THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

The EU/EEA OCABR network; maximising resources through work sharing and mutual recognition

Global availability of critical reagents for biologicals testing. Current status, challenges and possible solutions. IABS webinar in collaboration with HIS

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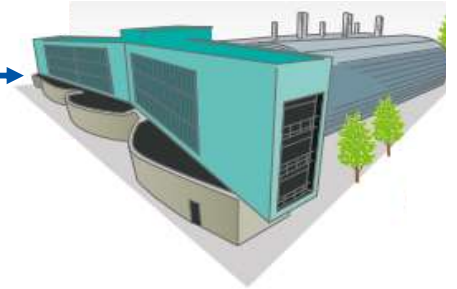
The EDQM, an entity within the Council of Europe

COUNCIL OF EUROPE

- Founded in **1949**
- **Intergovernmental** organisation, Strasbourg
- **46** Member States
- More than **700 Million** Citizens

The **European Directorate for the Quality of Medicines & HealthCare** (EDQM)



- Founded in 1964
- Work in the framework of a **Partial Agreement, 39 Members & the EU**
- Ensures the availability of and access to good and safe quality medicines, Substances of Human Origin (SoHO) and consumer health products

The EDQM, Areas of Work

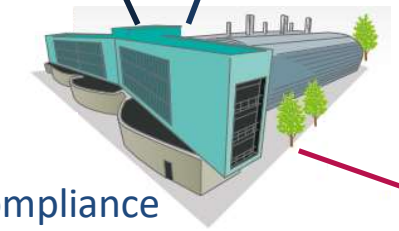
MEDICINAL PRODUCTS

- Official standards for manufacture and quality control of pharmaceuticals (e.g. API, excipients and finished products) & Reference Substances (RS)
  - European Pharmacopeia Commission-treaty body - and its expert groups
  - BSP Steering Committee
- Granting Certificates of Suitability verifying compliance of pharmaceutical substances with pharmacopoeial standards and carrying out inspections of manufacturers of active substances

CEP Steering Committee

- Control of medicines through collaboration pool expertise and effectively use limited resources with the aim of achieving effective public quality control of medicines in Europe and beyond

OMCL network, its working groups & specific Networks



CONSUMER HEALTH: Cosmetics & Food Contact Material

- Safety standards for cosmetics and food contact materials
- Control of cosmetics *e.g. Market surveillance, proficiency testing*

- 2 Intergovernmental Committees (CD-P-MCA, CD-P-COS) and their expert groups
- OCCL Network

SUBSTANCES OF HUMAN ORIGIN (SoHO)

- Quality & safety standards
- Data collection
- Improving quality system/capacity building of Blood and Tissues & Cells Establishments *e.g. Proficiency testing, audits*

- 2 Intergovernmental committees (CD-P-TS and CD-P-TO) and their expert groups
- National Focal Points (NFP) Network

PHARMACEUTICAL CARE

- Policies & model approaches for the safe use of medicines
- Cooperation to combat falsification of medical products

- 1 Intergovernmental committee (CD-P-PH), subordinate bodies and its expert groups

EDQM, the European Medicines Regulatory Network and Global Cooperation

European Union & its bodies
- European Commission
- European Medicines Agency
- European Communicable Disease Centre

EMRN

- Political dialogue
- Mutual representation
- Technical cooperation
- Legal/regulatory cooperation

EMRN

World Health Organisation

- Mutual representation/representation
- Technical cooperation

The **European Directorate for the Quality of Medicines & HealthCare** (EDQM)

EMRN confirmed as WHO Listed Authority as of May 2024

National authorities (HMAs)
Licensing authorities, inspectorates, control laboratories, pharmacopoeia authorities

EMRN

OMCL = Official Medicines Control Laboratory

Definition: Terms of Reference for the General European OMCL Network (GEON) of the Council of Europe)

- OMCLs are public institutions which support (or are part of) regulatory authorities in controlling the quality of medicinal products for human and veterinary use (available on the market / intended to be placed on the market).
- OMCLs test medicinal products independently from manufacturers

