EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Compliance check and validation

Presented by: Peter Karolyi
Paediatric Medicines Section

An application for marketing authorisation under Article 6 of Directive 2001/83/EC in respect of a medicinal product for human use which is not authorised in the Community at the time of entry into force of this Regulation shall be regarded as valid only if it includes, in addition to the particulars and documents referred to in Article 8(3) of Directive 2001/83/EC, one of the following:

(a) the results of all studies performed and details of all information collected in compliance with an agreed paediatric investigation plan;

Validation (of MAA or variation)

An application for marketing authorisation under Article 6 of Directive 2001/83/EC in respect of a medicinal product for human use which is not authorised in the Community at the time of entry into force of this Regulation shall be regarded as **valid only if it includes**, in addition to the particulars and documents referred to in Article 8(3) of Directive 2001/83/EC, one of the following:

(a) the results of all studies performed and details of all information collected in compliance with an agreed paediatric investigation plan;

Compliance check

An application for marketing authorisation under Article 6 of Directive 2001/83/EC in respect of a medicinal product for human use which is not authorised in the Community at the time of entry into force of this Regulation shall be regarded as valid only if it includes, in addition to the particulars and documents referred to in Article 8(3) of Directive 2001/83/EC, one of the following:

(a) the results of all studies performed and details of all information collected **in compliance with** an agreed paediatric investigation plan;

Compliance check

Principles:

- Administrative check
- Judged as "black or white"
- Non negotiable
- Not an assessment (only exceptionally)

A prerequisite of validation, consequently:

- A "high-level" check and/or parallel process to validation are legally not feasible

Compliance check – what's new?

(not too much, really)

- New guidance provides more clarity on principles and practice
- Distinction between "full" and "partial" check
- Improved procedural guidance and forms
- Clarification of the scope ("concerned" condition only)
- Clarification on the effect of deferral

Compliance checks

- EFPIA: low percentage (5.5% on 54 total) of negative compliance check =
  - ✓ 3/17 final/full CC
  - ✓ 0/34 interim CC
- EMA: 3.8% on 104 total =
  - ✓ 1/25 final/full CC
    (positive after modification)
  - ✓ 3/79 interim CC
    (1 positive after modification, 2 are recent - 2011)
- Good agreement of data, good compliance, good results!

Compliance check – what went wrong?

Only one full compliance check with negative outcome:

- A blood test replaced by another similar one
- No balanced age distribution as required
- Delay of three weeks

- Deviations were accepted retrospectively in a modification procedure
- Compliance confirmed in a new compliance check procedure

- Could have been prevented by a modification request on time

Compliance check – what went wrong?

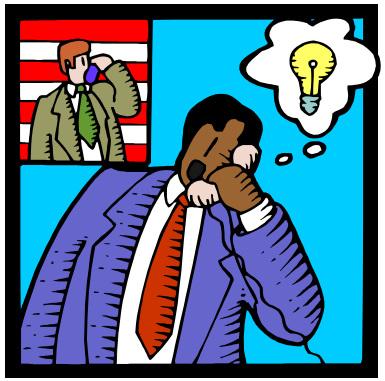
Examples of partial checks with negative outcome:

- Deviation in sample size:
  - "At least 200 evaluable patients. 50 patients per each treatment group."
  - Result: 201 patients: 51+54+48+48
- Deviation in study population (age) (and several other deviations…):
  - "Healthy 2-month-old infants (55 to 89 days of age, inclusive)"
  - Result: Some infants enrolled were slightly older (max 97 days)
- Missing endpoint:
  - One secondary endpoint listed in the opinion has not been addressed

- All these negatives could (probably) have been prevented by a modification request on time

E) EMA suggestions / proposals

- Prevent problems with compliance check
  - ✓ Check carefully draft opinion as submitted by Paediatric Coordinator after D90
  - ✓ Particularly elements highlighted in yellow or otherwise
  - ✓ In case of doubt, contact Coordinator
  - ✓ Request compliance check in advance of the relevant regulatory procedure



Validation (of MAA or variation)

An application for marketing authorisation under Article 6 of Directive 2001/83/EC in respect of a medicinal product for human use which is not authorised in the Community at the time of entry into force of this Regulation shall be regarded as **valid only if it includes**, in addition to the particulars and documents referred to in Article 8(3) of Directive 2001/83/EC, one of the following:

(a) the results of all studies performed and details of all information collected in compliance with an agreed paediatric investigation plan;

(Paediatric) Validation

- Is this submission subject to either Art. 7 or 8 of the Paediatric Regulation?
- Is the proposed new indication (or route or pharm. form) covered by the submitted PIP Decision?
- Is the proposed new indication covered by a waiver?
- Is there any study/measure that had to be completed/initiated before the date of submission?
- Are the results of all overdue studies included in the PIP submitted?
- Is there a positive compliance check for every submitted study?
- Are the remaining (not yet due) studies deferred?

Thank you for your attention!

Any questions ?

peter.karolyi@ema.europa.eu