



Phase 2



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Progress

For small and medium-sized companies with great ideas, progressing a new medicine through development and into larger scale projects can seem challenging. As the complexities and workstreams increase, so can the rewards, however the journey can still seem uphill. Sound familiar?

With an expert team and clear strategic guidance, the pathway to success can become a series of successful milestones and accomplishments.

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 topics.

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.

At InsideReg, our core values of integrity, excellence and dedication form the foundation of everything we do. This includes our pricing. We know that investment and funding is hard won, so our focus is on maximising the value in everything we do, offering flexible pricing models, so that you can select what works best for you and your project.

In this brochure, we summarise the key steps that you will make as you progress from a First in Human Clinical trial at Phase 1, to Phase 2, outlining the support we offer at each stage.

Welcome to Phase 2

Congratulations on the successful completion of Phase I. Now that product safety has been established, we can focus on demonstrating efficacy and progressing through a number of regulatory gateways, many of which can be value-adding from an investment perspective.

The FDA, European Medicines Agency, MHRA and Swissmedic offer enhanced support for the development of innovative medicines, particularly in rare diseases and indications where the current Standard of Care is simply not enough.

Two main schemes are available: The PRIME (EU) or Breakthrough Therapy (USA) schemes, which can be applied to using proof of concept data, and the Orphan Drug Designation (EU and USA), which should be supported by relevant non-clinical models or patients affected by the condition, indicating clinically relevant outcomes.



The Priority Medicines Scheme (PRIME) and US Breakthrough Designation

We all strive to bring innovative medicines to patients as quickly as possible, with each member of the internal or extended team playing their part in making a real difference to patients. EMA is also committed to support industry in this objective and has developed the PRIME scheme, which was introduced in 2016, building on the existing regulatory framework of scientific advice and accelerated assessment. The scheme is well aligned in principle with the US Breakthrough Scheme, intending to offer enhanced support for medicinal products of major public health interest that have potential to address an unmet medical need. The FDA and EMA regularly exchange information regarding these programs, and this can smooth the path to Parallel scientific Advice procedures within these two markets, if both are a priority for the Sponsor.

This PRIME scheme now offers early dialogue and support with the following benefits:

- Early appointment of a Rapporteur
- Scientific advice at key milestones
- Accelerated assessment

Applications to the PRIME are free of charge, however like the Orphan Drug Designation Application, detailed and robust preparation is key to optimise the product and data positioning.

We support you with:

Data review:

We review the data generated to date and advise on completeness and whether any additional information could benefit the application

Outcome evaluation:

Based on our extensive experience we can estimate the probability of success, also advising on the optimal timing of an application

Submission preparation:

We can provide the level of support that best fits you and your product from a high level review with a short call to discuss our advice, through to authoring the application from the raw data and submitting on your behalf.

PRIME holding for non-EU Sponsors:

Many start-ups are based outside the European Union and are therefore unable to access this scheme. Additionally, the cost of maintaining a legal entity in the EU starting at approximately 3500 Euros per annum can be prohibitive. By using InsideReg's office in Ireland, we hold the PRIME designation on your behalf until you are ready to establish a legal entity in the EU.

Orphan Drug Designation

Is your target indication chronically debilitating or life-threatening with a low prevalence (not more than 5 per 10,000) in the EU? Are you expecting to demonstrate significant benefit over the current treatment, or is there no satisfactory treatment available? If so, an application for Orphan Designation could be successful. Holders of Orphan Drug Designation status benefit from the following incentives offered by EMA:

- Protocol assistance (scientific advice for Orphan medicines) fee reduction
- Access to Centralised Procedure for MAA
- Market Exclusivity: 10 years
- Fee reductions
- Grants

Even if the prevalence criteria is met, access to the scheme is not guaranteed, and a high quality submission is critical to demonstrating to EMA that either there is no satisfactory treatment currently available, or the product is likely to offer significant benefit. Our Clinical and Regulatory Subject Matter Experts can perform an independent review of the current regulatory landscape and standard of care (of existing), and the data generated to date, evaluating the realistic probability of success based on the current EMA expectations. We then guide you on the preparation of the application document, advising on prevalence, current standard of care and existing treatments, and positioning your data and justifications to maximise the chances of success. We can also advise on whether a pre-submission meeting could be beneficial.

The application for Orphan Designation must be submitted through the EMA online platform called IRIS. When making an application to EMA for the first time, the submission via IRIS needs to be preceded with establishment of the Sponsor in the EMA database, SPOR. All user rights need to be correctly assigned and the Research Product Identifier, and all sites involved, correctly registered. For many of our clients, an ODD submission will be the first time that a submission platform has been used and as such, our Submissions Experts are available to support with all the necessary preparatory steps, ensuring that everything is ready well in advance of the submission.

Perhaps you are not established in the EU yet? No problem. We can submit and hold the ODD on your behalf.

Orphan Drug Designation

We support you with:

Regulatory landscaping, and data review: We review the current regulatory landscape and summarise the current regulatory expectations. We perform a critical review of the data generated to date, advise on completeness and whether any additional information could benefit the application.

