Guidance note on new assessment routes in a no-deal Brexit

Further information on the new assessment routes including targeted assessment, accelerated assessment and a rolling review.

Published 18 March 2019
Last updated 8 August 2019 — see all updates

From:

Medicines and Healthcare products Regulatory Agency

Contents

The MHRA is introducing certain new routes of assessment for evaluation of marketing authorisation applications. They include targeted assessment, accelerated assessment and a rolling review.

Targeted assessment (TA) process

The “Targeted Assessment (TA)” process is intended to support the timely availability of new medicines for patients in the UK.
The MHRA will evaluate the marketing authorisation application together with the Committee for Medicinal products for Human Use (CHMP) assessment reports submitted by the applicants, and will reach its opinion on approvability within 67 days of submission of a valid application to the MHRA.

This section provides guidance on the procedural aspects for the targeted assessment process.

Eligibility for TA

The TA route is available for products containing new active substances or biosimilar molecules that wish to obtain a marketing authorisation in the UK. These products will also have to have received a positive scientific opinion from the CHMP in the centralised authorisation procedure in accordance with regulation 58 of the Human Medicines Regulations 2012, as amended by the Human Medicines (Amendment etc.) (EU Exit) Regulations 2019.

While applications can be accepted after the approval of an EU marketing authorisation, the intention of the scheme is based on submission of the application to MHRA immediately following the CHMP opinion. TA is also applicable to those products that are seeking orphan status, conditional marketing authorisation or marketing authorisation under exceptional circumstances.

There is a separate process for applications in transition on exit-day (inflight applications). TA is intended for applications where UK was not involved in the discussions at CHMP.

There is a fee payable as applicable. See our guidance on fees for further details.

Submission of applications for TA

The applicant should submit the same dossier (CTD modules) as that submitted to European Medicines Agency (EMA) for the centralised procedure together with the sequential assessment reports from CHMP from day 120, through to the final day 210 opinion. The day 210 opinion does not refer to the EPAR which is generated several weeks later.

It is the responsibility of the applicant to ensure submission of all assessment reports including questions raised by CHMP and the responses. Omission of CHMP reports may render the application ineligible for targeted assessment.

The short assessment timetable including consultation with Commission on Human Medicines (CHM) and its expert advisory groups requires specific submission dates for receipt of applications.

The time window for submission of the documentation (the dossier and available CHMP reports) will begin after day 180 of the centralised procedure. The MHRA will publish a set of submission dates to facilitate planning submissions.

The application will be valid for assessment to start when the day 210 CHMPopinion is provided to MHRA. In order to achieve the timelines the applicant must ensure that the day 210 opinion is submitted to the MHRA within 3 days.

A pre-submission meeting with MHRA in advance to facilitate planning is encouraged, but is not mandatory. Pre-submission meetings offer the opportunity to enhance joined up work with National Institute for Health and Care Excellence (NICE) Health Technology Assessment (HTA) evaluation process.

Validation of an application for TA

The eligible applications that have progressed through the centralised procedure by the EMA will be deemed valid on submission to the MHRA. The MHRA will endeavour to complete all validation steps after submission to ensure that all sequences are made available on the portal in order to progress to targeted assessment. The clock for MHRA assessment will start as soon as day 210 CHMP opinion is provided. See our guidance on making submissions to MHRA through the portal in a no-deal scenario.

Evidence of a check of compliance with a Paediatric Investigation plan agreed by EMA/PDCO (Paediatric Committee) where appropriate should be provided.

Applications that refer to an Active Substance Master File (ASMFs) should ensure that the file has already been submitted to MHRA or included in the submission. We recently published updated guidance on how to handle ASMFs if the UK leaves the EU without a deal.

Assessment and expert advice

The assessment process clock will begin on submission of a valid application. The multidisciplinary assessment teams in the Licencing Division of MHRAwill carry out the assessment of the application informed by the CHMPdeliberations as detailed in sequential assessment reports (day 120 through-to day 210 opinion).

