EMA
EUROPEAN MEDICINES AGENCY

The EMA regulatory framework

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EMA workshop on non-clinical data for regulatory decision-making on the efficacy of medical countermeasures

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EMA **endorses the 3Rs principles** of replacement, reduction, and refinement of the use of animals in biomedical research.

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-principles-regulatory-acceptance-3rs-replacement-reduction-refinement-testing-approaches_en.pdf

Introduction and background

Randomised, double-blind, placebo-controlled efficacy and safety **studies** are the **cornerstone of regulatory approval**

Circumstances in which randomised clinical studies **unethical** or **unfeasible**

- **Exposure to lethal or permanently disabling toxic threat**
- **Low/sporadic prevalence** and **case numbers**

Serious public health threats, including chemical, biological, radiological and nuclear threats (CBRN) → **significant risk** for public health

Medical countermeasures (MCMs) are **urgently needed**

→ **Preparedness** for the next outbreak/incidence

→ **Regulatory flexible approaches** needed to ensure preparedness

EU medical countermeasures approved under CMA/MAUEC

Product Name (INN)	MAH	Therapeutic indication	MA approval	Approval status	MA type
Tecovirimat SIGA (tecovirimat monohydrate)	SIGA Technologies	**Treatment** of **mpox, smallpox, cowpox**	06/01/2022	Approved	MAUEC
Dectova (zanamivir i.v.)	GSK	**Treatment** of **complicated and potential life-threatening influenza** when resistance to antivirals or other antivirals not suitable	26/04/2019	Approved	MAUEC
Gohibic (vilobelimab)	InflaRx GmbH	**Treatment** of adult patients with **SARS-CoV2-induced** acute respiratory distress syndrome **(ARDS)**	14/11/2024	Approved	MAUEC
Imreplys (sargramostim)	Partner Therapeutics	**Treatment** for exposure to myelosuppressive doses of radiation with **H-ARS**	19/06/2025	Approved	MAUEC
Nyxthracis (obiltoxaximab)	SFL Pharmaceuticals	**Treatment** of **inhalation anthrax** in combination with antibacterial drugs	18/11/2020	Withdrawn 02/08/2024	MAUEC
Imvanex (Live Modified Vaccinia Virus Ankara))	Bavarian Nordic	**Prevention** of **smallpox, mpox** and disease caused by vaccinia virus	31/07/2013	Approved	MAUEC
Zabdeno (Ad26.ZEBOV-GP [recombinant]) **Mvabea** (MVA-BN-Filo [recombinant])	Janssen-Cilag	**Prevention** of disease caused by **Ebola virus**	01/07/2020	Approved	MAUEC
Ervebo (rVSVΔG-ZEBOV-GP, live)	MSD	**Prevention** of disease caused by **Ebola virus**	11/11/2019	Approved	CMA (now full MA)
Foclivia (pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted)	Seqirus	**Prophylaxis** of **influenza** in an officially declared pandemic situation	18/10/2009	Approved	MAUEC
A**djupanrix** (split virion, inactivated, adjuvanted)	GSK	**Prophylaxis** of **influenza** in an officially declared pandemic situation	10/10/2009	Approved	MAUEC
Pandemic influenza vaccine H5N1 AstraZeneca (live attenuated, nasal)	AstraZeneca	**Prophylaxis** of **influenza** in an officially declared pandemic situation	20/05/2016	Approved	CMA
Incellipan (live attenuated, nasal)	Seqirus	**Prophylaxis** of **influenza** in an officially declared pandemic situation	19/04/2024	Approved	CMA
Pandemic Influenza Vaccine H5N1 (whole virion, inactivated, prepared in cell culture)	Baxter AG	**Prophylaxis** of **influenza** in an officially declared pandemic situation	16/10/2009	Withdrawn 11/09/2023	MAUEC
Pumarix (split virion, inactivated, adjuvanted)	GSK	**Prophylaxis** of **influenza** in an officially declared pandemic situation	04/03/2011	Withdrawn 11/02/2015	MAUEC
Daronrix ((whole virion, inactivated, adjuvanted)	GSK	**Prophylaxis** of **influenza** in an officially declared pandemic situation	21/03/2007	Withdrawn 24/06/2013	MAUEC
Arepanrix (surface antigen, inactivated, adjuvanted, prepared in cell cultures)	GSK	**Prophylaxis** of **influenza** in an officially declared pandemic situation	23/03/2010	Withdrawn 13/12/2010	CMA
Humenza (split virion, inactivated, adjuvanted)	Sanofi Pasteur	**Prophylaxis** of **influenza** in an officially declared pandemic situation	08/06/2010	Withdrawn 14/06/2011	CMA