OMCL is a recognised term in the EU legislation





General European OMCL Network (GEON)

- **Devised in 1994** by the EU Commission & Council of Europe (CoE)
- To promote the **collaboration of OMCLs across Europe** (and beyond) in the area of quality control of marketed medicinal products for human and veterinary use
- **Set up and coordinated** by the EDQM
- Network activities are **co-financed** by the EC (on basis of a contribution agreement) and COE

The GEON organisation:

- **All OMCLs fall under the global umbrella of the GEON and uphold the same quality standards; ISO/IEC 17025**
- Specific activity networks carry out dedicated activities e.g. market surveillance, batch release of biologicals, falsified/illegal medicine testing etc.
- EDQM: **Secretariat and co-ordination** of the Network activities and joint programmes

2024: 30th Anniversary of the Network

General European OMCL Network

https://www.edqm.eu/en/omcl-network

GEON Objectives

Protecting **public** (human) and **animal health** through independent surveillance testing of medicines (and other products)

The GEON works to…

- Promote and facilitate work-sharing among the OMCLs
- Continue to foster the mutual recognition of test results
- Achieve harmonisation in testing standards and laboratory controls
- Facilitate the exchange of knowledge and expertise
- Provide a platform for sharing scientific information and surveillance strategies

Benefits of Networking

The GEON is designed to allow OMCLs to network and collaborate…this is achieved in many ways:

- Annual Meetings
- Working Groups
- Tailored audit and training visit programmes
- Symposia, workshops, seminars and training programmes
- Co-ordinated common sampling and testing activities
- Sample exchange activities and collaborative testing
- Shared databases

This all contributes to a meaningful and value-added surveillance of medicines on the European market

GEON and its specific activity Networks

GEON

Quality Management Programmes
Mutual Joint Audits/Visits
Proficiency Testing Studies
Post Marketing Surveillance (PMS)
Medicines Testing
Falsified/Illegal Medicines

EU/EEA restricted activities
Subset of OMCL in the restricted networks

Human OCABR

Vet Batch Release

Centrally Authorised PMS

MRP/DCP PMS

Almost 70 **OMCLs** from **40+ countries**
Members and Observers of the European Pharmacopoeia Convention
- **Full, associate**
- **Plenary meeting 1/year**

Each Network/restricted network has its own:
- Terms of reference
- Advisory Group
- Activity program

Each of the restricted networks focuses on specialised activities and includes a subset of OMCLs from the GEON

Participation linked to:
- EU/EEA membership
- Specific competencies within the OMCL

Official Control Authority Batch Release (OCABR):

Independent testing of each batch pre-market for:

Human blood derived medicinal products

Vaccines for human use

OCABR is embedded in EU legislation

EU legislation*

- A 'may' clause that allows member states (MS) to perform control testing on each batch of vaccine or human blood derived medicinal product
- It requires recognition of the test results between MS to avoid duplicate testing
- It sets time limits for completion of the controls

As a result:

- Each batch is tested independently by a qualified OMCL
- Each batch is tested only once for the EU/EEA and the results are recognised by all MS.

* Article 114 of Directive 2001/83/EC as amended

Key Players in OCABR

- Individual Competent Authorities (CA)/Official Medicines Control Laboratories (OMCLs)
  - Responsible for the release of individual batches according to the defined rules
- EU Official Control Authority Batch Release (OCABR) Network
  - Work together to define and apply codified rules based on the Directive and to communicate information on issues and batches to the network members – **Network activity co-sponsored by the EU Commission and the Council of Europe.**
- Manufacturers
  - Important partners in the process. Exchange with OMCLs for method transfer. Produce and submit batches according to the defined rules and communicate with CA/OMCLs and the network on relevant issues.

OCABR Network

Who ?

