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Regulatory strategy: keeping the end in mind

How a regulatory strategy can optimize drug development from the laboratory to the clinic

Regulators hold the keys to progressing drugs ("medicines" or "drug products") through development milestones, and on to marketing authorization. By anticipating the complex and ever-changing needs of regulators, and presenting robust rationale and the required quality, safety and efficacy data, roadblocks to progressing a drug to clinical trials and subsequently on to marketing authorization can be minimized.

Consequently, drug developers should seek to develop a detailed regulatory strategy, based on good science as well as regulatory requirements, as a central pillar of both preclinical safety assessment and clinical phase development, facilitating efficient progress to market. A disciplined development of a regulatory strategy that actively embraces regulatory needs and anticipates regulators' concerns will facilitate a smooth road to success.

This white paper outlines key considerations drug developers should build into their regulatory strategy early in development. **You will learn:**

Five common pitfalls that prove costly to developers—in time, increased cost or underused resources

Practical strategies that should be considered as part of optimizing the plan

How to **identify areas of risk & opportunities** for exploitation of supportive solutions that will ensure a rounded & complete strategy

section 1

Common pitfalls that result in delays and missed opportunities

The TPP is a format for summary of product development; a dynamic document that should evolve during the process of development. Regulators encourage pharmaceutical sponsors to develop and submit a TPP to facilitate discussions, guide development, and review the submissions against the final intended product.

Pitfall 1 – Failure to develop a well-defined target product profile

Because submission of a Target Product Profile (TPP) is voluntary, it is easy to underestimate the contribution that this document, and the process of putting it together makes to the regulatory process. Rather than being merely viewed as additional work, the document acts as an important strategic planning tool, and should be in place at the start of a drug development program. The lack of a TPP, or an incomplete profile, can result in the conduct of inappropriate and/or unnecessary studies that underutilize time and materials, as well as cause delays, missed opportunities and potential cost implications if additional studies and data may need to be generated and subsequently presented.

To guide the regulatory roadmap, developers must communicate as much as possible about what is intended for the product as it reaches market. By establishing the intended properties of the final product (clinical indication, patient population, etc.), the main considerations for the program can then be mapped out and evidence gaps identified. An optimum TPP, which will be updated throughout the process, is essential for this process, as it will keep everyone: developers, contract research organizations (CROs), marketers and regulators on track toward the desired end state. A clear TPP can help regulators identify issues and contribute proactively, for example, by understanding intended labeling and discussing whether the proposed outcomes of studies are likely to be enough to support drug developers' claims.

The United States (U.S.) Food and Drug Administration (FDA) cites, "The TPP embodies the notion of beginning with the goal in mind," and the sponsor specifies the labeling concepts that are the goals of the drug development program, documents the specific studies intended to support the labeling concepts, and then uses the TPP to assist in a constructive dialogue with the U.S. FDA; this is equally true for other regulatory bodies such as the European Medicines Agency (EMA). As the basis for this dialogue, the FDA recommends that the TPP must be "factual and genuine." [1,2,3]

Therefore, the TPP provides the opportunity of a structured template, holding the development plan together and guiding the process to a planned conclusion, and should be in place at the start of a drug development program.

Pitfall 2 – Inaccurate product classification

A lack of enough information about the product risks inaccurate classification (e.g., new chemical entity [NCE], biologic, medical device, or combination product), that may in turn result in completion of studies that are not required, or the conduct of inappropriate studies, affecting the utilization of resources and impacting on the efficiency of the approval process (e.g., clinical trial application, CTA). In the worst case, if this inaccurate product classification is not recognized before submission, it can result in a delay or even rejection of the application.

Product classification continues to grow in complexity. There are borderline medicines, compounds with multiple mechanisms of action and medical products combined with medical devices—all of which may be classified differently in different regulatory regions. For example, a drug combined with a medical device is classified as a medicinal product in the European Union (EU), but as a drug-device combination in the U.S. This will affect the regulatory process through which the product must follow; in the EU, such a product would only require CE marking (Conformité Européene, i.e., European Conformity) for the device part, but different rules apply in the U.S.

Additionally, classifying a complex product (e.g., combined advanced therapy medical product; CATMP, a product that includes one or more medical devices or active implantable medical devices, as well as cells or a tissue component) is difficult and necessitates guidance from the regulatory body (e.g., Committee for Advanced Therapies [CAT] in the EU).

Gaining the correct understanding of the final product classification ensures assumptions are addressed early and the opportunity to develop a straight course for the development program are assured.