Comparison of marketing authorisation types

	Standard marketing authorisation (MA)	Conditional marketing authorisation (CMA)	Marketing authorisation under exceptional circumstances (MAUEC)
Legal Basis	**Article 8 (3)** of Directive 2001/83/EC	**Article 14-a** of Regulation (EC) No 726/2004.	**Article 14 (8)** of the Regulation (EC) No 726/2004
Authorisation based on:	**Full** and **comprehensive data** package	**Favourable benefit/risk without comprehensive data** Comprehensive data are **still being generated** post authorisation in agreed timelines.	**Comprehensive data** on efficacy and safety **cannot** or are **unlikely** to be **obtained**
Data requirements and exceptions	**Demonstrated positive benefit/risk** balance based on full scientific data on quality, non-clinical and clinical data	**Fulfilling legislative criteria** • Applicant **likely** to be **able** to provide comprehensive data **and** • Fulfilment of **unmet medical need and** • **Benefits** of immediate availability **outweigh the risks** related to additional data still being required.	**Specific reasons foreseen in the legislation:** • **Rare indications** → **cannot** be reasonably expected to provide comprehensive evidence, **or** • **Present scientific knowledge** → comprehensive information **cannot be provided**, **or** • **Contrary** to **principles of medical ethics** to collect such information.
Obligations	**May have** condition like PAES, PASS	**Will have specific obligations** and **other conditions**	**Will have specific obligations** and **other conditions**
Validity of the MA	**Five years** • **Renewable** based on a **re-evaluation of the B/R** • **May** then be **valid** for an **unlimited period**	**One year** • **Annual renewals** based on **reconfirmation** of **B/R** • **Comprehensive data** are provided → **switched** to a **standard MA**	**Five years** • **Renewable** and **annual reassessment** of **B/R** • **Not intended** to be **switched** to a standard MA

→ **MA type agreed** on a **case-by-case basis**
→ Depends on **comprehensiveness** of **data** collected and expected to be collected

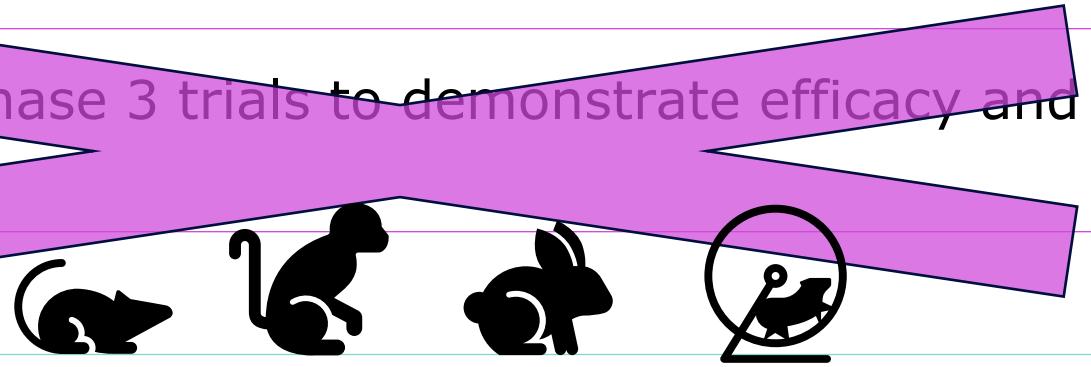
https://www.ema.europa.eu/en/guideline-scientific-application-practical-arrangements-necessary-implement-regulation-ec-no-5072006

CHMP ADOPTED FINAL Exceptional circumstances -15 Decemeber-05

EU approval based on non-clinical efficacy data

Not feasilble

- Phase 2 or Phase 3 trials to demonstrate efficacy and safety in humans



Feasible

Animal efficacy data as **pivotal evidence of efficacy** and extrapolation of dose and efficacy to humans