- Activity restricted to 27 EU Member States, EEA states plus any countries with a specific agreement concerning batch release (e.g. Switzerland) (Israel is involved for vaccines based on the ACAA). EMA involved in decisions for products that are Centrally Authorised = OCABR Network
- EDQM, DBO co-ordinates and facilitates network activity and acts as the secretariat
- As a 'May' clause any MS may choose to apply OCABR or not for a given product group. Some MS do not apply it at all however all MS receive information on results, in particular when a batch is rejected
- Observer status via Memorandum of Understanding: Exchange information but no mandatory mutual recognition e.g. Canada, United Kingdom, Australia, Taiwan- FDA

Quality Management Systems in the OCABR Network

In light of the mandatory mutual recognition, it was agreed that OMCLs must have externally audited QMS meeting the standards of ISO/IEC 17025 in order to issue a valid EU OCABR certificate

- QMS includes:
  - Use of defined SOPs
  - Demonstrated method and equipment validation and maintenance of competence
  - Proof of proficiency (e.g. Formal PTS, blind sample testing etc.)
  - Use of recognised reference standards (International Standards and EDQM BRPs)
  - Regular performance review

There are 2 options for OMCLs to have a recognised external audit

- Participation in a Mutual Joint Audit of the General European OMCL Network
- Audit by the National Accreditation Body covering the appropriate scope of activity

The OMCL may use one or the other – some use BOTH

Main Goal

The main goal of the EU legislation and the supporting structure of the CA/OMCLs and OCABR is to ensure good, high standard and consistent quality vaccines for human use throughout the EU and to facilitate access to patients and the movement of these goods throughout the territory.

A qualified OMCL tests a batch for the whole network and results are mutually recognised → Saving resources and facilitating access.

Achieving the Goal

- Effective mutual recognition requires:
  - Trust and confidence
  - Transparent procedures
  - Adherence to common rules
  - Open communication
- Networks' role is to provide a framework for application of the Directive using commonly agreed procedures and methods, guidelines for testing, platforms for confidential information exchange on batches and methods and work sharing
- An effective OCABR network results in optimisation of resources while assuring safe, good quality products
- A common EU OCABR release certificate is valid throughout the EU - and beyond – this reduces testing – benefits MAH, and Member States.

OCABR Procedure and Guidelines : Key pillars

Administrative Procedure

Framework for harmonisation and transparency

Provides:

- Guidance for OMCLs and MAH and legal context
- Outline of steps for OCABR
- Tools for information exchange between Member States and with MAH
- Format for EU recognised certificates and annual reports

Product Specific Guidelines (PSG)

Available for all products undergoing OCABR in the EU

Provides:

- List of samples to be supplied by the MAH
- Tests to be performed by the OMCL (Section 2)
- Model template for protocol submission (Section 3)
- Statement of compliance for signature by MAH

Elaborated and adopted by the OCABR network for a harmonised approach

Available on the EDQM website with regular updates

https://www.edqm.eu/en/omcl/human-ocabr-guidelines

PSG: Format and content

Section 1

INTRODUCTION
Legal context and Ph. Eur. requirements

Section 2

TESTS TO BE CARRIED OUT BY THE OMCL FOR OCABR
Provides an indication of the number and type of samples to be supplied and lists the tests to be carried out by the OMCL performing OCABR.

Section 3

PRODUCTION INFORMATION and FINAL BATCH TESTING

- These sections are models that may vary for different products subject to the same guideline.
- A protocol for a specific product may differ in detail from the model provided. The essential point is that all relevant details demonstrating compliance with the Marketing Authorisation for a particular product should be given in the protocol submitted.
- Results of tests should be provided with sufficient details to allow recalculation of potency or quantity of active substance. Results of qualification tests for reference material should also be included.

Section 4

CERTIFICATION BY THE MANUFACTURER
Attestation by the manufacturer that the batch is compliant with the MA and must be signed by the Qualified Person. In addition, they must attest that the OMCL performing OCABR has been notified of all relevant approved variations that have an impact on product specifications or data supplied in section 3 of the protocol.

