Advances in analytics or Introduction new/innovative analytical methods

New analytical techniques, a regulatory assessor’s perspective

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Disclaimer: Personal views only, meant to initiate further discussion. Does not necessarily reflect view of MEB, PhEur, or other organisations I work with
Introduction new/innovative analytical methods

- WHAT?
- WHERE?
- HOW?

- Triggers for introduction new technology
Main applications of analytics in module 3

- Characterisation
- Development and process validation
- Release controls and stability
- Comparability and biosimilarity
New and advanced analytical technologies, a regulators perspective

New analytical technique in quality assessors mind

- Analytical technique not frequently encountered
- Seemingly complicated design and data output
- Wish to consult specialists or dr Google
What are New analytical techniques?

- Anything but conventional HPLC and flatbed EF
- Capillary Electrophoresis
- Anything hyphenated, involving complicated spectroscopic detection
- Advanced high resolution spectroscopic techniques
- Light scattering techniques
- New labelling technology
- Q-PCR based techniques
- Not new but not often applied
- .............
Getting involved with New analytical methods

For manufacturers
- Extending analytical capability in development/control lab setting
- New products
- Process changes
- New requirements (e.g. new contaminants)
- Improvement (whatever reason)

On the desk of a regulatory assessor:
- New dossiers
- Variations
- Scientific advices
- Research and controls activities
Possible role(s) of quality assessor

Basic rule: Particular attribute should be addressed, method is a means

- Assessing / applying requirements of methods proposed by company
- Compare such methods with existing/established test methods
- Trigger introduction (suggest .... request) new technology
Application of new analytical technology:

- A New chemical entities
- B Established substances

Most technology related in dept discussions will be on A or B?
Areas in which new technologies are applied

1. Improved characterisation structure and purity of biopharmaceuticals by more efficient and high resolution and high sensitivity methods
2. Better characterisation of complex heterogeneous substances
3. Characterisation of ATMP’s
4. Rapid and/or more sensitive detection adventitious agents
5. Faster and simpler routine QC tests
1- improved characterisation biopharmaceuticals

• In dept characterisation of structural aspects
• rDNA derived proteins (new, biosim, variation): novel and established technology addressing all primary structural aspects with high specificity
• Higher order aspects
• Impurities (id and bioactivity)
2- Characterisation complex heterogeneous substances

• Mixtures of compounds
  – Complex glycosylation patterns of rDNA proteins
  – Extracted proteins
  – Glycaminoglycans (e.g. heparins)
  – Glatiramoids
3- characterisation ATMP’s

- Less well characterised biologicals
- CTP: Established methods, yet uncommon in pharmaceutical manufacture
- GT: advanced molecular biological techniques
4- Rapid and/or more sensitive detection adventitious agents

- Virus detection
- Mycoplasma
- Common culture based technology for bioburden/sterility
- ATMP trigger introduction rapid microbiological methods
5- Faster and simpler

- Very relevant for manufacturer’s release testing
- Assessor focuses on resolution, accuracy and sensitivity
New and advanced analytical technologies, a regulators perspective

How will methods be assessed?

A. characterisation/development studies, incl. comparability/biosimilarity
B. release testing, stability studies
How will methods be assessed?

1: characterisation, development, incl. comparability/biosimilarity

- Focus on results
- Is structure and impurities adequately covered
- Where relevant: explain method
- Level of detail (design, description validation): ‘case by case’
- Consider impact on method and test results for application
Guidance on analytical methods

ICH Q 5 E Comparability of Biotechnological/Biological Products
• The measurement of quality attributes in characterisation studies does not necessarily entail the use of validated assays but the assays should be scientifically sound and provide results that are reliable.

EMA Guideline on similar biological medicinal products: quality issues:
• demonstrate that the selected methods used in the biosimilar comparability exercise would be able to detect slight differences in all aspects pertinent to the evaluation of quality (e.g. ability to detect relevant variants with high sensitivity).
• Methods used in the characterisation studies form an integral part of the quality data package and should be appropriately qualified for the purpose of comparability.
NtA on level of detail module 3

NTA 2B, CTD module 3:

“All analytical test procedures described in the various sections of the chemical, pharmaceutical and biological documentation must be described in sufficient detail to enable the procedures to be repeated if necessary (e.g. by an official laboratory). All procedures need to be validated and the results of the validation studies must be provided.”
How will methods be assessed?

2: release tests, stability studies

- Description
- Validation
- When reference to European Pharmacopoeia: check relevancy of statement

- Reluctant introduction of new technology 😞
Examples of triggers new analytical methodology

- Biosimilarity and comparability exercise
- Concern on aggregates (orthogonal techniques)
- Replacement of bio assays in batch control
- New contaminants
Examples of triggers for introduction new technology:

**Heparin contamination event 2008**

- Routine tests not revised for many years
- Could not detect high level of contaminant
- NMR and CE methods to be introduced within weeks
- NMR is now routinely applied
- Pharmacopoeial monographs thoroughly revised

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Notes on specific release test techniques

- **Electrophoresis**
  - flatgel electrophoresis / staining or capillary techniques

- **Chromatography**
  - Adaptation to new equipment

- **Spectroscopy (NMR, MS)**
  - Clear advantages not (yet?) used in routine testing
What can regulators do to facilitate new technology?
New and advanced analytical technologies, a regulators perspective

In a nutshell

In an assessor’s perspective New analytical technology is

- Means to address particular quality attribute
- Relevant for new and old biologicals
- Level of detail associated with aim and relevancy of the method
- Innovation more prominent in characterization and development studies
- Conservative approach in innovation routine controls
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Hoefnagel