Requirements:

1. **Prevents/treats** a **serious, life-threatening** disease
2. **Complete CMC** and **non-clinical package** is available
3. **A relevant animal model** reflective of the human disease is available
4. **Efficacy** is demonstrated in **well-controlled animal efficacy studies**
5. **Clinical trials** on safety, pharmacokinetic and pharmacodynamic data in humans and animals → **allow selection** of an **effective dose in humans**
6. MCM is **reasonably likely** to **provide a clinical benefit** in **humans**
7. **Specific obligations** to conduct a PAES, in case of an outbreak

Requirements for the animal model

As **reflective** as possible to the **human disease**

- **Clinical course** of the disease
- **Exposure** to the drug
- **Route of challenge**

Establishment of the **challenge agent and inoculation dose**

Suitable for the **investigational product**

- **Pharmacological action**, PK and pharmacodynamic responsiveness,
- **ADME profile,**
- **On and off-target binding affinities**
- **Receptor/ligand occupancy** and **kinetics**

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-and-mitigate-risks-first-human-and-early-clinical-trials-investigational-medicinal-products-revision-1_en.pdf

Requirements for the animal efficacy study

- Well-controlled, **randomised, blinded, placebo-controlled** studies in **different** relevant **animal species**
- **Reliable and relevant animal model** has been **established**
  → use of **one animal species** may be considered sufficient.
- **Inoculation dose**, **route** of **exposure** and **preparation** of the **challenge agent**
- **Relevant primary efficacy endpoint** to desired effect in humans
  → e.g. reduced mortality, increased survival
- **Dose, administration route** and **timing of administration** medicinal product
  → **reflective** of the **intended use** in **humans**

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Prediction of human dose and safety, PK and PD studies

- **Prediction of the human dose** needed for efficacy:
  - **Animal efficacy studies** and **comparative pharmacokinetic (PK) and pharmacodynamic (PD)** and **immunogenicity studies**
  - **Potential use of Model-informed drug development** (MIDD) in line with ICH-M15
- Investigate the **predicted dose** and **duration** → inform about safety, PK, PD and immunogenicity (vaccines) of investigational product in humans
- **Healthy volunteers** or, if possible, infected patients
- Conducted under the **existing requirements** for **establishing** the **safety of new drugs (ICH-S7A)**
- **Size and composition** of **human safety database** should be in line with **usual EMA standards** (ICH-S7)
- For serious public health threats, available safety database **may** in many cases **not encompass infected patients** → **important limitation**

Totality of data

→ Should **allow** for **selection** of an **effective dose in humans**

→ **Reasonably likely** to **provide a clinical benefit** in humans

Summary and conclusion

Preparedness against **serious public health threats** → paramount and of **utmost importance**

EMA **supports developers** of **MCMs** for serious public health threats including CBRN agents

Flexible regulatory approaches can be **applied** for serious public health threats

Marketing authorisation type will be decided on **case-by-case and dependent on:**

- **Comprehensiveness** of **available data** at the time of MAA
- **Likelihood** of collecting of **comprehensive data post-marketing**

Seek **EMA ETF advice** early in clinical development

- Whether the **product qualifies** for **flexible regulatory approaches**
- **Development program** of the MCM
- **Choice, development** and **relevance** of the **animal model** for demonstrating of efficacy

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Thank you

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Specific type of MA: Pandemic influenza vaccines

- **Specific type** of MA to **develop and authorise** a vaccine **before an influenza pandemic**
- Based on the **long-standing experience** with influenza vaccine strain updates
- Usually include a **strain of avian influenza** (A/H5N1) that few patients have been exposed to and could **potentially cause a pandemic**
- Tested to determine tested to determine if **adequate immunogenicity** is generated **against strains included** in the vaccine
- Include often **more than one virus strain**
- Pandemic preparedness vaccines can be **authorised but not marketed** before an influenza pandemic.
- In case of pandemic: MAH can include the strain in the authorised pandemic preparedness vaccine → authorised pandemic vaccine
- Advantage: Fast approval, as safety and efficacy has been demonstrated with other pandemic strains