Structuring a Pharmaceutical/Biologic Development Plan

Devising a Comprehensive Regulatory Strategy for Success

I. Introduction

Developing a new therapeutic agent is a challenging, lengthy and expensive process. The rate of success is low. Of the drugs and biologics that would enter clinical development, only 12% will gain marketing approval based on recent compilation of approval rates. This percentage is skewed higher by anti-infective drugs that have a 16% probability of gaining marketing approval after entering clinical trials. On the other hand, only 3% of therapeutic agents addressing central nervous system (CNS) indications make it to commercial availability (*Dowden H and Munro J; Nature Reviews: Drug Discovery 2019; 18: 495-496*)

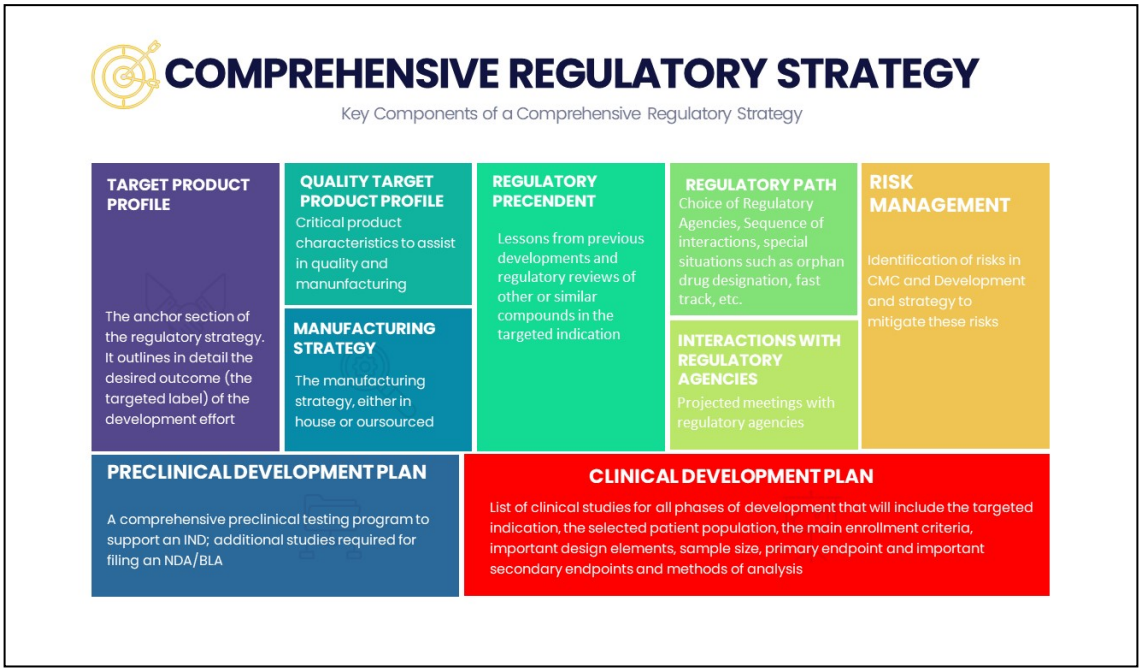
The reasons for this low rate of success is not necessarily lack of efficacy or higher than expected toxicity. In many cases, the efficacy of the new agents is obscured by a number of choices in the process of development. These new pharmaceutical entities(NMEs) may be multifactorial and complex (which is the case for various biologics), their mechanism of action may be poorly understood, the clinical situation targeted may be inappropriate, the type and timing of intervention could be wrong, the Phase 2 studies may fail to provide adequate information for the pivotal phase (as it is frequently the case in oncology), and the endpoint may be insensitive to the effects of the drug (as it is usually the case in CNS clinical development). Many other issues also intervene including an overestimation of the event rate and the attendant underpowering of the study. In some studies, little attention is paid to the degree to which enrollment criteria modify the event rate and learning phase studies poorly address this issue.

Therefore, planning the development process as comprehensively as possible allows a organization to have a clear idea of what it intends to achieve, the obstacles it faces, and the resources required. This is where BCR&DS can effectively help. It can define to the best possible extent both the final “destination” of the development effort (the targeted label) and the process required to take the sponsor to this destination. Documenting a comprehensive regulatory strategy is not a one-time event. As the knowledge regarding the NME in development increases, such a strategy may be amended in sections to incorporate the new information.

The sections below summarize the main elements of a comprehensive regulatory strategy.

II. The Key Elements of a Comprehensive Regulatory Strategy

A comprehensive regulatory strategy is a single document that brings together various elements of the development process such as the proposed target product profile, the regulatory pathway, relevant regulatory precedent and disease/syndrome information and summaries of the preclinical and clinical studies. Several elements of this document can be regarded as "living", being continuously updated during the process of development.



