



Phase 3



CONTENTS

To approval and beyond

Procedure Selection

SAMs and Type C meetings

PIP

Pre-procedural steps

Eligibility Request

ATC code application

Name Review Request

Letter of Intent

Pre-submission meeting

MAA authoring or review

Lifecycle maintenance

To approval and beyond

The journey from Phase 3 to MAA is exciting as we conclude the final steps in our development work and prepare to request approval of an MAA such that long-awaited revenue can be generated. The workload and importance of careful planning however, should not be underestimated.

No matter how big or small your company, the last stage can be the hardest. This is when we make the final preparatory steps for that all important marketing authorisation approval, however this is the time when we are thinking about commercialisation, with everything that involves. As the pace and number of workstreams continues to increase, the journey can seem to grow in complexity further, particularly in the EU.

With an expert team and clear planning, the pathway to MAA approval becomes a series of manageable steps,

which are easily accomplished and build towards that all important approval and launch date.

InsideReg is a Regulatory Affairs Consultancy founded in 2018 by ex MHRA Quality Assessor Dr Laura Millichamp. The Company mission is to use unique insights and expertise to advance the development and registration of human medicinal products indicated in the prevention and treatment of diseases.

All our Subject Matter Experts bring tens of years' experience to the team, and most are ex-regulatory authority assessors.

This uniquely positions them to share key insights into the workings of the Regulatory Authorities, their mindsets and likely approaches on Clinical, Non-Clinical and CMC issues.

We know that your product is unique, and so we focus on creating teams bespoke to each project, optimising alignment between SME and client. There are no layers of management, and each SME works directly with the client counterpart.

This personal approach means that we blend seamlessly into your team, working alongside each of you to support your company objectives.

In this brochure, we summarise the key steps that you will make during the last major stage in your journey to a licensed and commercialised medicinal product, outlining the support you will need.

Procedure Selection

As with many steps on the journey so far, careful and thorough preparation and planning continues to be key. The pathway to a European Marketing Authorisation is complex, highly administrative and each step must be properly executed.

For companies who have no or limited experience of the EU approach, the complexities can be disorientating. We understand.

There are many pre-procedural steps to a Marketing Authorisation Application and the Centralised Procedure (CP) is by far the most complex. For products such as new active substances intended to treat HIV/AIDS, cancer, diabetes neurodegenerative diseases, auto-immune and other immune dysfunctions, viral diseases, ATMPs, Biologicals, and Orphan Medicines, the Centralised Procedure is mandatory. For all others, an alternative procedure such as a Mutual Recognition (if already approved in at least one other EU member state), National, or Decentralised Procedure might be more appropriate.

With our in-depth experience of the available options, our Regulatory Experts are ideally placed to advise on the best strategy for your product,

considering factors such as legal basis, Member State preferences and the current regulatory landscape in each market.

Once the strategy has been defined, our highly experienced Regulatory Experts have developed checklists, project plans and roadmaps to guide you through this process smoothly from start to finish ensuring nothing is missed. This precision driven approach is imperative as we continue to build the relationship between you the Applicant, and the Regulatory Authorities, driving towards the submission of a high-quality dossier that best reflects the Applicant, and instils confidence in the Assessing team.



Procedure Selection

The MAA process begins as early as possible with a plan of all the documents needed. If we have already supported you through Phase 3 or earlier steps, we will already have identified any risks, and started developing mitigation strategies to help smooth the process. If we are just starting on this adventure together now, our Expert teams of mostly ex-Authority Assessors can perform a cost effective high level gap analysis of the data generated to identify any potential Major Objections, and support you accordingly.

Thereafter, the dossier sections can be authored as soon as data is generated and finalised just prior to submission. Indeed, it can be preferable to work on “live” versions of dossier sections that are developed concurrently with the data, usually CMC, to reduce timelines. This can also minimise the authoring work needed between Phase 3 and MAA submission as these live documents mature simultaneously to the product.

We support you with:

Strategy and planning: We perform a landscape analysis to review the currently approved products to evaluate whether there have been any recent changes and evaluate the impact. Thereafter, we propose the best strategy for your product, from both a legal basis and procedural perspective.

