A customized system/procedure contributing to good quality vaccines in EU and beyond

OCABR
Coordinated by EDQM / Council of Europe

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OCABR=Official Control Authority Batch Release  why?

- At its origin because the biologicals, vaccines and plasma derivates but also hormones-insulins and HGH-, were using complex manufacturing processes and control methods, involving biological methods such as animals or cell cultures which could be subject to important variability. It was thought that a system with double independent testing, one by the Manufacturer and one by the Control Laboratory (OMCL), was giving a better insurance concerning the Quality of the product to be used.
OCABR

- Initially implemented by UK, De, NL, CH, USA in the fifties/sixties
- Followed by BE, IT, FR, etc in the seventies/eighties
- On a National basis but an international forum existed already through the WHO / ECBS meetings
OCABR in EU (1)

- In 1989 development of specific Directives for Biologicals which recognises the value of Batch Release by the Authorities for Vaccines and Blood derivates but no longer for Hormones and other biologicals which at that time were rapidly becoming more and more well characterised products with high quality purification steps - often Biotech engineered
OCABR in EU (2)

- In order to avoid a chaotic situation whereby products could have to undergo as much as 15 different (re)controls in addition to the Manufacturer’s exhaustive control
- A codified system was established prescribing the optionnal possibility by Member States to require OCABR but with the obligation to mutually recognise each others and not to unnecessarily repeat the independent (re)control if already been performed by an Authority within the EU
OCABR in EU currently

- Article 114 of Directive 2001/83 outlines the issue
- It is an optional provision
  - Therefore application of regulation is not mandatory
  - But when a Member State decides to apply it
  - Then clear rules to follow
    - no repeat of the tests
      - Issuing of a certificate
    - Defined system
      - Administrative procedure and technical guidelines
      - Mutual recognition
      - Transparency
- Applicable in EU/EEA (Norway) and CH (Specific MRA)
Batch Release Guideline

- EC Administrative Procedure for Official Control Authority Batch Release
- Medicinal Products Derived From Human Blood and Human Plasma
  - 6 product specific guidelines
- Immunological Products Consisting of Vaccines
  - 39 product specific guidelines
## Batch Release Guideline (2)

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<td>Diphtheria, Tetanus, Pertussis (Acellular Component), Poliomyelitis (Inactivated), Hepatitis B (rDNA) with separate Haemophilus Type B Conjugate Combined Vaccine (adsorbed) (new guideline)</td>
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<td>Hepatitis A (Inactivated) and Hepatitis B(rDNA) Combined Vaccine (Adsorbed)</td>
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**Batch Release Guideline**

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<td>Typhoid Polysaccharide Vaccine</td>
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<td>Vaccine Containing Vaccinia Virus Produced in Cell Culture (Smallpox Vaccine) (new guideline)</td>
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<td>45</td>
<td>Yellow Fever Vaccine</td>
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</table>
Batch Release Guideline (6)

- New guidelines are under development
  - Varicella vaccine
  - Liposomal influenza vaccine
  - Hepatitis A, typhoid combined vaccine
  - OPV (oral Polio) monovalent vaccine
OMCL=Official Medicines Control Laboratory

Definition

• "...is a public institution which only performs laboratory testing for a competent Authority, independently from a manufacturer, for medicinal products (human or veterinary) prior to and/or after marketing for the general surveillance of medicines in relation to the safety, quality and efficacy
  - Subcontracting is possible especially when the know-how and/or technical competence is lacking but ensure absence of conflict of interest

• Performs Compliance controls against the authorised MA specifications /requirements of the European Pharmacopoeia/PhEur to ensure Quality, Safety + Efficacy
  - eventually preauthorisation testing to ensure that the proposed methods are appropriate
Implications for the OMCLs

- Communication - transparency
- Quality assurance
- Technical competence and ongoing performance measurements
- The SOLUTION
  - Integration of the OMCL Network
  - Building MUTUAL CONFIDENCE
OMCL Network

• Active participation of all members of the Network concerned including new MSs whether or not they do perform the actual testing

• Why? As we all have a desire to
  – Share know-how and experiences
  – Share work (in order to avoid duplication/saving of resources)
  – Do better together instead each in isolation = OPTIMISATION

