Role of Official Medicines Control Laboratories (OMCL) in assessing quality of biologicals.

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Disclaimer

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• According to the EMA policy (0044 MA/513078/2010)
  – No direct conflict of interest
  – One indirect conflict of interest (Household member currently working for a pharmaceutical company)
Medicines

• The quality, safety and efficacy of medicines need to be carefully assessed before a given product is authorized for either clinical trials or commercialization.
• This assessment is characterized by a multiple approach, based on document assessment, inspection and analytical testing.
• This multidisciplinary approach requires a number of different capabilities and experience.
• Lack of this interactions may cause:
  – incompleteness of assessment
  – missing of potential quality and safety issues
  – overall negative impact on the final users.
Regulatory authorities and analytical testing

- Various regulatory bodies in Europe have different organization to keep a multidisciplinary approach in place in a harmonized way.
- Regulatory Agency has capability, under the very same umbrella, to assess dossiers, run analytical pre and post authorization testing and carry on GMP inspection
- In other cases some of these activities, usually the analytical one, are held by an Official Medicines Control Laboratory (OMCL)
- OMCL may remain a separate and/or partially independent body from the Regulatory Agency
- OMCL are structured in a Network with strong links between laboratories
NRA and OMCL interaction in Italy

• Regulatory activities are carried out by the Agenzia Italiana del Farmaco (AIFA – National Regulatory Authority)

• there is a regulated agreement with Istituto Superiore di Sanità (ISS) which is the Official Medicines Control Laboratory (OMCL-IT_ISS-H) in Italy.

• ISS has scientific, analytical and technical capability to perform, upon request by AIFA, dossier evaluation, product analysis and inspections

• This also applies to investigational medicinal products, when requested by AIFA (which is the Competent Authority)
Istituto Superiore di Sanità (ISS)

• ISS is the leading technical and scientific body of the Italian National Health Service
• Mission: Research and Control for Public Health
• Main activities include
  • research
  • control
  • training in public health
• ISS is involved in collaboration and consultation with other institutions responsible for public health, including the Ministry of Health, the Italian Medicines Agency, regional health authorities, local health authorities and hospitals
Italian OMCL: how it is organized

• The Italian OMCL (OMCL-IT_ISS-H) is part of the Istituto Superiore di Sanità

• Departments and Centers involved:
  – National Centre for Immunobiologicals Research and Evaluation (CRIVIB)
  – Dept. Of Hematology, Oncology and Molecular Medicine (EOMM)
  – Dept. of Pharmaceutical products (FARM)

• CRIVIB and EOMM are part of the OCABR network, whereas the FARM Dept. performs post-marketing surveillance only on non-biological medicinal products.
**Italian OMCL Activities**

**Control**

**OCABR** (Autonomous activity)
- Bacterial and Viral Vaccines
- Human blood products
- Plasma Pool Testing

**Post-Marketing Surveillance**
- National level
- European level

**Pharmacovigilance**
- Vaccines
- Human blood products
- Other Biological/Biotech products

**Evaluation**

**Quality and safety assessment** of MAA for biological/biotech products for human use
- National
- Centralized
  - PMF
  - Scientific Advice
- Decentralized
- Mutual Recognition Procedures

**Evaluation of Clinical trials applications**
Audits of ISS for its OMCL Analytical Activities

ISO 17025
  • Vaccines (EDQM 2010)

ISO 17025 and ISO 9001
  • Vaccines (WHO 2006)
Assessment Activities
(Upon request by AIFA)

- Quality and safety assessment of MAA for biological/biotech products for human use
  - National
  - Centralized
  - Decentralized
  - Mutual Recognition Procedures

- Evaluation of Clinical trials applications
  - National Phase I
  - Voluntary Harmonized Procedures

- Scientific Advice
  - National
  - Centralized
Type of products
(Upon request by AIFA)

- Vaccines
  - Viral vaccines
  - Bacterial vaccines
- Human Immunoglobulin preparations
- Other blood derived products (clotting factors, albumin)
- Monoclonal antibodies
- Recombinant proteins
- “Old” biologics (heparins, urine-derived products, ....)
- Allergens
- Chemical drugs
- ATMP

PMF is evaluated in the context of both national and centralized procedures
ISS assessment activities

• CDT
  – Module 2 (QOS)
  – Module 3
    • Viral safety (all biologicals/biotech products)
    • Biostatistics (comparability, definition of specs, stability)
    • Quality assessment

  – Module 4
  – Module 5 for exceptional cases (vaccines)
Other ISS-OMCL Activities

- Research activity, focusing on development of analytical methods to be applied for evaluating quality, safety and efficacy of biological/biotech products for human use
- Participation in and coordination of national and international collaborative studies aimed at the standardization of methods and reference preparations
- Participation in Proficiency Testing Studies (PTS) and organization of External Quality Assessment studies
- Participation in EMA Working Parties and Drafting Groups
- Participation in the Groups of Experts of the European Pharmacopoeia
Role of an OMCL in assessing quality of Biologicals

• Pre-marketing (pre-authorization) level:
  – Clinical trials.
    • quality of products assessed from the dossiers but also tested by analytical methods.
    • This would lead to the independent confirmation (or disproval) of data provided by the applicant.
    • This could have some importance when impurities are tested whose level could influence the safety of the product under trial.
Role of an OMCL in assessing quality of Biologicals