PSG: Test Methods for OCABR

OCABR Tests

Section 2 of the product specific guideline

OMCLs test only a few critical parameters with added value for independent evaluation

Tests are chosen by consensus and approved by the OCABR network

The main focus is potency and safety

Specifications for pass/fail are outlined in the European Pharmacopoeia monographs and the marketing authorisation (MA). They are not part of product specific guidelines

Methods

- Use of compendial, MA or fully validated in-house methods
- Demonstrate appropriate validation for use of method for the product in the OMCL
- Use of official standards Biological Reference Preparations (BRPs) (or validated in-house standard) established in International Units (where possible)
- QA systems in place: ISO 17025 is the agreed reference
- **Obligation to use the fewest animals possible and in the most humane way (application of 3Rs)**

Main principles of OCABR

OCABR by the OMCL: A given batch is tested in 1 OMCL

Test samples

Set of tests agreed by all Member States and listed in guidelines from EDQM

Protocol Review

Quality test results of the manufacturer checked for compliance

Issue OCABR Certificate

Certificate Valid in EU/EEA + CH and IL by mutual legal agreement

Also recognised (by reliance) by many non-EU/EEA countries

Non-Compliant Lots Rejected

Test samples

Non-compliant

If either

Protocol Review

Non-compliant

NO OCABR CERTIFICATE

Inform
All Member States
and manufacturer

Batch not released
to patients

Manufacturer's arrangements with the OMCL(s)

- **Company's responsibility to set up OCABR with preferably >1 OMCL in sufficient time**
  - Inquiry of interest, exchange information, meetings – be prepared to explain the proposed control strategy, test methods, target dates and anticipated capacity (OMCLs are bound by confidentiality within the regulatory network)
  - Provide concrete feedback on the final choice to the selected OMCLs **and** to those not selected
- Timelines include method transfer, network agreement on OMCL tests and creation/adaptation of OCABR GL
  - Contact should be as soon as control strategies are defined and methods are validated and there is a clear sign a marketing authorisation application (MAA) will proceed
  - Minimum to define OMCL(s) and start transfer is when MAA is submitted (EU 'normal' timeline from submission without stops is 210 days)
- Keep communication lines open and inform OMCLs of any changes impacting OCABR ASAP
- Common meetings with all involved OMCLs is recommended – allows synergy, support and coordination – highly beneficial for OMCLs and companies

OCABR Procedure: Timelines

OCABR Testing

- An OMCL has 60 days to complete the procedure.
  - This is a maximum – actual time usually much shorter if there are no issues
  - The count starts after receipt of all the necessary elements from the manufacturer (samples, completed signed protocol)
  - To gain time testing is often done in parallel with the manufacturer i.e. samples are sent to the OMCL before the manufacturer has completed their own testing.

