Current WHO perspectives
Monkeypox therapeutics
Research considerations

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Research is at the core of WHO’s mandate

The Constitution of the World Health Organization (WHO) defines that one of WHO’s key roles is to promote, conduct and coordinate research in the field of health.

At the request of its 194 Member States in May 2015, the World Health Organization (WHO) convened a broad network of experts to develop an **R&D Blueprint for Action to Prevent Epidemic**. A global strategy and preparedness plan was developed to allow for the rapid activation of research before and during epidemics.

“By embedding research at the heart of the pandemic response we can achieve two goals: to help end the acute phase of the current pandemic and protect us from the epidemics and pandemics of the future.”

Tedros Adhanom
Director-General,
World Health Organization (WHO)
REQUESTS the Director-General:

(1) to strengthen the global, regional, national and subnational pandemic preparedness system, support implementation by States Parties of the International Health Regulations (2005) and of core capacities required under the International Health Regulations (2005)*, provide clear guidance regarding requirements for States Parties under the International Health Regulations (2005), build and strengthen tailor-made support and tools for States Parties through regional and country offices and continue working collectively and collaboratively with partners and States Parties to bridge identified gaps in core capacities required under the International Health Regulations (2005), including through international cooperation, when requested;

(2) to make recommendations to Member States to build a more robust, transparent, consistent, scientific, evidence-based and cohesive International Health Regulations (2005) monitoring and evaluation framework that enables accurate assessment and reporting on national capacities in consultation with States Parties as well as actions to improve International Health Regulations (2005) implementation;....

* Includes research

REQUESTS the Director-General:

(2) to review existing guidance and develop, following the standard WHO processes, new guidance as needed on best practices for clinical trials, including on strengthening the infrastructure needed for clinical trials, to be applied in normal times and with provisions for application during a public health emergency of international concern, taking into account relevant initiatives and guidelines as appropriate such as those led by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and other organizations by providing, as appropriate:

(a) ..... 

(b) guidance on best practices for non-State actors in the design and conduct of clinical trials and in strengthening the global clinical trials ecosystem to meet the needs of major population groups that the intervention is intended to benefit, with a particular focus on under-represented populations, developed in consultation with WHO Member States; ......

Strengthening WHO preparedness for and response to health emergencies

Strengthening clinical trials\(^1\) to provide high-quality evidence on health interventions and to improve research quality and coordination
Have we learnt the lessons?

As of July 6, 2022

4367 RCTs for COVID therapeutics

1268 (29%) completed

1356 (31%) recruiting patients

749 published some results

575 terminated, suspended, withdrawn

https://www.who.int/teams/blueprint/covid-19
Have we learnt the lessons?

https://www.who.int/teams/blueprint/covid-19
<table>
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<tr>
<th>Name</th>
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| Tecovirimat| Targets the membrane protein VP37 of vaccinia virus required for the production of extracellular forms of viruses. It is proposed that this blocking of viral spread allows for development of an adaptive immune response to clear the virus. | EU: authorized for the treatment of orthopoxvirus associated infections (smallpox, monkeypox, cowpox, vaccinia virus) since January 2022 under exceptional circumstances  
Canada: authorized | The evidence for the anticipated antiviral effect in humans comes from the in-vitro and in-vivo nonclinical studies. PK-PD analyses to support the clinical dose regimen and safety data derive from clinical studies in healthy individuals. |
| Brincidofovir | Brincidofovir (lipid conjugate of cidofovir) is an orthopoxvirus nucleotide analog DNA polymerase inhibitor.                                                                                                            | US: Approved by FDA in June 2021 under the agency’s Animal Rule treatment of human smallpox disease caused by variola virus in adult and pediatric patients, including neonates.  
EU: Not approved | No clinical efficacy data available  
Efficacy studies were conducted in the rabbitpox model and the mousepox model. Early treatment (<6 days post challenge) with brincidofovir resulted in significant improvement in survival relative to placebo. |
| Cidofovir  | inhibits DNA polymerase                                                                                                                                                                                                 | EU and US: authorized for the treatment of CMV retinitis in patients with AIDS and normal renal function | Documented activity against poxviruses in in vitro and animal studies. Important nephrotoxicity which limit its use as a first line therapeutic option. |
The US FDA Animal Rule, which allows findings from adequate and well-controlled animal efficacy studies to serve as the basis of an approval when it is not feasible or ethical to conduct efficacy trials in humans.