CASE STUDY **Based on the classification of product**

The sponsor's challenge:

- A pharmaceutical sponsor developing a novel immuno-oncology biologic for the treatment of breast cancer requested regulatory advice on the preclinical safety requirements to support their planned first-in-human (FIH) clinical trial

The Fortrea solution:

- After review of available information, our regulatory specialists suggested that their molecule, a peptide, would be classified and regulated as an NCE rather than a biologic because it was manufactured by chemical synthesis
- They also advised that even though their molecule should be classified as an NCE, it still had properties of a biologic. A detailed preclinical program of studies was therefore undertaken, which combined the required studies for an NCE but included additional endpoints that reflected the biologic nature of the molecule (e.g., antidrug antibody response, biomarkers of immune response)

Outcome for the sponsor:

- Our regulatory team provided clear guidance ensuring that the safety assessment and subsequent development plans were aligned to regulatory expectations. Consequently, the sponsor was able to start their planned clinical study on time following successful regulatory approval of the preclinical package of work

Pitfall 3 – Inexperience with requirements and conduct of scientific advice meetings with regulatory authorities

A scientific advice meeting provides advice on the most appropriate way to generate robust evidence on a drug's benefits and risks. The goal of the meeting is to decide what to include in regulatory packages, in particular those for discussion at milestone regulatory advice meetings (e.g., end-of-phase II meeting). Incorrect information could result in confusion or missed opportunities just as under-preparation and over-preparation of key briefing package documents can lead to poor communication, if sufficient evidence is not provided. Further meetings may be needed at an extra cost not only in development time, but also in any fees owed to the regulatory agency.

Experienced CROs can advise customers on what is required for the briefing package for regulatory meetings (e.g., pre-investigational new drug [pre-IND] meeting with the U.S. FDA and scientific advice/protocol assistance meeting with the EMA), and/or whether to approach regulatory authorities (e.g., MHRA [Medicines and Healthcare Products Regulatory Agency] in UK) for further scientific advice. For both CTA documents and authority meetings, sufficient information must be available regarding chemistry, manufacturing and controls (CMC), preclinical safety assessment and clinical trials (if applicable). If the anticipated studies (e.g., those demonstrating purity, stability, identity and quality) are not appropriately documented or included according to guidelines the first time, this work may need to be repeated, possibly losing many years of previous work and delaying the progress of the therapeutic.

In addition to preparing for regulatory authority meetings, the development team should anticipate a requirement to respond promptly to questions that arise from such meetings.

According to the EMA, two out of three drug development programs submitted for scientific advice were considered not suitable for a future assessment of the drug benefits and risks. Following scientific advice, 63% of these trials were modified to include a better way to assess the drug's effectiveness.[4]

CASE STUDY Based on CMC gap analysis

The sponsor's challenge:

- Phase II clinical trials were being planned for a promising metal-polymer complex being developed for the treatment of a common cancer. The pharmaceutical sponsor involved did not have a robust regulatory strategy and had regulatory feedback raising a number of significant CMC questions
- During a scientific advice meeting, the agency suggested that further product characterization was required to meet regulatory guidelines with respect to impurity levels. This also meant that some of the preclinical and clinical data generated to date using the current test material was also not acceptable to the regulatory agency
- The sponsor approached Fortrea for its regulatory and scientific consultancy on the CMC part of their product in order to address the agency's major concerns

The Fortrea solution:

- Fortrea recommended a quality-by-design approach (QbD) for their product development. In order to produce a homogenous product, several purification refinements were suggested, including use of a high performance liquid chromatography (HPLC) with a gradient elution to generate multiple fractions with narrow molecular weight distribution thereby allowing removal of potential impurities (e.g., heavy metals) at the same time
- Fortrea also recommended approaches to improve the solubility of the product using formulation additives; to characterize the purified product based on a set of criteria applicable to medicinal polymer product (e.g., polydispersity < 1.1); to establish trend analysis; to define appropriate in-process controls (IPC); to use orthogonal methods for characterization; and thereafter tighten the product specification accordingly
- The critical quality attributes (CQAs) were identified, and suggestions were made to reduce endotoxin content further and introduce a new reference standard. Our advice also included suggestions on the container and closure system and stability bridging plans to meet the regulatory requirements

Outcome for the sponsor:

- The Fortrea team's gap analysis document on their CMC data acted as a clear roadmap for the sponsor, ensuring that the CMC requirements for their product were aligned to current EU requirements

Pitfall 4 – Missing out on beneficial opportunities of expedited programs

Many companies are not fully aware of the range of beneficial programs that are available and, consequently, valuable opportunities to underpin the development program with scientific, legal, regulatory support and financial incentives provided via the regulatory agencies are missed.