The teams will collaborate with the Vigilance and Risk Management Division regarding assessment of the Risk Management Plan (RMP). Risk management issues will be addressed within this timeframe, and the day 210 CHMP decision that reflects Pharmacovigilance Risk Assessment Committee (PRAC) discussions will provide the basis for the RMP activities in the UK.

The MHRA will consult CHM for advice during evaluation of all TA. The CHMmeeting dates will be published on the MHRA website. The MHRA may additionally wish to seek advice / input from therapy area experts (specialty Expert Advisory Groups).

The targeted assessment will operate to a 67-day cycle, with the CHMconsultation and provisional decision madeby 6 -weeks (day 42) after clock start. Any UK specific points for clarification relating to the application and the RMP will be raised during assessment and expected to be finalised by the time of grant of UK marketing authorisation. A clock-stop is not envisaged.

In the event MHRA differ in their conclusions from the CHMP opinion as regards the approvability of the application on the basis of serious risk to public health in the UK, a request for further information will be sought from the applicant and the timeline will revert to a day 150 timetable. See link for definition of serious risk to public health.

The process will then follow the standard appeal processes for national applications with a clock stop to facilitate responses.

Publications

Conclusion of the targeted assessment will lead to publication of a UK-Public Assessment Report (PAR) for the product.

Accelerated Assessment pathway

The ‘Accelerated Assessment’ process is aimed at enhancing the availability of novel medicines for patients in the UK. Under this scheme, the MHRA will evaluate the marketing authorisation application and will reach its opinion on approvability within 150 days of submission of a valid application.

This section provides guidance on the procedural aspects for the accelerated assessment process.

Eligibility for Accelerated Assessment

The Accelerated Assessment option is available for all products containing new active substances, including biologicals for whom the applicants wish to obtain a marketing authorisation in the UK. This is as per regulation 58 of the Human Medicines Regulations 2012, as amended by the Human Medicines (Amendment etc.) (EU Exit) Regulations 2019. The scheme is based on submission of an independent standalone application to MHRA.

There is a fee payable as applicable. Please see our section on Fees for further details.

The Accelerated Assessment route can be used for products that are seeking orphan status, or a conditional marketing authorisation or products fulfilling the criteria for exceptional circumstances.

How to apply for Accelerated Assessment

All applicants interested in seeking Accelerated Assessment should contact the MHRA (designated coordinator) well in advance of the intended date of submission. The letter requesting Accelerated Assessment should include the intended date of submission of the dossier.

The applicants should submit a valid, full application to the MHRA for evaluation. The accompanying cover letter should detail the intention to seek orphan status or MA under exceptional circumstances as applicable. Separate guidance will be published on criteria for orphan marketing authorisations, those considered under exceptional circumstances and conditional marketing authorisations.

The MHRA will operate a 'fixed submission date' system to facilitate consultation with the CHM and the dates of CHM meeting. MHRA will publish a set of dates to facilitate planning the submissions and coordinating with appropriate meeting dates of CHM.

A pre-submission meeting with the MHRA assessment teams is encouraged. At the meeting the company may present their intentions, a short summary of the dossier, verify the new active substance status and raise any special issues such as requests for consideration for conditional MA or MA under exceptional circumstances. Pre-submission meetings offer opportunity to enhance joined up work with NICE HTA evaluation process.

Validation of applications for Accelerated Assessment

Applications should be submitted through the MHRA portal. See our separate guidance on how to make submissions to MHRA through the portal in a no-deal scenario.

A valid application/dossier for Accelerated Assessment should include common technical modules (CTD modules 2-5), a UK specific CTD module-1, and an appropriate Risk Management Plan. Appropriate justification and compliance with paediatric requirements and investigation plans should be included.

Compliance with the Paediatric Investigation Plans will be performed as part of the validation. To prevent delays at the time of validation, the applicants are encouraged when possible to request a compliance check by the MHRAat least one month prior to the planned submission of a regulatory application.