Outcome evaluation:

Based on our extensive experience we can estimate the probability of success, also advising on the optimal timing of an application

Submission preparation:

We can provide the level of support that best fits you and your product from a high level review with a short call to discuss our advice, through to authoring the application from the raw data and submitting on your behalf.

ODD holding for non-EU Sponsors:

Many start-ups are based outside the European Union and are therefore unable to access this scheme. Additionally, the cost of maintaining a legal entity in the EU starting at approximately 3500 Euros per annum can be prohibitive. By using InsideReg's office in Ireland, we hold the ODD on your behalf until you are ready to establish a legal entity in the EU.



Paediatric Investigational Plans (PIPs) and initial Pediatric Study Plans (iPSPs)

Treating children is not easy, and traditionally, investigational medicines were only studied in adult populations leaving a gap in demonstrable safety and efficacy in the paediatric population. In 2007, the Paediatric Regulation came into effect in the EU, intending to better protect the health of children by making clinical studies in the paediatric population mandatory. Later, the Guideline on Pharmaceutical Development of Medicines for Paediatric Use (EMA/CHMP/QWP/805880/2012 Rev.2) was published by EMA providing helpful guidance on regulatory expectations for formulations intended specifically for this population. In the US, the equivalent requirement is described in Section 505B(e) of the Federal Food, Drug and Cosmetic Act, as amended by the Food and Drug Administration Safety and Innovation Act (FDASIA), effective from July 9, 2012, providing that iPSPs are submitted early in the development process.

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.

Paediatric studies are not mandatory for all indications and products, and as such, our Expert Team can support you by reviewing the current regulatory precedent, conditions and requirements, then advising on the correct regulatory pathway: Deferral, Waiver, PIP Submission.

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.



Paediatric Investigational Plans (PIPs) and initial Pediatric Study Plans (iPSPs)

We support you with:

PIP strategy: We evaluate the current regulatory landscape for the target indication and advise on the correct strategy for your product.

Paediatric Development Plan: Our Clinical Experts have in depth expertise in the development of medicines for paediatric use, including in rare diseases and offer support ranging from high level conceptual study design, all the way through to detailed written study protocols ready to execute.

Streamline data generation: With our teams comprised of or including ex-Agency Assessors, we deliver paediatric development plans that focus on generating a robust data set, thus de-risking next steps and gaining regulatory approval with minimal questions raised.

CMC advice: It is not enough to have a robust clinical development plan using the adult formulation. Paediatric medicines should be specifically designed with the paediatric population in mind. Our Lead CMC Expert actively contributed to the Guideline on Pharmaceutical Development of Medicines for Paediatric Use and as such is ideally placed to advise on regulatory expectations during development of child-friendly formulations.

Scientific Advice

Innovation is exciting, but with guidance and regulations lagging behind technical advances, we are often venturing into the unknown. This journey is never taken alone. You are supported not only by our Expert Consulting teams, highly skilled in identifying the potential challenges early in development, raising them for productive brainstorming sessions and collaborative solution-finding, but also the Regulatory Authorities. One of the most frequent outcomes of discussing innovation, is that we recommend a scientific advice meeting.

There can be several objectives for a Scientific Advice meeting: Value adding, for example, when questions are posed regarding a clinical trial protocol and non-clinical data generated to gain Regulatory Authority endorsement for the next step. Technical advice on data which is being generated, or is planned, but there is no guideline in force and direction is needed on current regulatory expectations. Early engagement is useful for educating the regulatory Authorities on new technologies or highly innovative approaches, smoothing future applications by enhancing dialogue and their familiarisation/level of comfort with the technology.

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.

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.

Scientific Advice

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. 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.

Question identification and selection: Identification of 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.



CMC

Ready to scale up? Great! At this stage, for biological products, the site of manufacture and scale are often adjusted leading to the need for a comparability study. For small molecules, additional CMC data is likely to be available and there may be decisions to be taken around aspects such as lead formulation and formulation optimisation. We are also starting to think about Phase 3 manufacture with a view to developing a commercialisable manufacturing process and formulation. Having a clear strategy now is key and it is imperative to ensure that the CMC data continuity, so that we continue to bridge to the batches used during toxicity studies and the Phase I trial.

All our CMC Experts are ex-Regulatory Authority Assessors, each with over 15 years' experience in the regulatory and technical aspects of CMC. We can focus on a defined project such as developing a comparability plan/protocol, writing scientific advice/agency meeting briefing books, but also regularly accompany clients throughout their development journey, holding positions such as "Acting Director of CMC", or just by remaining available to support calls, meetings and ad hoc questions.

We support you with:

Streamlining data generation: Identifying the necessary data to be generated that is sufficient for the assessor to make their decision, but not so much that it becomes expensive.

De-risking approach: our CMC experts have many years of experience in data submission and requirements at early stages of development, enabling them to advise on challenges such as specification setting and minimum data requirements for approval.

CDMO relationship management: The reports generated by CDMOs are the source data for the regulatory documents. An early review by a regulatory expert ensures that no data is missed and that clear audit trail from IMPD to source data is maintained.