In the EU, small and medium-sized enterprises (SMEs) have special status which offers access to various financial incentives (e.g., 90% fee reduction in obtaining scientific advice from the EMA). SME status is also important for access to EU support programs targeted specifically to support product development. For example, the EU (PRIME) scheme for priority medicines provides free advice; PRIME was "launched by EMA to enhance support for the development of medicines that target an unmet medical need…to optimize development plans and speed up evaluation so these medicines can reach patients earlier."[5] Drugs for serious disorders can also qualify for "fast-track approval," which requires limited data for regulatory applications.[6]

There are also beneficial programs related to the type of product being developed, especially those that target rare or orphan diseases. The mission of the U.S. FDA Office of Orphan Products Development (OOPD) is "to advance the evaluation and development of products (drugs, biologics or devices) that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions".[7] The Committee for Orphan Medicinal Products (COMP) is the EMA committee responsible for recommending orphan designation of medicines for rare diseases, established

in 2000. An orphan designation from this committee allows a pharmaceutical sponsor to benefit from incentives, such as reduced fees (e.g., 100% fee reduction for designated orphan products) and protection from competition once the medicine is placed on the market. Orphan drug status affects the regulatory requirements in different regions in different ways; a chosen CRO should have the expertise to help file for orphan drug status in different regulatory regions.

Innovative treatment developers could discuss the scientific, legal and regulatory aspects of their medicine with the EMA early in development through the Innovation Task Force.[8, 9]

Diligent research and consultation with experts during preparation of the regulatory strategy will maximize the opportunity to access beneficial programs that may provide financial or scientific support, or even find ways to expedite the product's entry to market.

Facts on orphan drugs

In the EU, 92 orphan medical products (OMPs) were approved between 2010 and 2022.

- 89% of the OMPs were based on 'full application'
- 86% of the sponsors received protocol assistance whereas 64% of the marketing authorization applications (MAA) benefited from the accelerated assessment
- 53% were based on the small molecules
- 40% of the OMPs have oncological therapeutic indications
- 56% of the OMPs are intended to treat only adults
- 71% of the products were approved based on a single pivotal trial[10]

Expedited pathway*	Competent authority
Priority review	U.S. FDA
Breakthrough therapy designation	U.S. FDA
Accelerated approval	U.S. FDA
Fast-track designation	U.S. FDA
Limited population pathway	U.S. FDA
Regenerative medicine advanced therapy	U.S. FDA
PRIME (priority medicine)	EU EMA
Accelerated assessment	EU EMA
Conditional marketing authorization pathway	EU EMA
Authorization under exceptional circumstances	EU EMA
Adaptive pathways	EU EMA
Priority review	Japan PMDA
SAKIGAKE designation system	Japan PMDA
Conditional and term-limited approval	Japan PMDA
Priority review	Canada HC
Priority review	Australia TGA
Provisional approval	Australia TGA
Supporting pathways	**Competent authority**
Orphan drug designation	Multiple
Micro, SMEs status	Multiple
Scientific advice	Multiple
Parallel scientific advice	EMA & U.S. FDA
Innovation Task Force	EU EMA
Qualification of novel methodologies	EU EMA
Certification of advanced therapy medical product (ATMP) quality and nonclinical data for SMEs	EU EMA
ATMP classification	EU EMA

Table 1: Summary of global expedited and supporting pathways

** can be used in combination with supporting pathways*

Pitfall 5 – Disjointed regulatory and preclinical strategies

The preclinical strategy must be planned in detail to set up the clinical trials for the product. Specific studies provide data which guides, and ensures, some elements of the clinical program and the regulatory submissions required to reach FIH studies. Failure to adequately identify the contribution of the results, or the need to complete certain preclinical studies, risks serious delays in the program moving into the clinical phase.

One of the most common hurdles early in the safety program is the need to produce adequate quantities of the test item, the production of which must also be ensured and able to provide adequate scale-up. This is particularly important for biologics where minor batch variations can cause significant safety and efficacy challenges. One Good Manufacturing Practice (GMP) batch of material for all nonclinical studies is advisable, although not essential. Additionally, the purity of the material for the clinical package must be the same as, or better than, for the nonclinical program.