• Build a true MUTUAL CONFIDENCE to

• Apply the MUTUAL RECOGNITION legally prescribed
OMCL Network(2)

- Ensure that suitable QA system is in place
  - Audit programme
  - Accreditation?
- Performance measurements
  - Proficiency testing studies
  - Training
  - Exchange of experience / personnel
OCABR current situation

- **2 major vaccines manufacturers in EU**
  - GSK Bio released at about 80% of its production by ISP (under Dr. Dobbelaer’s responsibility) in Be other releaser Afssaps/Fr, Nibsc/Uk, PEI/De, ISS/It
  - Sanofi-Aventis Pasteur released similarly at about 82% by Afssaps (under the responsibility of Dr. Fuchs) in Fr other releaser ISP/Be, Nibsc/Uk, PEI/De, ISS/It

- **Other manufacturers**
  - MERCK released by Afssaps essentially for those of the products co-marketed with Aventis Pasteur and by RIVM/Nl or Nibsc/UK
OCABR current situation (2)

- Other manufacturers (continued)
  - Chiron by ISS/It, Pei/De and Nibsc/Uk essentially
  - NVI by RIVM/Nl
  - Berna by Swissmedic/Ch essentially, recognised through a special agreement with EU (MRA)
  - Small local manufacturers in new CEEC Member States Biomed-PL, -CZ, situation not yet clarified as regards marketing in other EU countries
    - requires updating of manufacturing authorisation (licence)
    - can remain on local markets ONLY for a given short period of transition up to 2008 at most
  - Imported vaccines from third countries CRO, Cuba, Korea etc must have an updated Marketing Authorisation EU compatible, each batch has to be tested by qualified Person of the official importer in one of the EU Member States and batch released by an OMCL of EU
OCABR current situation (3)

- Specific cases of
  - Influenza several manufacturers
    - Gsk Bio PEI/De, Nibsc/Uk
    - Sanofi Aventis Afssaps/Fr
    - Berna Swissmedic/Ch
    - Chiron ISS/It
    - Solvay RIVM/Nl
  - TBE Bifa/At and PEI/De
  - BCG almost only 1 manufacturer left in EU
    SSI/Dk released by DKMA/Dk, Nibsc/Uk, Afssaps/Fr and Bulgarian Manufacturer??
OCABR current situation (4)

- Some figures from two leading OMCLs in matters of Batch Release by Authorities
  - Afssaps France about 1600 lots examined in 2004
    - no failing/rejected batches
    - number of persons involved about 65
    - operational costs not including salaries of the personnel about 650 000 Euros
  - ISP Belgium about 1450/1500 lots tested and released also no failing/rejected lots
    - number of persons involved about 45
    - operational costs excluding costs of personnel about 420 000 Euros
OCABR outcome

- To define an **EU Quality standard mark** for vaccines and plasma derivates which demonstrates the Know-how and seriousness of the EU based bioindustry concerned used beyond the EU territory for export and fully recognised by WHO.

- Gradual decrease of batches rejected
  - since two years no failing batches were discovered and in 2002/2003 only a very few cases (influenza, cholera and hepatitis B) discovered by both the Manufacturer and the OMCIs testing for release (in parallel) but the product never went to the market therefore no need for recall as the system prevents the product concerned from being commercialised.

- Producers have declared their willingness to gradually commercialise only one common quality grade within the next few years fulfilling the European Pharmacopoeia Standards not always applied and required by authorities in the past in the CEEC countries.
OCABR Outcome (2)

- A Network of OMCLs with
  - Good QA system in place
  - Competent
  - Performant
  - Dedicated
  - Reliable

- Implementation of TRUE Work Sharing through an integrated Organisation in the European system regulating medicines
OCABR finally

- Not a police system but a joint effort between industry and authorities to make (only) excellent vaccines available to doctors and patients in EU
- Procedure is meant to ensure that good quality and safe vaccines are used for healthy vaccinees but does not cover the question of pharmacovigilance (the immunological process in humans is a complex issue) still needed as a separate programme
General conclusion

- The European Batch Release system is a reliable secure system to ensure good quality vaccines
- It is transparent based on pooling together resources efficiently to the benefit of patients
- Driven by mutual confidence and work sharing
- Estonia can make best use of the system at low costs but high benefits there is very very little risk that their patients and medical professionals get bad quality products