Project Management:

For each project, we map out each step aligning timelines and milestones with company objectives, resource and budgets, so that a realistic submission date is defined. We then identify possible questions and develop risk mitigation strategies so that we are fully prepared to respond to questions. We support you at each step to keep the project progressing, on time, and at the expected quality.



SAMs and Type C meetings

At this stage in development, the dataset is more mature and we are starting to move towards commercialisation. Whilst there may still be some technical questions remaining, for example regarding comparability of biological products following a pre-commercialisation scale up of manufacturing process, the more usual value of Scientific Advice at this stage is to align regulatory expectations and to gain pre-agreement with the Regulatory Authorities on the data to be presented within the MAA submission.

Our Expert Consulting teams, highly skilled in identifying the development of clear and cohesive storylines and preparing data for presentation to Regulatory Authorities, have extensive experience in leading and supporting Scientific Advice Meetings.

Preparation for a Scientific Advice meeting is a committing and detail-oriented process. The strategic considerations are also important, and the selection of the best Regulatory Authority and procedure for advice is key. Thereafter, it is imperative that the questions are very carefully selected, posed precisely and well supported by the Company position to elicit the advice needed. Our deep knowledge of the current regulatory landscape and Authority Expectations ideally places our Experts to guide you through the objective setting so that a clear direction and strategy is set from the outset.

Whilst the FDA have different meeting types depending on the stage of development, a number of advice procedures are available in the EU: Centralised, National and the Simultaneous National Scientific Advice (SNSA) being offered until end 2024. Our Expert teams can advise on the best procedure, and countries to approach depending on the questions to be asked, meeting objective and likely response from each Authority.

Scientific Advice can be offered in written or face to face meeting format. We support with meeting preparation, identifying possible areas for discussion focus, assigning team roles and responsibility and preparing slides. We then rehearse together to ensure that a clear messaging and highly professional image is presented to the Regulatory Authorities.

SAMs and Type C meetings

We support you with:

Objective setting: The objectives for a Scientific Advice meeting are usually a combination of several considerations, however a principal objective should be identified to underpin the data and question positioning.

Question identification and selection: Identification of scientific advice questions is an art form. Each one should be precisely worded and supported with a clear company position setting out our justification for the proposed data acceptance or agreement with proposed next steps.

Briefing book authoring: We offer a range of support, tailored to best suit the client needs and budget, from a high level review of the briefing book that you have prepared through to a full service model where we author the documents from first principles using raw data and laboratory reports.

Meeting preparation: Scientific Advice can be offered in written or face to face meeting format. We support with meeting preparation, identifying possible areas for discussion focus, assigning team roles and responsibility and preparing slides. We then rehearse together to ensure clear messaging and a highly professional image is presented to the Regulatory Authorities.

Application Process: We guide you through the entire application process, managing all communications with the Regulatory Authorities on your behalf, ensuring a smooth process and timely receipt of advice.

FDA Agent: Our US colleagues act as your US Agent managing all the submission activities on your behalf, ensuring timely follow up and using their excellent relationships with FDA staff to optimise communications.



PIP

Paediatric studies are not mandatory for all indications and products, so our Expert Team perform a review of the current regulatory precedent, conditions and requirements, then advise on the correct regulatory pathway: Deferral, Waiver, PIP Submission.

PIPs are expected to be complete by the end of Phase 2 in the EU, no later than 60 days after the EOP2 meeting in the US, and earlier submission of plans is encouraged by both EU and US Regulatory Authorities. If the PIP (Waiver or Deferral) has been submitted prior to the end of Phase 2, now is the time to apply for the PIP Compliance Check.

Left it a bit late? Don't worry, our Expert Team are available to expedite the preparation and submission of an overdue PIP as a priority.

Part of preparation for an MAA submission is ensuring that the PIP (or Waiver or Deferral) is approved. With only 60 days initial assessment timeline and using our good relationship with the Regulatory Authorities, it is straightforward to put this in order and achieve this milestone promptly.