Approval of a drug under the Animal Rule imposes three additional requirements, which are summarized below (for greater detail, see 21 CFR 314.610(b)(1) through (3) for drugs and 21 CFR 601.91(b)(1) through (3) for biological products):

1. **Postmarketing studies to provide evaluation of safety and clinical benefit** if circumstances arise in which a study would be feasible and ethical (i.e., in the event an emergency arises and the drug is used). A plan or approach to conducting such a study must be included with the new drug application (NDA) or biologics license application (BLA).

2. **Restrictions to ensure safe use**, if needed (e.g., restricting distribution to facilities or health care practitioners with special training, requiring specified types of follow up, or imposing record keeping requirements)

3. **Information to be provided in the labeling to patient recipients** that explains that for ethical or feasibility reasons, the drug’s approval was based on efficacy studies conducted in animals alone. This drug labelling should also include all the other relevant information required by FDA at the time of approval (e.g., directions for use, contraindications, a description of any reasonably foreseeable risks, adverse reactions).

Products approved under the Animal Rule are **subject to postmarketing recordkeeping and safety reporting** applicable to all approved drug and biological products. Information on withdrawal procedures, submission of promotional materials, and termination of certain requirements for products approved under the Animal Rule is specified in the regulations.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/208627Orig1s000SumR.pdf

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**2018** Because smallpox is a serious and life-threatening disease but does not occur naturally, clinical efficacy trials are not feasible, and human challenge studies in healthy subjects are unethical. Therefore, tecovirimat was developed under the Animal Rule (21 CFR part 314, subpart I), which supports a regulatory approval pathway in which studies using suitable animal models contribute directly to drug approval.(3)

NDA 214460
NDA 214461

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approved in any other application under section 351 of the Public Health Service Act."
We reference the June 26, 1986 approval of Vistide (cidofovir) injection (NDA 200638),
which contains the same active moiety as that contained in Tembexa (brincidofovir)
tablet. See section 566A(a)(4)(D) of the FD&C Act.

SUBPART I APPROVAL REQUIREMENTS

Approvals under 21 CFR Part 314, Subpart I (Approval of New Drugs When Human
Efficacy Studies Are Not Ethical or Feasible) are subject to three requirements:

(1) Approval with restrictions to ensure safe use. This subsection permits the Agency
require postmarketing restrictions as are needed to ensure safe use of the
drug product, commensurate with the specific safety concerns presented by the
drug product. We have concluded that TEMBEXA (brincidofovir) can be safely
used without restrictions on distribution or use.

(2) Information to be provided to patient recipients. This subsection requires
applicants to prepare labeling to be provided to patient recipients for drug
products approved under this subpart. We have concluded that the FDA-
Approved Patient Package Insert meets the requirements of this subsection.

(3) Postmarketing Studies. This subsection requires you to conduct postmarketing
studies, such as field studies, to verify and describe the drug's clinical benefit and
to assess its safety when used as indicated when such studies are feasible and
ethical. We remind you of your postmarketing requirement specified in your
submissions dated March 30, 2021 and April 16, 2021, stating that you agree to
conduct a field study in the event of a smallpox outbreak. This requirement,
along with any agreed upon completion dates, is listed below.

4050-1 Conduct a field study to evaluate the clinical response, drug
concentrations, and safety profile of brincidofovir (BCV) when used for the
treatment of human smallpox disease due to variola virus infection. This
trial should evaluate BCV vs. standard-of-care (i.e. active control) vs. BCV
as an add-on-therapy to standard-of-care.

Draft Protocol Submission: 02/2022
Final Protocol Submission: 07/2022

Submit final reports to these NDAs as supplemental applications. For administrative
purposes, all submissions relating to this postmarketing requirement must be clearly
designated "Subpart I Postmarketing Requirements."

We update guidelines periodically. For the most recent version of a guidance, check the FDA Guidance
Documents Databank: https://www.fda.gov/RegulatoryInformation/GuidanceDocuments/default.htm
Health Canada - The Extraordinary Use New Drugs (EUND) pathway was developed to allow a mechanism for authorization of these drugs based on non-clinical and limited clinical information.


Study plan and suspension of a Notice of Compliance

Sponsors must include "a plan for monitoring and establishing the safety and effectiveness of the new drug under the conditions of use recommended that includes procedures for gathering and analysing data" (C.08.002.01(2)(b)(ix)) for both an EUNDS and AEUNDS. This plan is essentially a clinical study or studies, intended to verify the effectiveness of the EUND under the conditions of use (its indications). The plan should be tailored to suit the conditions under which the EUND will be used (its indications). This plan should describe in detail the study design and the procedures to gather and analyze information on the effectiveness and safety under the proposed conditions of use. The plan(s) should include a rationale for the study design, a description of population to be studied, including any vulnerable or special populations (e.g. pediatric, elderly etc.), procedures for collecting information, and the proposed statistical analysis. Criteria for determining lack of efficacy should be clearly stated.