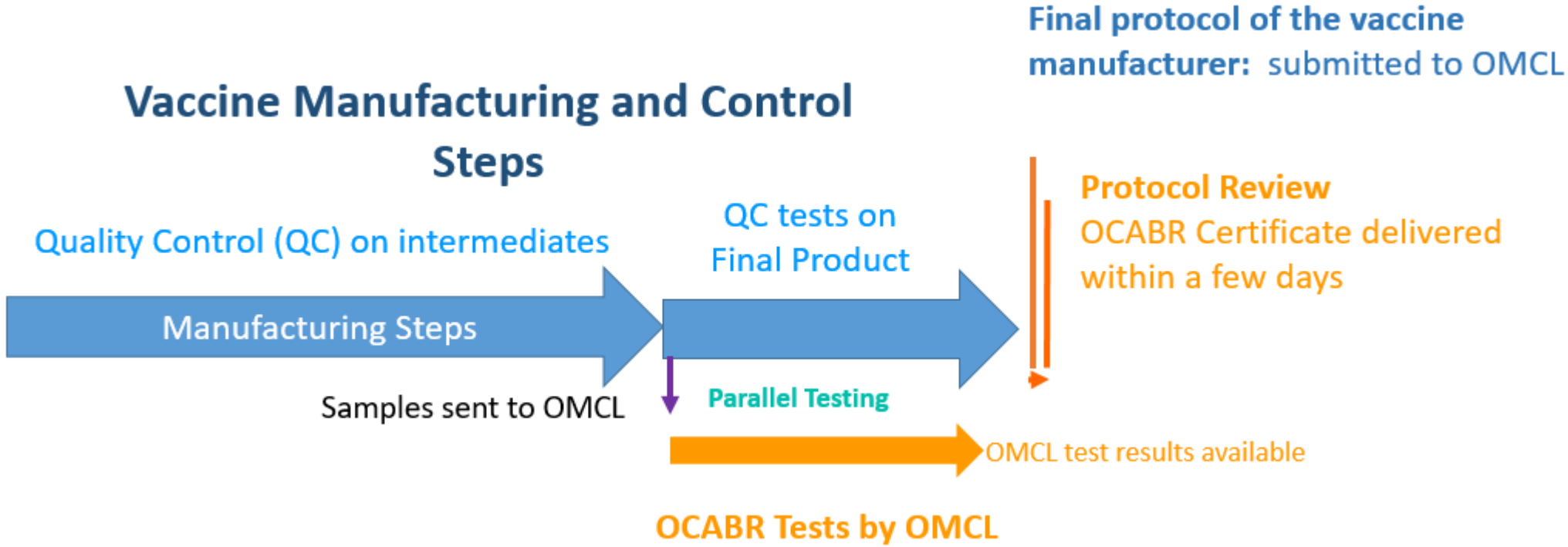
OCABR Administrative Release

(accepting an OCABR certificate from another OMCL)

- CA/OMCL has a maximum* of 7 working days after receipt of the required documents from the MAH – the real time is usually shorter
- MS may designate the specific procedure within this time frame (passive or active)