Thereafter, we draft or review the application documents, ensuring the data and justifications are well positioned and in line with current regulatory expectations. We can also publish and submit the PIP on your behalf, liaising with the regulatory authorities until successful completion of the application.

We support you with:

PIP preparation and submission: Our Clinical Experts have extensive experience in the development of paediatric medicines, across a range of indications, including rare diseases. We can author a PIP from first principles, review and comment to optimise a PIP prepared internally, and manage the entire submission and compliance check procedure on your behalf via the correct online platforms. If the PIP is overdue, we can prioritise and expedite the preparation of a PIP (or Waiver or Deferral), using our excellent relationships with the Regulatory Authorities to ensure that it is approved as quickly as possible.

Status check: A PIP Compliance check is an administrative, but mandatory step on the pathway to MAA submission in the EU and UK. We can manage this process from start to finish, ensuring a right first-time application, effective communication with the Regulatory Authorities, and timely completion.

Pre-procedural steps

Eligibility Request

In terms of procedural steps, the first is to confirm eligibility to the Centralised procedure. This is compulsory for all products regardless of whether or not they fall under the mandatory scope. Products for which the Centralised procedure is mandatory should submit a simple statement of the legal basis and the reason why the procedure is mandatory should suffice.

For products for which the centralised procedure is optional, a little more detail should be added to justify the choice of procedure. Don't forget that both National (followed by MRP) and DCPs are also open to new drug substances and where commercialisation is planned in only a limited number of markets, we can help you select the best regulatory procedure for your product depending on your commercial objectives.

The eligibility of a medicinal product for evaluation via the Centralised Procedure must be requested to the European Medicines Agency (EMA) by the applicant. The eligibility request must be provided to the EMA between 18 and 7 months before the MAA is filed and a formal response from EMA is received within a month.

ATC code application



Pre-procedural steps

The Anatomical Therapeutic Classification (ATC) classification is a system in which medicinal products are divided into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties. An ATC code is a set of 6 letters and numbers issued by the World Health Organisation (WHO) that identifies and classifies an active substance according to its therapeutic use.

Prior to submitting an MAA, an ATC code application should be submitted. The procedure is straightforward, and there is no fee, however there are some key considerations.

The submission comprises an application form (completed online), and a justification document. The justification document should include the relevant information such as chemical structure, relationship to other drugs, mechanism of action, indication and proposed classification. It is imperative that the document is precisely and clearly written because there is no opportunity for clarification or presentation of additional information during the procedure. This justification is appended to an online application form and submitted online.

Confirmation of receipt will then be issued by WHO (by e-mail only) and within 6-8 weeks, a draft ATC code is usually assigned. The draft ATC code is then approved at the next working group meeting and published online, together with a deadline for receipt of objections. Any objections received are discussed at the next Working Group meeting at which point either the draft ATC code is made final, or in the event of objections being upheld, a new ATC code is published and a deadline for new objections set. Once the ATC code is considered final, it is published on the WHO website and publication and the applicant notified by e-mail. Timing of submissions is important. In order to limit the number of ATC codes granted to active substances that are not subsequently marketed, an ATC code application should be submitted only when the submission date of the MAA is known, taking into account that the WHO ATC code committee meet twice yearly, in March and October. Premature applications will be rejected by WHO. Generally, submission of an application two meetings prior to the intended MAA submission date is likely to be accepted. The deadlines for submission are published on the WHO website and are approximately 2 months before each meeting.

Ideally, the ATC code application should be submitted to the World Health Organisation prior to submitting the MAA. However, it is possible to make the submission whilst the MAA is under review.

Pre-procedural steps

Name Review Request

The name review procedure evaluates the acceptability of the (invented) name of the medicinal product from a public health point of view. The assessment is performed by the EMA Name Review Group (NRG) and is based on a number of criteria. The applicant should inform the EMA of the proposed (invented) name(s) for his medicinal product at the earliest 18 months and preferably 4-6 months prior to the planned submission date of the MAA and ideally after eligibility has been confirmed.

