Rolling reviews: a useful tool to speed up the regulatory review process

Rolling reviews have been in the media spotlight because of a global need to approve COVID-19 treatments and vaccines quickly. This article provides an overview of how rolling reviews work and the process in several key regions

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Regulators around the globe have reviewed marketing authorisation applications (MAAs) for COVID-19 vaccines and treatments at record speed. One of the tools they used to speed the review cycle is the use of so-called rolling reviews or rolling applications.

With rolling reviews, data are submitted and reviewed as they become available instead of waiting for the full data package – nonclinical, clinical and quality – to be available and submitted at the same time. By being able to review data as they become available, regulators can assess and request additional information and clarifications quicker than in a traditional review pathway.

The first batch of information submitted is usually nonclinical information as this is likely the first information to be available. Chemistry, manufacturing and controls (CMC) information is often submitted in a second stage, with clinical modules submitted last.

This approach requires a close collaboration with the health authority reviewing the application to ensure timelines and submission planning are agreed upfront. It also creates additional hurdles for the regulator during the review, as it will require a close planning of resources to review the application.

The pandemic has brought the rolling review approach under broad attention as several vaccines and treatments, including the antiviral Veklury (remdesivir) of Gilead Sciences, and the Pfizer/BioNTech, Moderna and Oxford-AstraZeneca COVID-19 vaccines, have been approved by regulators worldwide using this pathway.

This article will discuss how different regulatory authorities have approached the implementation of rolling reviews in the assessment of COVID-19 vaccines and treatments.

European Union

A rolling review is one of the regulatory tools that the European Medicines Agency (EMA) uses to speed up the assessment of a promising medicine or vaccine. Normally, all data on a medicine's effectiveness, safety and quality and all required documents must be submitted at the start of the evaluation in a formal application for marketing authorisation. In the case of a rolling review, the EMA's Committee on Human Medicinal Products (CHMP) reviews data as they become available from ongoing studies, before a formal application is submitted.

Such rolling reviews for COVID-19 are conducted under the EMA emerging health threats plan and starting them requires specific agreement by the COVID-19 EMA pandemic Task Force (COVID-ETF).[1,2]

The assessment of the rolling review is performed by the rapporteur and co-rapporteur and the outcomes are adopted by the CHMP.

The key features of rolling reviews are that:

- Each rolling review submission occurs in eCTD (electronic common technical document) format with an application form, a Module 2 overview and

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responses to a cumulative listing of all outstanding questions from previous review cycles
- There can be several rolling review cycles, with each cycle normally requiring a two-week review, depending on the amount of data. Responses to the list of questions from previous rolling review cycles are to be incorporated into subsequent rolling review submissions.

Once the CHMP decides that sufficient data are available, the formal application should be submitted by the company.

United Kingdom

The UK national regulator Medicines and Healthcare products Regulatory Agency (MHRA) has implemented a rolling review process as part of its national applications following Brexit.[3] This process can be used for any MAA for new active substances, including biologics. Applications for biosimilars are also eligible under this route.

Developers wishing to enter the rolling review should request a pre-submission meeting with the MHRA to discuss the product, its intended target populations and the data in each module to be submitted. Companies should specify if the future MAA is intended for the UK, Great Britain (England, Scotland and Wales) only, or Northern Ireland only.

The quality, nonclinical and clinical data may be submitted separately or jointly, depending on the specific development pathway and/or availability of data. Submission should be in the CTD format (modules 3–5, as appropriate). The assessment cycle for each submitted module will be completed within 60 days. Following each assessment cycle, a module assessment summary (MAS) will be issued by Day 60. The MAS will offer the applicant opportunities to update the module where required or to provide additional information where needed. The pre-assessment process may also include consultation with the Commission on Human Medicines (CHM) and/or therapy area experts (specialty expert groups).

It is recommended to have a pre-submission meeting with the MHRA around 90 days in advance of the intended submission of the final phase of the MAA. The UK paediatric investigation plan (PIP) compliance check (CC) should be performed 60 days before the submission. The final application/dossier should include submission of any unassessed modules or data, which may include the clinical module, UK-specific CTD module 1, consisting of an appropriate risk management plan (RMP), UK CC and/or orphan designation application (if applicable). The SmPC/PIL may be submitted as Word documents in the 'working documents' folder. There is an option to put the UK-specific SmPC/PIL/labelling text/ mock-ups in the UK-specific eCTD folder structure. Once the MAA is validated, the assessment clock starts, and the final phase should be completed within 100 days in two stages as 60 + 40 days with an intervening clock off period. A request for further information (RFI) may be issued by Day 60 and the applicants may discuss issues with the MHRA within 30 days. The clock resumes on Day 61 when the RFI response is received by the MHRA, and the CHM will be consulted, with the final decision on approvability reached by Day 100. If applicable, orphan status will be determined at the time of grant of the MA, after which refund of any relevant application fees (eg, scientific advice, MAA) may be claimed by the MA holder.

United States

In the US, rolling review is available for products under Fast Track and Breakthrough Therapy Designation (BTD).[4] Products under a new drug application (NDA) or a biological license application (BLA) can apply for rolling review through this route. Several COVID-19 vaccines, like the ones from Moderna and Pfizer/BioNTech received fast track designation in the US.

Fast Track – introduced in 1997 – is designed to facilitate the review of drugs intended to treat serious conditions as well as address an unmet medical need. The determination of what is an unmet medical need is made by the US FDA based on a number of criteria such as survival, day-to-day functioning, etc.

BTD was introduced in 2012 to support the development of drugs intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints.

In order to benefit from rolling review, companies will obtain preliminary FDA agreement on the proposal at the pre-NDA or pre-BLA meeting. For products with BTD this can be done earlier, for example at an end-of-phase 2 meeting.