The outputs of the studies must be such that they provide the regulatory agencies with the right information about the likely clinical effect of the product and how the safety assessments proposed for the clinical program have been determined. This may require time spent in design of assays for specific markers, or detailed studies to correctly identify the test species that will demonstrate potential for clinical effect, as well as ensuring investigations into the possible side-effect profile.

The trial-and-error approach often used by smaller biopharmaceutical sponsors lacks the necessary internal expertise, risks driving up costs and adds complexity and risk to the coordination of the steps required to successfully reach FIH studies.

Tips on scientific advice

Advice from a national agency (e.g., MHRA, UK or FDA, U.S.) only applies in that country; therefore, for global development programs, multiple agencies must be approached in order to obtain advice in all countries where the trial will be performed.

Advice from an agency is not binding on the agency or the sponsor company, but deviations from the advice given must be justified.

An EU-wide opinion can be obtained via the EMA. In this case, the opinions represent a consolidated opinion from all member states of the EU. Once an EU-wide opinion has been obtained, often national regulatory authorities will refuse to meet companies to discuss development of the same product.

It is prudent to only approach national agencies for advice early in development when clinical trials are likely to be performed in small numbers of countries, and then obtain wider scientific advice covering the whole of the EU via the EMA later in development when many countries could be involved.

section 2

Producing an integrated, optimal program

One of the important goals of a preclinical and early clinical drug development is to identify if the product will be successful, or to reduce the risk of financial loss by identifying risky candidates as soon as possible. This relies on efficient translation of the preclinical data to inform the clinical trial stage but also transcribing observations into possible clinical outcomes.

Planning for maximum efficiency and lowering risk

Characterizing the intended end product is essential for developing an optimal program, which will operate with parallel timings across some of the key regulatory and scientific requirements. The TPP maps the direction in which the product is heading; therefore, production of the TPP is the essential initial step.

Insufficient planning is most likely to impact time to approval as steps may not run as efficiently as possible. A "multidimensional" plan, considering key regulatory requirements in parallel with CMC, preclinical and clinical aspects, can support the development strategy. Creating the right plan ensures success entering FIH studies, and throughout the clinical program. A sound plan starts with the preclinical investigations, feeds result into a constantly maturing TPP and continues beyond initial marketing authorization.

In addition to regulatory requirements, detailed scientific conduct of the studies must also be considered at the planning stage. Key elements to consider before work can include the provision of sufficient test material and a plan for a manufacturing scale-up capability to support the full program.

The plan will also include a multitude of decision points that require data from ongoing investigations to support future stages, **such as:**

- Route of administration decisions (key for regulatory and preclinical work)
- *In vivo* model selection (including the possibility of a nonstandard model or even development of a bespoke model)
- Bioanalytical method development for clinical parameters to monitor both efficacy and safety parameters in the clinical phase

Accepting failure or exploiting successes

An effective plan will also outline well-defined go/no-go decision points, and clearly explains for the entire workgroup the associations of the outputs of each stage on others. For example, due to tight timelines key laboratory-based testing, simulation and modeling might be missed (e.g., crystal form, size and surface area), although it is likely that these crucial parameters affect behavior and performance of the active pharmaceutical ingredients (API). A common delay, resulting from omitting this type of investigation, involves the development of an acceptable formulation to administer the test item. This coordination of toxicology and manufacturing can then also ensure that high-quality product is available when it needs to be (and with all the information on purity, stability, identity and quality correctly documented).

These decision points might constitute a delay in the program while key assays, or perhaps an animal model, are developed, or may constitute a business decision to cease further development of a product if certain positive clinical outcomes cannot be ensured, or potential negative clinical impacts are indicated.

Dovetailing parallel requirements for success

The aim of maximum efficiency and low risk in the shortest time frame can be optimized by creating an appropriate TPP and using it as the core basis for the plan of activities. This ensures the collection of sufficient preclinical data in accordance with set timelines to support IND and CTA submissions.

Although many preclinical studies must be completed to inform the FIH clinical trials, preclinical development will continue. Studies aiming to support late clinical phases (e.g., chronic repeated-dose toxicity studies), or others that are required for marketing approval (e.g., carcinogenicity studies), will continue while the first clinical studies start. Planning studies to be run in parallel is a challenge because results must often be delivered in time for applications for the next phase of clinical trials or marketing approval.

All effort should be made to eliminate unnecessary experiments and toxicity studies, shorten the time to regulatory approval and reduce overall risk associated with the program.