A. Target Product Profile

A target product profile (TPP) for the therapeutic agent entering the development phase is an essential exercise. It describes, in regulatory terms (using language typically included in package inserts), the goals of the development effort for each property of the drug. The TPP will include the target indication, the specific patient population, the expected/targeted therapeutic efficacy and clinical safety; It will also include the intended formulation, the physical form of the drug, the route of administration, expected dosing regimen(s), storage conditions and targeted stability/expiration period.

For each section of the TPP, the attributes assigned to specific properties can be obtained from various sources: from the discovery process and early non-clinical information, the efficacy and safety of competing drugs/biologics in the indication to be studied, or, if these are not available, from the class of compounds that the therapeutic agent belongs to.

The TPP may include a variety of scenarios (minimal, base, optimal), with different attributes assigned to drug properties for each of these scenarios.

During the process of development, if the value of any property falls below the assigned attribute of the minimal scenario, a go/no-go decision process may be initiated. These scenarios can be used in a variety of ways, especially in planning and further development.

Further details on Target Product Profiles, what they need to include and the way they are compiled can be found at www.adrclinresearch.com/target product profiles.htm.

B. Quality Target Product Profile

The Quality Target Product Profile (QTPP) essentially lays out a list of quality attributes that should be present in intermediates and the final product. It identifies critical attributes and process parameters. In that context, it creates the foundation for the analytical and testing processes employed by Quality Assurance (QA) and testing (QC) that need to be employed in the manufacturing of the NME in question. The development of key assays and their performance characteristics should also be addressed in this document.

C. Manufacturing Strategy

This is an essential component of the regulatory strategy. Although BCR&DS can provide guidance, this section should be authored by groups or persons with the appropriate expertise. However, it is important that these experts interface successfully with BCR&DS, because certain issues in manunfacturing may require interaction with the regulatory agencies and should be carefully mapped in the appropriate section of this document (Interactions with Regulatory Agencies).

D. Regulatory Pathway

Defining the regulatory pathway for major agencies such as the FDA, EMA, and PMDA is important because the interaction of sponsors with these agencies differs during the process of development, as does the review of the final submission. A comprehensive regulatory strategy will include a specific process and sequence of approaching these agencies for consultation during the development process.

Furthermore, a comprehensive regulatory strategy will address specific situations as they apply to the test drug/biologic for various regulatory agencies such as applications for orphan drug status, accelerated review, breakthrough treatment etc., including the timing of such submissions/requests during the development route.

E. Interactions with Regulatory Agencies

The comprehensive regulatory strategy will try to outline the interactions with the regulatory agencies both in terms of type and timing. Of course, the projected interactions (meetings) may be modified depending on the issues that arise in discovery, manufacturing and clinical development.

F. Regulatory Precedent

It is more thank likely that other companies have attempted to license similar compounds or compounds of the same class in the targeted indication. Their experience is an important consideration for the current development plan. Therefore, identifying the issues faced in their effort, the studies completed and questions faced by the regulators is very important in finalizing the regulatory and development strategy. For drugs and biologics developed in the last decade there are substantial resources available in the regulatory agency websites that include the summary basis of approval and the various reviews by the examiners of the application. Furthermore, a number of publications in medical and biological journals may provide interesting information that will inform the development process.

It should be understood that the record is biased towards success. If a company never submitted a BLA and NDA because studies failed or other obstacles appeared, no information on that failed process may be easily uncovered. Occasionally, certain failed attempts echo in scientific publications, but this is not always the case. Regulatory intelligence should try to complete the record as much as possible and highlight areas of concern for which inadequate information is available

G. Issues on Disease/Syndrome resulting from ongoing research that have not encountered by the regulators

In most cases, a substantial period of time elapses between the release of novel drugs for a specific disease or syndrome and the commencement of an effort to approve a new medicinal entity (NME). There are also areas of unmet need without previous regulatory record. A comprehensive regulatory strategy will list the research and treatment choices that have been presented in the literature since the last major drug release addressing it, as well as the experience of the drugs/biologics post-licensure. In many cases, a long period of time may have lapsed, and a variety of other treatment modalities may have been introduced to cover the likely deficiencies of the existing drug armamentarium. In addition, research may have progressively uncovered more elements of the pathophysiology of the disease and key pharmacodynamic issues that may be directly relevant.