• Pre-marketing (post-authorization) level
  – In some cases for certain products it is foreseen either permanent or temporary batch release.
  – Good manufacturing practice level. For products to be authorized for clinical trials or commercialization, inspections are regularly carried out.
  – When novel methods are developed and used their validation and performance on the field can be more comprehensively assessed by mixed teams where experts from the OMCL are also included.
Role of an OMCL in assessing quality of Biologicals

• Post marketing level:
  – OCABR (when applicable)
    • a certain type of biologicals, either manufactured traditionally or obtained via genetic engineering approaches are entitled to be batch released according to directive 2001/83, art. 114.
    • OCABR assures that each individual batch of the biological product is tested independently by the OMCL of a given MS before releasing it on the market.
    • This approach further reassures that the quality is confirmed by independent testing during an extended testing period according to specific methods capable of monitoring Critical quality attributes of the product.
OCABR Network: advantages

- **Facilitates** mutual recognition of analytical results among MSs by fostering the use of harmonised approaches
- **Provides** a platform for exchange of information
- **Promotes** work-sharing and maximisation of resources (e.g. no repetition of OCABR by a second MS)
- **Creates** a unified voice for feedback and exchange with manufacturers, regulatory authorities, the European Commission, and the European Pharmacopoeia expert groups
OCABR: Pillars of the system

• Administrative Procedure
  – Describes the steps to be followed by individual Member States and MAH when applying OCABR
  – Provides a series of templates for important documents (e.g. Certificates of compliance, etc.)

• Product specific guidelines
  – States tests to be performed by the OMCL on samples (a commonly agreed subset of the tests performed by the manufacturer for release) – section 2
  – Provides a common protocol template for manufacturers – section 3
  – Human OCABR: Presently about 60 product specific guidelines
Quality Assurance

- Sharing of work and exchange of results requires a mutual confidence among OMCLs
- Reliability of testing results is a pre-condition for a fruitful sharing
- Common approach on Quality Assurance
Quality Assurance activities within the OMCL Network

- General QA system
  - Harmonisation of QA policies
  - ISO/IEC 17025 quality standards
- Specific assistance and maintenance programme for network QA system
  - Specific guidelines
- Audit Programme
  - Mutual Joint Audits (MJA)
  - Co-operation with EA is developing
  - Mutual Joint Visits, Tutorials, Training Visits
- Proficiency Testing Schemes (PTS) organised by EDQM
- EDQM Biological Standardization Program (BSP)
  - Establish standardized reference material to improve assay harmonization
  - Develop/standardize methods for biologicals
Role of an OMCL in assessing quality of Biologicals

• Post marketing level:
  – Post marketing surveillance
    • Products can be sampled from the market after the authorization has been granted.
    • According to the MS involved, several approaches are followed and samples are obtained from various places (manufacturing site, the wholesalers, hospitals and pharmacies)
    • this procedure should be able to assess the cold chain (if needed) or more in general the distribution chain of the various products
    • This sampling point should represent the worst case scenario since it is normally the last step before the product reach the patient
    • For example in Italy the approach is largely to sample from Pharmacies within or outside the hospitals.
CAP Programme

• Since 1995 European Commission granted Community Marketing Authorisations
• Need of a co-ordinated approach for controlling such products
• EMEA responsibility and supervision
  • EDQM operational co-ordination
  • Involvement of EU/EEA Inspectorates and OMCLs
• Annual monitoring exercise
  • products selected through a risk-based approach
• Additional, important tool in the supervision of medicinal products placed on the market
Post-Marketing Surveillance
MRP/DCP

✓ Voluntary post-marketing surveillance scheme for MRP/DCP
✓ MA application for these products based on identical dossier in different MSs
✓ Work-sharing aimed at optimal use of analytical resources:
  • By reducing duplication of MRP/DCP testing
  • By offering testing of MRP/DCP to other participants
✓ Sharing of the test results, offering individual MSs and other bodies
  • A broader and in-depth overview of MRP/DCP on the EU market
  • The opportunity to focus the national surveillance activities by taking advantage of the testing work of other OMCLs
Role of an OMCL in assessing quality of Biologicals

• Post marketing level
  – Counterfeits

  • Quality of medicines, including biologicals is strongly related to the quality of the production process, of the manufacturer(s) and of the GMP status of the site(s)
  • When counterfeiting is a problem, analytical testing is an important firewall which can prevent or at least strongly limit the diffusion of these products.
  • OMCLs and OMCL Network is strongly involved in assuring that only properly manufactured products are distributed on the market and reach the patients.
Role of an OMCL in assessing quality of Biologicals

• Use on the field.
  – After the marketing authorization is granted, the product is normally administered to an increasing number of subjects.
  – This leads to an exposure rate which is not comparable with the exposure which was achieved during clinical trials.
  – It is expected that a number of issues can arise from this larger use of the product.
  – Important events (adverse events/pharmacovigilance and quality defects) can occur.
  – They may represent an important target of analytical evaluation by the OMCL.
Pharmacovigilance, complaint and quality defects

- Adverse events are often associated with the medicinal product itself.
- However, adverse events can be associated with specific quality defects, which can be present in a given batch of product, in several batches or in a few final containers.
- Independent analytical testing by the OMCL is fundamental.
- Full understanding of specific complaints may be better achieved when the investigation includes the presence of OMCLs.
Conclusions

• Taken together, the above mentioned examples clearly support the idea that the overall quality of a medicinal product including biologicals, relies upon a number of approaches where the analytical experience and capability plays an important role.

• From several points of view, cooperation between assessors, GMP inspectors and OMCL experts needs to be strengthened and improved, with the final common goal of a better quality and more controlled biological products.
Thanks for your attention!