Letter of Intent

Once eligibility is confirmed, the Letter of Intent (LoI) and request for pre-submission meeting can be submitted, either separately or together. It is possible to submit the eligibility request, LoI and PSM request simultaneously, however it should be borne in mind that whilst this clearly optimises efficiency, sufficient time should be planned between the submission of these documents, PSM and intended submission date. Consequently, it is recommended to submit each document in a stepwise fashion where possible.

The applicant must notify the EMA of his intent to submit an MAA via the Centralised Procedure. Based on this notification, the EMA will proceed with the appointment of a Rapporteur and a Co-Rapporteur who will lead the assessment of the application. The letter of intent must be provided to the EMA 7 months before the MAA is filed. The (Co-) Rapporteurs appointment procedure takes one month.



Pre-procedural steps

Pre-submission meeting

Unlike the SAM and ODD procedures, the PSM is mandatory for Centralised procedure. This is an important opportunity to not only introduce the product to EMA and to ask any procedural questions but also to educate the Agency, particularly if the product is unusual.

In practice, the Pre-Submission Meeting (PSM) can take much longer than 1 month to arrange and as such, it is advisable to submit this request a few months prior to the 7 months pre-submission milestone. Similarly, a little more time between the PSM and submission date can provide additional space to incorporate recommendation made by EMA during the meeting.

This meeting enables the applicant to get feedback from the EMA regarding specific issues prior to finalising the MAA. It also permits establishing contact with the EMA Product Team Members who will be closely involved in the procedure.

The meeting takes place 7-6 months prior to the planned submission date of the MAA. The pre-submission meeting request should be sent to EMA after the Letter of Intent and 6 weeks prior to the targeted meeting date and is comprised of the documents listed in the table below.

The meeting is held remotely via teleconference. The applicant provides a 20-30 minutes presentation on the product development. Then the MAA pre-submission meeting request form is used as the agenda to support the discussion of the applicant issues. The meeting minutes are prepared by the applicant and sent to the EMA for review and approval.

Pre-procedural steps

We support you with:

Checklist:

Our Regulatory Experts perform an initial check of the available data and activities completed to date starting from the PIP, and develop a regulatory plan, taking into account data availability, the planned MAA submission date, and other inputs such as WHO meeting dates and the EMA timetables. We then support you through in achieving each milestone.

Documentation:

The documentation needed for each application/pre-submission step is clearly defined by our Expert Team, who offer the level of support that best suits each project/client, adapting as the project progresses. We can author documents from first principles, presenting them for client review and approval prior to submission, or can take a supporting role in which we provide high level comments to help optimise the chances of that right first time submission.

Submission:

We help you prepare and submit each application on your behalf, keeping you fully up to date with communications and next steps.

Agency Communications:

We can manage all communications on your behalf, keeping clear track of each step and proactively preparing for the next. This ensures all activities are fully visible and kept on track and on time.

Meeting Preparation:

The Pre-Submission Meeting with EMA is an important milestone and has numerous objectives. It is imperative to prepare thoroughly and carefully select topics for discussion continuing to build that positive relationship with EMA. We support you with topic selection and positioning, meeting rehearsals and attendance so that even if this is your first time, it is a highly productive and enjoyable experience.



MAA authoring or review

The Marketing Authorisation Application is divided into five Modules: Administrative, Summaries, Quality, Non-Clinical and Clinical.

Authoring a MAA from first principles, using raw data, is a demanding activity requiring a team approach,

even if we start from mature Phase 3 documentation. Whilst each Module is stand-alone, consistency across all Modules is critical and good storylines are essential. All data needs to be accurately summarised from the initial reports such as manufacturing records, clinical and non-clinical reports and any discrepancies identified and properly managed early on.

Our well established, multi-disciplinary teams are well aware of this and work seamlessly.

With their extensive experience of reviewing all Modules of Marketing Authorisation Applications for all types of products across a broad range of indications, our Experts are ideally placed to author or review documents, highlighting any potential risks, and proposing mitigation strategies from the outset.

If time allows, some concerns have been identified during development, or if an asset has been acquired from another Sponsor, a gap analysis can be beneficial to raise any risks as early as possible and to re-review data against the current regulatory requirements. This proactive approach is ideal for avoiding surprises later on and enables us to plan for success accordingly.

