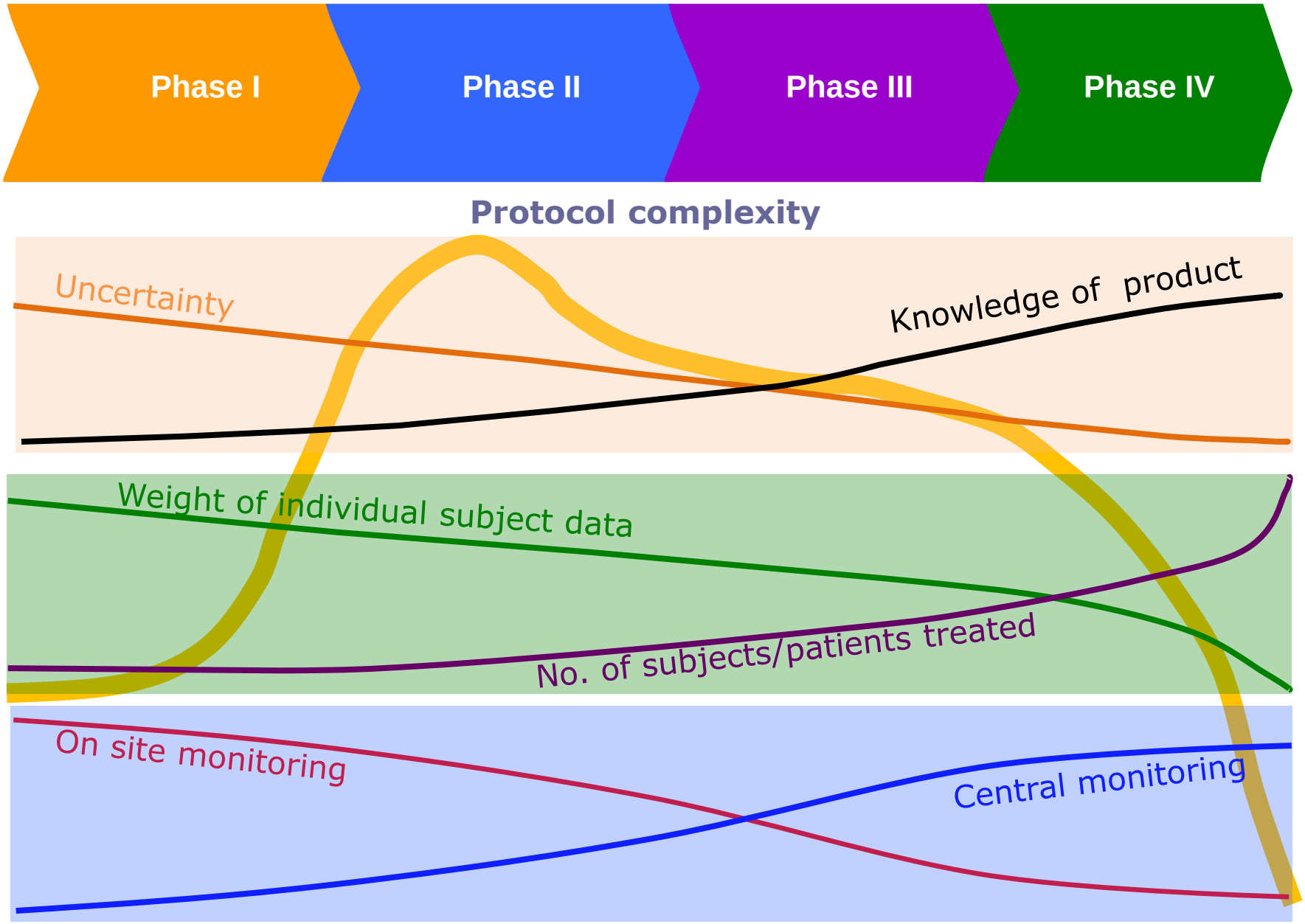
Draft regulation on clinical trials

Key features:

- Single dossier, single application portal for EU, encompassing regulatory and ethics review.
- Joint assessment of core information Part 1 between involved member states and national assessment of Part 2. Single decision per trial and per member state.
- Low intervention trials – marketed product within SPC or established medical practice – rapid assessment, dossier is simple, additional labeling only if required by study design.
- Emergency treatment trials
- Insurance, labeling

Introduced by EU Commission to Council of Member States and then EU Parliament for co-decision

Thoughts for the day and for the future



N.B.: The form of the curves, crossover, etc. are not based on specific data.
This is purely illustrative for discussion. Actual situation will vary case by case.

Prioritise

Design

Anticipate

Assess risks, accept or mitigate

Revise design

Implement

Train, Do, Check, Review, Adjust

Train, Do, Check, Review, Adjust

Don't just think of Corrective Action –
implement with **Preventive Action**

“Perfection is achieved, not when there is nothing more to add, but when there is nothing left to take away.” —

Antoine de Saint-Exupéry,

Thank you – questions – suggestions

Suggestions for next steps, case study workshops, Q and As etc
Email to
GCP@ema.europa.eu
and cc:
Noemie.Manent@ema.europa.eu

Subject line – Risk based quality management