* It is not an obligation to take 7 days

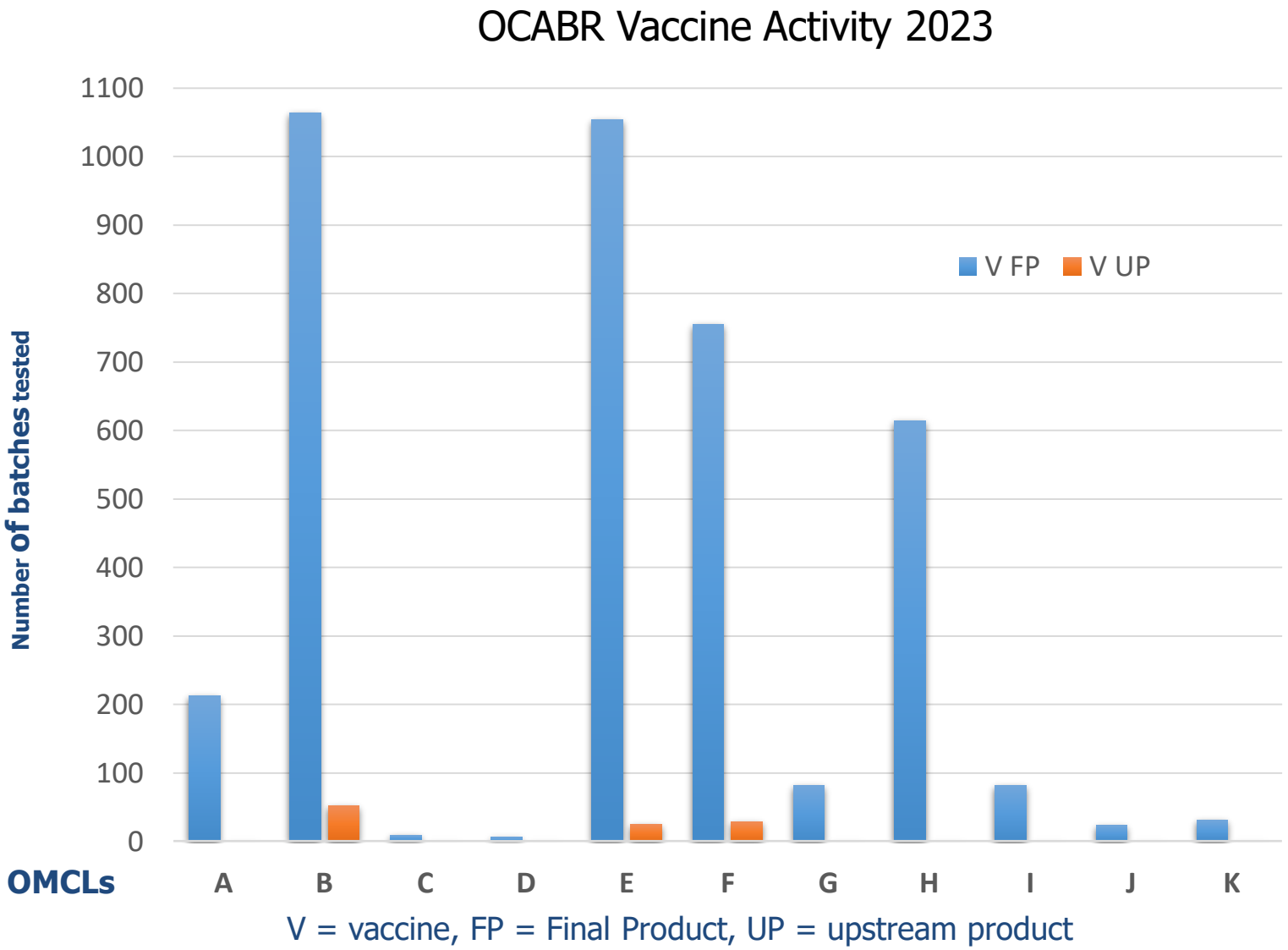
Parallel testing



- Encouraged to minimise the release time – especially important for complex tests or tests using animals
- Exists since a long time but heavily used and very effective during the COVID-19 crisis
- The company may withdraw the batch during parallel testing e.g. if they identify a quality issue through their own QC checks or if they have a change in distribution strategy. They should inform the OMCL ASAP to avoid wasting resources on testing at the OMCL.
- Information on the withdrawal is provided to all network members and observers.

Adapted from Milne et al. Npj Vaccines, 2023

Worksharing



11 OMCLs performed OCABR vaccine testing in 2023

OMCLs have different profiles and different capacities

Total = 3931 batches of vaccines (+106 monovalent bulks)

Work-sharing spreads the load and allows all MS access to independently controlled batches.

It was particularly important during the COVID-19 pandemic:
Between December 2020 until April 2024 >3700 of batches of COVID-19 vaccine representing billions of doses.
This was in addition to OCABR for other vaccines.

