Bioassays: the Italian OMCL experience

DISCLAIMER

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National Center for the Evaluation and Control of Medicines (CNCF)

- Issued in 2017
- Unique structure: Italian OMCL
- Assessment activities
  - Centralized procedures module 3 assessment for Biological/Biotech/ATMPs
  - Quality assessment for National and MRP/DC procedures
- Analytical activities
  - Batch release of blood product and vaccines
  - Post-marketing surveillance (National and CAP)
  - Participation in EDQM activities (BSP programme, PTS)
  - Participation in WHO activities (collaborative studies for IS development)
  - Bioassays development

CNCF Structure

- 2 Units
  - Chemicals
  - Biologicals and biotech
- Biological and biothech products unit
  - 6 thematic sections
    - Blood products
    - Biotech products
    - Viral vaccines
    - Bacterial vaccines
    - Biologicals (extraction)
    - ATMPs (gene and cell therapy)

Participation in EU activities

- CHMP Biologics Working Party (BWP)
- EDQM
  - Group 6
  - Group 6b
  - Group 15
  - Monoclonal antibodies working party (MAB)
  - Live biotherapeutic products working party (LBP)
  - Allergen working party
  - Gene therapy working group

Assessment activities

Centralized procedure

- Team: 5 units
- Assessment since 2011 (biotech products)
- Since then IT Quality assessment team evaluated
  - 24 MAA (coRapp, Rapp, peer reviewer)
  - 3 biosimilars
- Scientific advice
  - >10
  - Comparability/biosimilarity

Bioassays: Assessment

- Bioassay to demonstrate potency with reference to the MoA
- Inter-methods correlation
  - Appropriate statistical analysis to be performed
- Validation
- Method transfer
  - The transfer should be described in a detailed protocol
  - Transfer protocol should define max. variability
  - Repeatibility acceptance criteria should be defined on the first validation laboratory results

Analytical activities

Control testing on CAPs

- CAP Sampling and Testing programme
  - 1999: contract governing annual CAP Sampling and Testing Programme signed by EMA and EDQM
  - Started in 1999, since 2009 products are selected by a risk-based approach
  - IT participation since 2006 (mAbs, insulins, interferons)
- Counterfeit and stolen medicines
  - Herceptin case: vials stolen from Italian hospitals, manipulated and falsified and re-introduced under false credentials by unauthorized wholesalers into the legal supply chain

(http://www.aifa.gov.it/sites/default/files/OperationVolcano_0.pdf)

Control of mAbs

- Product-specific testing
- Is independent testing needed
  - – and feasible?
- OMCL network for mAbs testing (potency and physico-chemical)
  - Group started in 2018

Background

- EU: mAbs not tested routinely within the framework of Official Control Authority Batch Release (OCABR) testing.
- Experiences with potency assays for mAbs mainly limited to the CAP Sampling and Testing Programme.
- Chemical /biochemical analyses: a method, once established, can be applied to mAbs irrespective of their specific target.
- Potency assays: target- or even mAb-specific reporter cell lines need to be employed.

Rationale

- At present, OMCLs have only limited possibilities for *ad hoc* testing of a given set of mAbs without previous establishment of the respective potency assay.
  - Requests for such potency testing are often directed to the manufacturer's QC testing labs.
- Latest experiences with counterfeit/stolen mAbs: is there the need of independent OMCL testing?

Independent potency testing

- Not necessarily with independent methods
  - suitable method – e.g. MAH method, compendial method
- Competence distribution within the OMCL network
- Each participating OMCL responsible for one or more different potency assays

State of the art

- 11 OMCLs in the Network have already at this stage experience in running cell-based bioassay of mAbs
- To date potency assay experience available on 25 mAbs (3 additional mAbs planned for testing in 2019 and 4 in 2020)
- Foreseen difficulties in case of testing for competency building:
  - **reference material, cell lines and test samples** (purpose of sampling is not immediately related to market surveillance testing)

Some issues on potency testing

- From MAH to OMCL: increased variability
  - Routine vs single spot testing
  - Facilities and expertise
  - Release of batches vs confirmation of results
- Validation of Analytical Procedures [PA/PH/OMCL (13) 82 2R]
  - Document specifically addressed to OMCLs
  - Minimum validation, to be extended in case of suspected/detected non compliance

Minimum conditions for successful and reliable transfer

- System suitability
  - Specificity
  - Accuracy
  - Linearity
  - Repeatibility
- Number of repetitions
- Acceptable variability

OOS confirmation

- EDQM guidelines:
  - Evaluation and Reporting of Results – Core Document

    PA/PH/OMCL (13) 113 2R
  - Evaluation and Reporting of Results – Annex 1A

    Model Template for Failure Investigation of OOS Results PA/PH/OMCL (14) 87
- FDA guideline
  - Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production - October 2006

Bioassays development

- *In-vitro* assays
  - Ph.Eur. *In vivo* assay
  - 3Rs principles
  - Erythropoietin potency testing
    - Cell line from an erythroid lineage
- Evaluation of the impact of product heterogeneity on quality, safety and potency
- Validation follows ICH Q2(R1) guideline

Thank you!!