Starting with the end in mind

Finally, the development plan should also look beyond the first marketing authorization. In some situations, studies may be conducted post-approval, either as part of post-approval development commitments or to support a post-marketing safety evaluation. Product extensions or safety study requirements should be identified as early as possible so that they can be included in development plans, enabling them to be overlapped where possible to save time and resources.

Diligence in seeing the plan through to execution as early as possible will ensure that the intellectual property (IP) of the product is managed correctly, and the full commercialization strategy is supported.

section 3

Regulatory strategy checklist

In this section we provide a checklist to help make sense of the steps through which to proceed to maximize the chances of an "end in mind" strategy being developed and delivered efficiently.

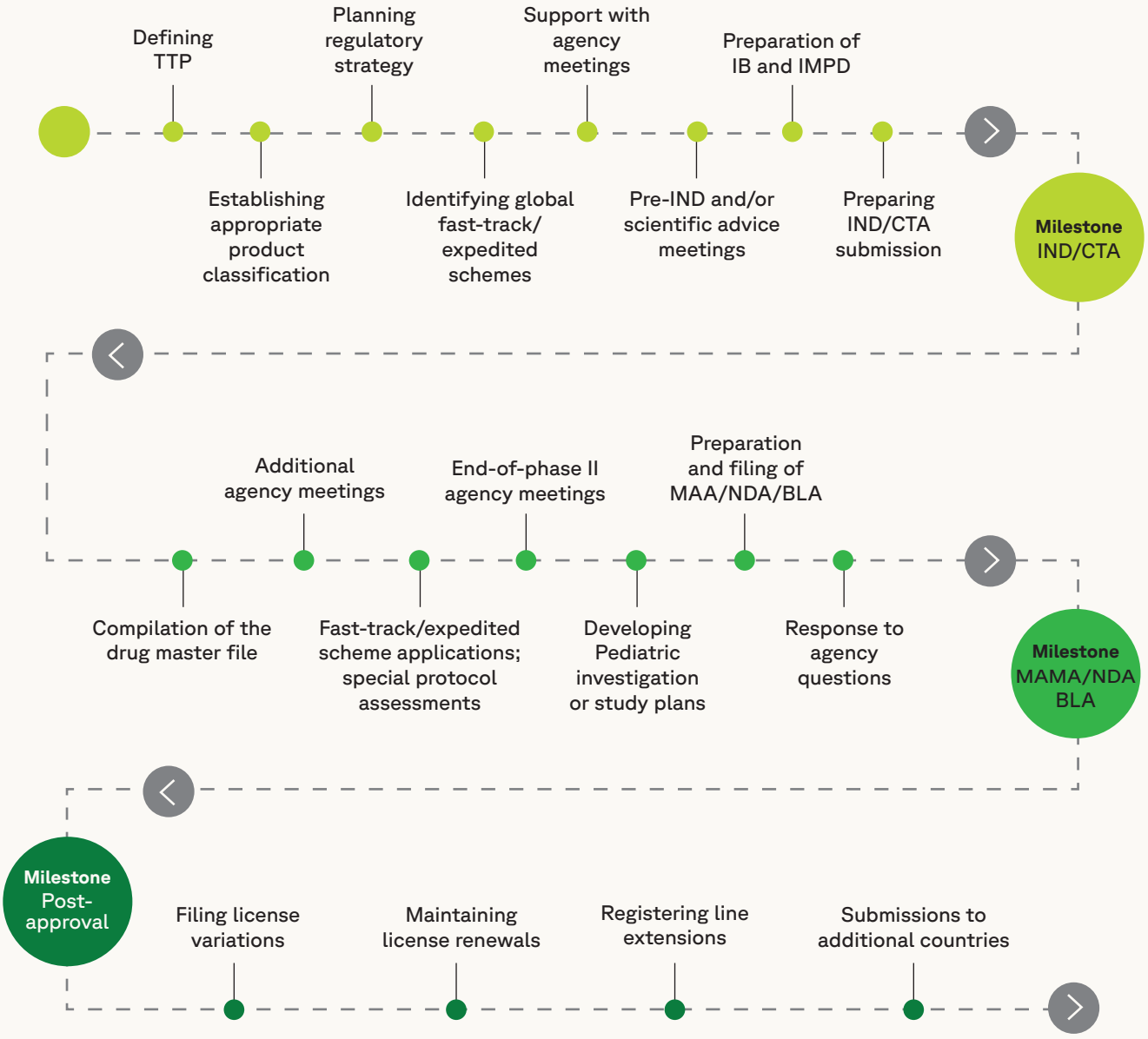

Figure 1: Regulatory roadmap for drug product development

Step 1 – Define the target product profile

Refer to the FDA and/or EU guidance for TPP. The TPP records what is known about the likely product prescribing information and what information is available, or needed, to verify those sections.