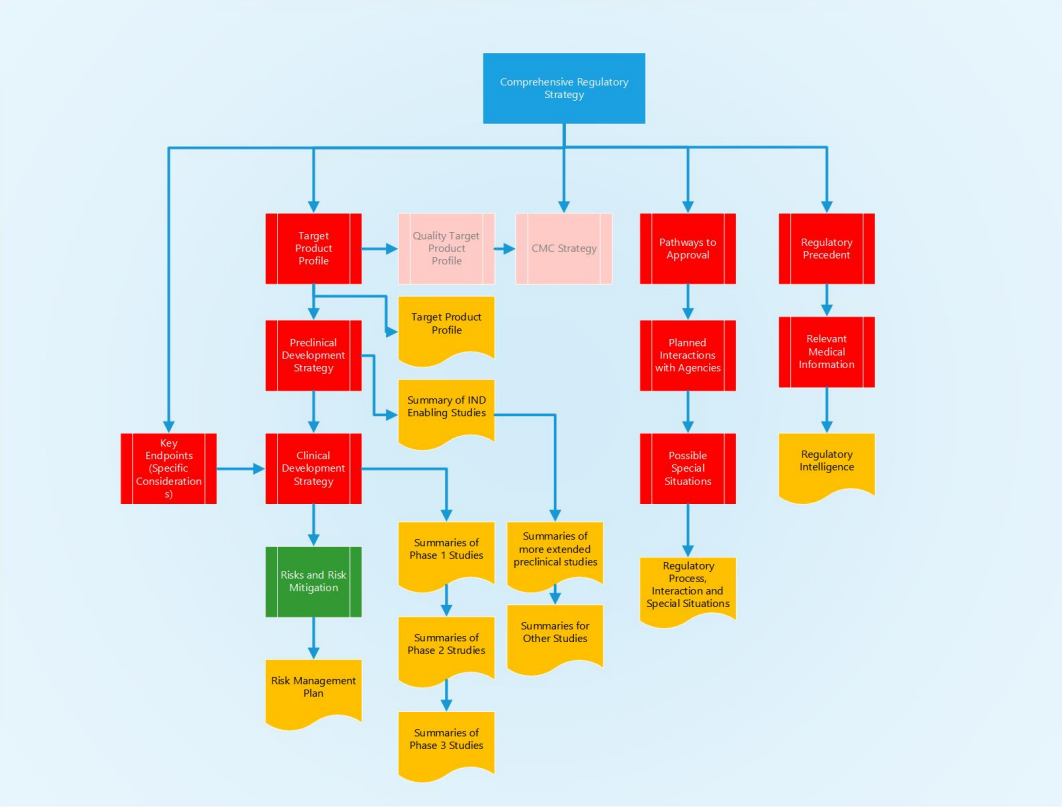
H. Key Endpoints

Key endpoints may well be addressed in the Regulatory Precedent, but in many cases, ongoing research provides novel information that should be considered. It is almost certain that the FDA examiners would be aware of this additional information, so advancements in the state of the art there should be carefully examined and listed and they should be incorporated into the preclinical and clinical development.

I. Preclinical Development

A concise strategy in preclinical development assists the sponsor in setting reasonable milestones and timelines. The studies required to support an IND will be listed. Additional studies that would need to be initiated post-IND (such as more extensive carcinogenicity studies) should also be discussed. It is important to understand that the guidelines of various agencies only provide a baseline of what needs to be done. There needs to be a good understanding of the NME in question and its mechanism of action to fashion an appropriate program

Figure: 1: The process of assembling a comprehensive regulatory strategy



J. Strategic Clinical Development

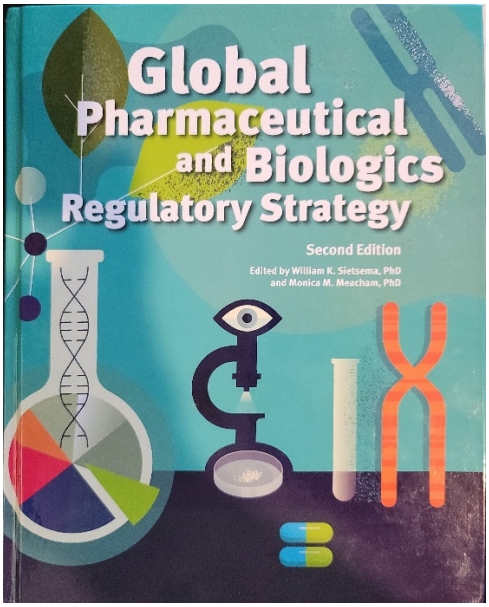
The proposed clinical development program will address the specific requirements of the sponsor as expressed in the TPP. The full program will incorporate the projected clinical studies in every phase of development; Summaries of the studies will be included that will provide information on the indication targeted, the population to be addressed, key enrollment criteria, sample size and primary and key secondary endpoints. The development of

specific clinical assays will also be addressed. In addition, a projected timeline will be developed utilizing key industry metrics which will also indicate projected interactions with the main regulatory agencies.

K. Intellectual Property

Possible actions regarding the maintenance and expansion of the intellectual property in association with the development effort will also be appended to the document

III. Further Reading



Anastassios Retzios and industry colleagues have authored a series of monographs in a textbook on “Global Pharmaceutical and Biologics Regulatory Strategy”, the second edition of which has been edited by William K. Sietsema and Monica M. Meacham (2020). This textbook can be obtained directly from RAPS (Regulatory Affairs Professional Society)