This study plan should also include the procedures for collecting and monitoring adverse events, the methods for determining the causal relationship between the EUND and the adverse event, and for assessing the effect of adverse reactions on the benefit-risk profile of the EUND. Where the EUND is being used prophylactically, a separate study may be required for monitoring the safety in subjects who are not exposed to CBRN substances.

To enhance subject safety and ensure data quality, the study or studies should be conducted in accordance with Good Clinical Practices as outlined in the Guidance Document: Good Clinical Practice: Integrated Addendum to E6(R1) ICH Topic E6(R2), published by Health Canada.
EMA example

Exceptional circumstances

A type of marketing authorisation granted to medicines where the applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because the condition to be treated is rare or because collection of full information is not possible or is unethical.


Why is Tecovirimat SIGA authorised in the EU?

The European Medicines Agency considered that Tecovirimat SIGA is effective at reducing mortality caused by smallpox, monkeypox and cowpox, based on animal studies. While the safety of the medicine was assessed in non-infected people, the side effects of Tecovirimat SIGA are expected to be similar in infected people and are considered acceptable. The European Medicines Agency therefore decided that Tecovirimat SIGA’s benefits are greater than its risks and it can be authorised for use in the EU.

There are no other treatments authorised for the monkeypox and cowpox infections, which although rare can be fatal. In addition, while smallpox has been eradicated, this is an extremely serious infection, for which no treatment exists should an outbreak occur.

Tecovirimat SIGA has been authorised under ‘exceptional circumstances’. This is because it has not been possible to obtain complete information about Tecovirimat SIGA due to the rarity of the diseases. Every year, the Agency will review any new information that becomes available and this overview will be updated as necessary.

What information is still awaited for Tecovirimat SIGA?

Since Tecovirimat SIGA has been authorised under exceptional circumstances, the company that markets Tecovirimat SIGA will provide data on the effectiveness and safety of the medicine in patients given the medicine should an outbreak of smallpox occur.

Treatments research priorities (from June 2-3 consultation)

Existing antiviral data come just from animal models, with continued uncertainties about their efficacy, especially against monkeypox.

Randomized trials with SOC control can be done and are ethical

- Strong support for evaluating antivirals for treatment of monkeypox.
- Randomized trials strongly encouraged by regulators.
- Even for approved products, could be conducted in patients with mild disease.
- Importance of defining who should be treated
- Possible interference antivirals/vaccine. PEP. Combination Rx. Vulnerable/special groups (e.g., pediatrics, pregnancy, immunocompromised).
- Effect of antivirals on virology, including drug resistance.
The most reliable data would come from placebo-controlled studies if there are concerns about ethics, they may be mitigated by genuine uncertainty about the effects of interventions under study.

Globally organized studies organized as equal partnerships enhance equity, speed, generalizability, local capacity & access.
Current WHO statement - Medical countermeasures

1. Use **antivirals** for the treatment of monkeypox cases **within a framework of collaborative research and randomized clinical trial (RCT) protocols with standardized data collection tools** for clinical and outcome data to rapidly increase evidence generation on efficacy and safety. This includes a scientific steering committee, common data management, and robust statistical analysis plan to satisfy regulatory requirements.

2. **Harmonised data collection for safety and clinical outcome** (using WHO Global Clinical Platform for Monkeypox) would represent a desirable minimum in the context of an outbreak such as current one.

When the use of antivirals for monkeypox in the context of collaborative research and randomized clinical trial (RCT) protocols is not possible then consider their use under expanded access protocols/observational studies.

https://cdn.who.int/media/docs/default-source/2021-dha-docs/20220706_monkeypox_external_sitrep_final.pdf?sfvrsn=1b580b3d_4&download=true
https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON396
Tools available that can facilitate collaboration

WHO platform for data collection
https://www.who.int/emergencies/outbreak-toolkit/disease-outbreak-toolboxes/monkeypox-outbreak-toolbox#:~:text=WHO%20suggested%20outbreak%20case%20definition,with%20an%20unexplained%20acute%20rash

WHO Case definitions
WHO Clinical and management guidance
Global CORE protocols with add-on studies that are locally relevant
WHO monkeypox research: What are the knowledge gaps and priority research questions?

https://www.who.int/news-room/events/detail/2022/06/02/default-calendar/who-monkeypox-research--what-are-the-knowledge-gaps-and-priority-research-questions