The following product properties are among the most important considerations when developing a TPP:[1,2,3]

- Indication and usage
- Dosage form and strength
- Administration route
- Contraindications/adverse reactions of the drug
- Patient population (e.g., pediatric/elderly)
- Drug interactions (e.g., drug-drug interactions)

Also consider:

- Target price and possible extensions
- Comparing the product with existing competitors to establish its niche

Step 2 – Identify the intended region(s) of drug development

This information helps in planning a precise regulatory pathway, as there are significant regional variations for regulatory requirements.

Consider:

- Study designs repeat-dose toxicity studies – do they equal or exceed the number of doses proposed in humans?
- Regulatory requirements: submit the IND in the U.S., or CTA in the EU, before starting any studies that will contribute to the portfolio
- Production techniques: statement of compliance confirming the Organization for Economic Co-operation and Development (OECD) Good Laboratory Practice (GLP) status and confirm whether the pivotal studies were conducted in a member of the OECD mutual acceptance of data (MAD) program
- Packaging: in the U.S., aqueous-based oral inhalation solutions, ophthalmic products and injectables must be sterile; sterilization in the final container is the method of choice. However, in EU, aseptic manufacture is seen as the least desirable method of choice. Only the stability of the product is considered as a factor in choosing the sterilization method

Step 3 – Understand product classifications according to regional regulatory variations

Regional differences in the way products are classified demand different regulatory paths to follow.

Consider:

- NCE
- Type of biologic (e.g., cell and gene therapy)
- Medical device
- Combination product (e.g., drug device combination)
- Combined product
- Other: Botanical or herbal products

Step 4 – Conduct thorough development planning and review regularly throughout execution

- Include timelines, company position, etc.
- Aim to achieve maximum efficiency and reduce risk
- Ensure collection of sufficient preclinical data in accordance with set timelines to support IND and CTA submissions
    - Sufficient test material of appropriate grade
    - Manufacturing scale-up
    - Development of bioanalytical methods
- Think long term – will there be other indications or product extensions that require additional studies that could be factored in sooner rather than later?

Step 5 – Consider the benefits of specific access schemes and financial opportunities/considerations

- Programs for micro, SME status
- Programs for specific types of product or indications
    - Orphan drug designation
    - Expedited and early access applications
- Financial or strategic support from schemes such as PRIME, Innovative Task Force, etc.

Step 6 – Extension of supporting solutions and collaborative engagement

- Review the checklist to identify key areas where the product team needs to gain further knowledge, skills and experience via a CRO

Understanding the commercial benefits of a well-planned regulatory strategy

There are numerous ways in which commercial success depends on an optimal strategy. Getting the TPP right the first time, while considering the end product, provides an understanding of the requirements for development of the product, the therapeutic niche and its eventual place in the market. The TPP is the core on which a successful development program is built.

However, there is a need to engage across the strands of the product's development to ensure the optimal path is followed, minimizing risk, costs and development time. Only by providing an integrated program can timeliness be achieved.

A sound plan will also facilitate the identification of, and application to, financial and scientific assistance programs that should be accessed wherever possible. A knowledge of these schemes, as well as an understanding of the potential product's market, will ensure that valuable opportunities are recognized and exploited.

A strategy that "begins with the end in mind" ensures that the vision guides the registration of the product. Such a well-planned strategy maximizes the protection of the IP of the product and safeguards its commercialization into the future.

About the author

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Dr. Sanjay Jain has been with Fortrea since August 2014 as Senior Director, Global Regulatory Affairs Strategy. Through this role, and previously as a drug and product development and regulatory professional, he has gained over 26 years of experience in the industry by facilitating the development of a wide spectrum of drugs helping clients with preparation of optimized regulatory pathways/strategies for drug/product development, supporting from pre-clinical development to clinical trial approval, and throughout clinical development.

Dr. Jain obtained a PhD in Pharmaceutical Sciences and Post-doctoral fellowship in drug delivery (UCL-SOP, London, UK). He has been an invited speaker in scientific meetings; an author and a reviewer of many peer-reviewed scientific and regulatory publications.

For More Information

https://www.fortrea.com/solutions/fortrea-consulting-services/regulatory-strategy-consulting.html

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WP_0048_Regulatory Strategy_0524