Publishing and Submission

Publishing and submitting the dossier is the last step in that long and challenging process of bringing a new product to market. This is the time when all that hard work, and all that data are finally ready for the regulatory authorities' review. The dossier is just a snapshot, a summarised overview, of all the hard work, dedication and commitment made over the preceding years. The quality of the submission should reflect that and further enhance the readability with clear and neat formatting, fully functioning hyperlinks and correctly ordered documents.

Responding to questions

Assessors raise questions for a number of reasons, namely:

- Missing information
- Unclear information
- Justification, or further explanation is required.

MAA authoring or review

The risk of receiving questions can be minimised by thorough preparation of the dossier, and a gap analysis, which can be conducted simultaneously. This is the most efficient way and allows preparation of data for the anticipated questions, post submission. In practice, however, this approach isn't always possible and a list of questions with an associated deadline will be received.

Firstly, try to remember that Assessors do actually want to approve products, so even the list of questions seems long on first glance, regulatory success is still close.

Secondly, read the questions carefully. They are usually well worded. The Major Objections will be particularly well thought through, so it should be possible to identify where in the dossier the assessor has identified a deficiency or lack of clarity.

Finally, the Assessor's job is to ensure all dossiers are consistent with the current regulatory requirements. By taking an honest look at the deficiency through their eyes we can almost always fully understand why the question has been raised.

Following these three initial steps, we can start drafting the responses that will resolve the points. In the event that additional data needs to be generated, we had probably already planned for that so now is the time to check the date of availability of that so that we can incorporate it into the responses.

Once the data and resource needed for a response has been quantified, a plan can be created, together with a timeline. If it seems that the responses cannot be prepared on time, or there is a risk to the response quality, we can contact the assessor or project co-ordinator by e-mail and ask for an extension. Ideally, a date by which you will respond in full should be proposed and once agreed, really should be met in order to build trust and credibility with the Authorities.



MAA authoring or review

We support you with:

Planning and Project Management:

Our Regulatory Project Managers develop a comprehensive plan from the outset incorporating all steps, requirements and timelines, clearly defining the roles and responsibilities.

Authoring:

Our Expert teams, often comprising ex-Regulatory Authority Assessors have many years of experience authoring and reviewing submission documentation. Our forward thinking, risk-minimisation approach means that we are ideally placed to position data and present it in the best possible light, minimising questions during the procedure. We can author the documents from first principles or just provide structure and guidance, being available for questions as you prepare the documents internally. Either way, our Expert teams provide all the support you need for that successful submission.

Compilation and publishing:

Our publishing team compile all the documents needed, checking them against Regulatory Authority requirements to ensure that complete and right first time submission. Each document is then checked, formatted and published. The final submission package is passed through Agency-Recognised validation tools and a validation report generated.

Submission:

We submit the dossier through the correct Regulatory Authority platform and retain the submission receipt.



Lifecycle maintenance

Once your product is marketed, there will be numerous activities to keep the license up to date. Perhaps you need to add an alternative drug substance supplier or drug product manufacturing site? Updating the packaging or labelling/SmPC? Maybe you have acquired a product from another company and need to register the Marketing Authorisation Transfer?

Our Regulatory Experts are highly experienced at variation planning, strategy and submission and we offer full “Affiliate” services in the EU, UK, and Switzerland.

We work in tandem with our clients’ regulatory departments, adapting the submission packages to suit the local markets and managing the submissions through the correct platforms in each country.

We support you with:

Variation strategy and planning: Our experienced Regulatory Experts have many years of experience in defining variation types, change codes and a streamlined regulatory strategy for variations, considering aspects such as future plans, timing and grouping possibilities where advantageous for the lifecycle maintenance of the product. We can lead and deliver this for you or provide a quick check to ensure that right first time submission.

Variation preparation:

We can author the submission package for you or review the documents that have been prepared to ensure all documentation is correctly presented, minimising the risk of questions and time to that all important approval and implementation.

Variation submission:

Our experienced submissions team can publish and submit the variations on your behalf, managing all Agency communications for you and keeping timelines on track.