At the pre-NDA/BLA meeting, the sponsor and the review division should discuss:
- The data that will be used to support effectiveness claims
- The schedule for submission of each portion of the BLA/NDA
- Description of portions of the application to be submitted separately.

A request to submit separate modules of an application should be included in the briefing package for the pre-BLA or pre-NDA meeting. If a sponsor seeks to submit portions of an application to the IND after the pre-BLA or pre-NDA meeting, the sponsor should make such a request and provide a proposed schedule for submission of portions of an application to the investigational new drug (IND) application as soon as possible.

A request for submission of portions of an application should be sent as an amendment to the IND.

Generally, the FDA only accepts the submission a complete section of a BLA or NDA, such as the entire CMC section, toxicology section, or clinical section. A section of a BLA or NDA should be submitted for review in the same format as to have been included in a complete BLA or NDA submission. The FDA only accepts final documents (including reports) as part of a rolling review.

Occasionally, the Agency accepts less than a complete section if it determines that the subsection would constitute a reviewable unit and be useful in making the review

process more efficient. Examples of such situations could be a CMC section lacking final consistency lot data and long-term stability data, a toxicology section lacking chronic toxicology data, or final study reports for some or all of the principal controlled trials without integrated summaries, etc.

Canada

In Canada the national regulator Health Canada also offers the possibility for rolling review in the current pandemic. The "Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19 (IO)"[5,6] allows for the filing of rolling submissions for vaccines and therapeutics for COVID-19.

Before filing an application for a rolling review, a certain level of evidence on the safety, quality and efficacy of their vaccine needs to be available.

To file an application for a rolling review, pharmaceutical companies should have, at a minimum:

- Nonclinical and clinical Phase II data that demonstrate promising evidence of safety and efficacy
- Confirmation that Phase III trials have started and there are enough people enrolled to provide evidence of safety and efficacy within a reasonable amount of time (expected to be within six months from initial filing)
- Evidence that manufacturing is in compliance with good manufacturing practice (GMP) and that product quality and consistency are well controlled.

Sponsors must also file a submission plan giving the anticipated timelines for submitting the various components of the application. A preliminary submission plan should be included in the initial filing.

The plan should describe the studies to be completed and the timing of when it is planned for submission to Health Canada. It should contain:

- List of study data (planned and in progress) and when data will be available
- Detailed information on when each component of the application can be expected (for example, quality)
- Commitment to market the drug should Health Canada authorise the sale under the interim order and marketing plans
- Dates of filing in other foreign jurisdictions (for example, EMA, FDA).

The plan should be discussed at pre-submission meetings to establish application content, available data and timelines of submission.

KEYWORDS

Pandemic; COVID-19; Vaccines; Rolling review; Marketing authorisation applications; Global health; UK; EU; Australia; Canada; US.

Australia

In Australia, the Therapeutic Goods Administration (TGA) is responsible for assessing all medicine applications, including COVID-19 treatments and vaccines. To be able benefit from a rolling review, medicines must be submitted under the provisional pathway.[7]

In order to submit an application under the provisional pathway, the developer must first submit a provisional determination application.

The TGA will assess this determination application against specific eligibility criteria, such as the nature of preliminary clinical data, evidence of a plan to submit comprehensive clinical data, and the clinical need. Based on this assessment the TGA will determine whether the medicine is eligible for registration via the provisional approval pathway.

It is highly recommended to arrange a pre-submission meeting with TGA to discuss a planned provisional determination application and subsequent submission for provisional registration. In this meeting it will be discussed if the medicine could be eligible for rolling review. This is decided on a case-by-case basis by the TGA.

To assist TGA with its planning and resourcing, it will need to be agreed with the TGA which additional data will be submitted in which timeframe.

Not only useful in times of health crises

Rolling reviews can speed up the review of promising medicines, not only in times of health crises. The big advantage is that information and data are submitted as they become available, and allow for review of these data in parallel with trial/manufacturing activities still ongoing.

This approach, however, requires a strong collaboration between applicant and regulator to define the planning and timelines for the submission of the different modules. This collaboration is achieved by frequent interactions between company and health authority before and during the application process.

This rolling review approach has proven useful during the current pandemic as it has allowed the (conditional) approval of a number of COVID vaccines and treatments at record speeds.

Following the pandemic, it could be advisable to evaluate if their use could be – where feasible – expanded to other marketing authorisation applications, where this is not already available. ■

References

1. EMA/863454/2018 EMA plan for emerging health threats. Available at: www.ema.europa.eu/en/documents/other/ema-plan-emerging-health-threats_en.pdf (accessed 5 March 2021).
2. EMA/213341/2020 EMA initiatives for acceleration of development support and evaluation procedures for COVID-19 treatments and vaccines. Available at: www.ema.europa.eu/en/documents/other/ema-initiatives-acceleration-development-support-evaluation-procedures-covid-19-treatments-vaccines_en.pdf (accessed 5 March 2021).
3. UK Medicines and Healthcare products Regulatory Agency Guidance: Rolling review for marketing authorisation applications, 31 December 2020. www.gov.uk/guidance/rolling-review-for-marketing-authorisation-applications (accessed 8 March 2021).
4. FDA Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics. Available at: www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics (accessed 8 March 2021).
5. HealthCanada: Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19. Available www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/interim-order-import-sale-advertising-drugs.html (accessed 8 March 2021).
6. HealthCanada: Information and application requirements for drugs authorized under the Interim Order: Guidance document. Available at: www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/interim-order-import-sale-advertising-drugs/guidance.html (accessed 8 March 2021).
7. TGA: Therapeutic Goods Acts – Provisional Approval Pathway. Available at: www.tga.gov.au/provisional-approval-pathway-prescription-medicines (accessed 8 March 2021).