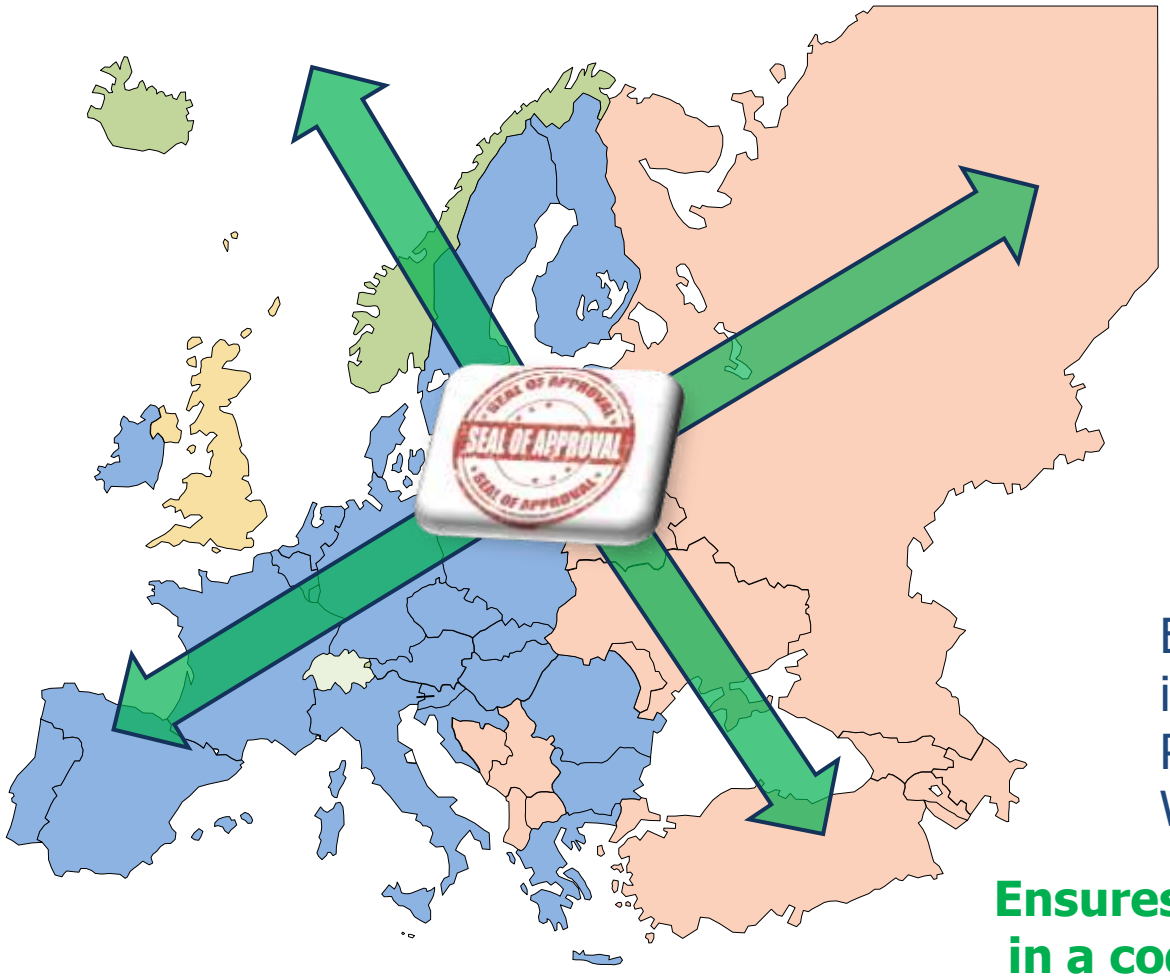
Critical reagents

- Critical reagents and reference standards/material for OMCLs come from different sources e.g.
  - Commercial sources
  - From international or regional standard setting bodies e.g. WHO/MHRA, EDQM
  - From the company (especially for product/company specific methods)
  - Self-prepared
- All routes require adequate qualification/quality control/monitoring
- In addition to specific reagents, dedicated and sometimes costly equipment must be acquired and maintained
- More OMCLs testing means more consumption of critical materials

Performance of testing in a limited number of qualified OMCLs reduces the demand for critical reagents – all benefit via recognition/reliance

EU OCABR – One for All – Recognition and Reliance

Recognition by legal obligation and Reliance by choice share similar benefits



EU OCABR Certificate is a
Seal of Approval recognised within the EU/EEA and beyond

- Transparent Consistent Procedure
- Publicly available product specific guidelines with clear criteria
- Qualified OMCLs
- A network of experience
- Work-sharing to save resources

EU OMCLs and EDQM promote reliance through participation in and contribution to the WHO-NCL Network for Prequalified Biologicals and other initiatives e.g. via CEPI, WHO CIP network

Ensures the availability of safe, good quality medicines in a codified and consistent way

Thank you for your attention

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