Applications that refer to an ASMFs should ensure that the file has already been submitted to MHRA or included in the submission. See our recently published guidance on how to handle ASMFs if the UK leaves the EU without a deal.

The MHRA will endeavour to complete all technical validation steps within a specified number of days after submission and will publish the timelines prior to commencement of the scheme. The assessment clock will begin after validation of the application.

Accelerated assessment process and expert advice

The multidisciplinary assessment teams in the licencing division of MHRA will carry out the assessment of the application collaborating with Vigilance and Risk Management of Medicines assessors for evaluation of the RMP. Consultation with the Devices division will be necessary if a companion diagnostic device is required for safe and effective use of the medicinal product.

The assessment process includes consultation with the CHM on fixed dates each month. The submission slots will be linked to the dates of CHMmeeting. The MHRA may additionally wish to seek advice/input from therapy area experts (specialty expert groups) during the assessment process.

The assessment process will run in two phases totalling 150 days with an intervening clock-off period between phase I and phase II. Assessment phase I including CHM consultation will be completed 80 days after clock start. Concerns arising from initial assessment will be raised with the applicant and should be addressed in the clock off period of 90 days. Phase II assessment will begin on receipt of the applicant’s

responses. Assessment in phase-I will also address eligibility for grant of orphan status or a conditional MA.

Based on the assessment, the MHRA will provide an opinion on approvability of the product by day 150, and if positive, will grant the MA.

Appealing a decision to refuse

If the MHRA refuse to grant the MA based on concerns noted, there is an opportunity for the applicant to appeal the decision to CHM.
The MHRAdecision letter will detail the appeal process and timelines.

The orphan status will be determined at the time of MA grant. If orphan status is not agreed and company wish to appeal this decision, the grant of a marketing authorisation will only be possible when the appeal process is completed.

Publication

Conclusion of the accelerated assessment will lead to publication of UK-Public Assessment Report for the product.

Guidance on the Rolling Review route

The Rolling Review is a new route for marketing authorisation applications intended to enhance development of novel medicines. It does this by offering on-going regulatory input and feedback enabling the applicants to ‘get it right first time’ and reduce attrition due to avoidable regulatory pitfalls.

Eligibility

Applications for any new active substances including biological products that wish to obtain a marketing authorisation in the UK based on submission of a ‘full dossier’ to MHRA are eligible for a rolling review.

Similar biological applications (biosimilar products) are also eligible for rolling review. A fee is payable for the evaluation as applicable.

Process and sequence

The process is envisaged as a phased, modular, iterative approach to evaluation of marketing authorisation applications. The details are currently being developed and some early proposals are presented below. The quality, non-clinical and clinical parts may be submitted singly or in combinations depending on the individual circumstances as data becomes available. It is expected that each module will be near completion to avoid multiple iterations of assessment of the same module.

Each assessment phase will progress independently permitting early identification of issues. Each assessment cycle with points of clarification raised will offer the applicant the opportunity and time for a comprehensive update of the modules prior to final submission.

The final phase will involve submission of a complete application including the remaining module together with updated versions of the modules evaluated previously. Technical validation of the full application will be undertaken prior to commencing the assessment.

As with targeted and accelerated assessments, compliance with paediatric requirements are expected to be addressed prior to the final phase. The final assessment is expected to be a single phase with the grant (or refusal in case of unresolved concerns) of the marketing authorisation. The RMPs will also be part of the final evaluations. Each phase of assessment (for quality, non-clinical and clinical modules) will attract a fee and further information will be provided in advance of the launch of the scheme.

Enhanced regulatory interaction and advice will be available during the rolling review process supporting the development process and reducing the risk of failure at the final stage.

Expert input

Consultation with expert advisory groups is anticipated at each stage and with CHM and therapy areas experts (Specialty EAGs) prior to grant of full MA. MHRA will publish further information on the details of the scheme in due course.