Ad hoc advice: At this stage of development, minor questions arise frequently. Our Experts are on hand to advise quickly and clearly, facilitating decision making and progress towards that next clinical trial batch.

Non-Clinical Studies

Non-Clinical studies can be time consuming and expensive. Animal model selection, number of animals to be used, and duration of studies, are some of the key questions on which we advise. Whilst most projects we support generate their own data package, some are known active substances for which we can cross-refer at least in part to literature or other data. Knowing the available options at the outset means that we can develop a clear non-clinical data generation pathway, streamlined and optimised. Ad hoc advice from a Non-Clinical Expert can be invaluable in answering these questions during this stage, particularly when they have a background as an Assessor/reviewer.

Once data is generated, writing up reports or reviewing those generated by CRO are critical to ensuring a smooth Phase 2 clinical trial application that is well written and demonstrates an acceptable safety profile.

We support you with:

Streamlining data generation: Identifying the necessary data to be generated that is sufficient for the assessor to make their decision, but not so much that it becomes un-necessarily expensive.

De-risking approach:

Our Non-Clinical experts have many years of experience in data submission and requirements at early stages of development, enabling them to advise on critical decisions such as animal model selection, number of animals, study design and duration.

CRO relationship management:

The reports generated by CROs are the source data for the regulatory documents. An early review by a Non-Clinical expert can identify early on any data that might need more careful positioning during presentation to regulatory authorities.

Ad hoc advice:

At this stage of development, minor questions arise frequently. Our Experts are on hand to advise quickly and clearly, facilitating decision making and progress towards that first clinical trial approval.

Troubleshooting:

This is research, and we understand that despite best efforts, sometimes not everything goes according to Plan A. By engaging a Non-Clinical Expert throughout the development stages, challenges are quickly addressed in the manner expected by regulators and the program kept moving in the direction of success.

Clinical Strategy

Further development of novel therapies requires a strategic mindset to maximise the opportunities, and ensure clinical trials are designed for success.

At InsideReg, this is achieved by ensuring optimum alignment of Consultant expertise and client needs to deliver high quality advice and continuous support in your development journey. Following the success of Phase I clinical trials, we continue to support with expert clinical trial design and advice relating to factors such as dose selection.

We objectively review Phase I data, identifying any areas likely to be a focus for the regulatory authorities, presenting strategies for positioning the data and addressing any questions. We also look forward to Phase 3 study design, highlighting any potential opportunities/challenges for consideration.

We support you with:

Clinical Strategy: The key conceptual design elements of a Phase 2 clinical study protocol are outlined, with focus on key areas such as justification of endpoints, clinically relevant effect sizes, study size, recruitment ease, number of centres. Opportunities for protocol and programme acceleration are identified wherever possible.

Clinical Development Plan: At Phase 2, the CDP is likely to need review, and possibly amendment based on Phase I data and any new operational constraints or changes in the overall strategy.

Clinical Study Protocol Authoring: Our Clinical Experts have tens of years' experience in designing Clinical Study Protocols that are acceptable to Regulatory Authorities. A natural follow on activity from the Clinical Strategy and CDP development, we can support you as much or as little as you need from a high level review with a regulatory focus, to full authoring starting from the CDP.



Preparing for submission of Phase 2 Clinical Trial Application

A Phase 2 Clinical Trial Application is a great opportunity to gather and review all data generated to date and to start thinking about Phase 3 plans. Whilst it might seem a stretch to start preparing for Phase 3 already, important preparatory steps and ideas can be presented to the Regulatory Authorities at this stage, to gain agreement, during opportunities such as an End of Phase 2 meeting.

If you have acquired an asset from another company, a high level gap analysis can be useful to identify any data gaps, and develop the right strategies prior to submission. The dossier should be well written, using the correct language and phrasing, to facilitate the assessor's review. Any challenging data should be carefully positioned and a risk mitigation plan put in place to manage questions so that approval timelines can be kept.

Whilst the EU uses a centralised submission platform (CTIS) for simultaneous submission and approval of CTAs, the UK and Switzerland have their own submission pathways. Our Regulatory Experts are available to guide you through a seamless submission using the correct platform for each market, using our own in house checklists, specifically designed to ensure that everything is present and correct for that right first time submission, taking applications smoothly through validation and into that all important review phase.

We also provide local representation services in these markets, acting as the contact point for the Regulatory Authorities. We take the lead and manage all the communications with the Regulatory Authorities on your behalf, so that you can focus on ongoing activities. Any questions received are reviewed by our Experts so that we can support you in positioning responses and submitting them in a timely manner, minimising the time to approval.

We support you with:

Data requirements checklist: Our highly experienced regulatory experts have developed checklists to streamline the gap analysis and ensure that everything is present and correct for that right first time submission.

Submissions: We collate and check all the documents, to ensure a complete submission is made from the outset, taking applications smoothly through validation and into the review phase.

Communication with Regulatory Authorities: We manage all the communications with the Regulatory Authorities on your behalf, so that you can focus on ongoing activities.

