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# Data Standardization Planning for Clinical Development Programs

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## ABSTRACT

Data Standardization within and across clinical development programs is now a requirement as Regulatory Authorities worldwide are all requesting that clinical data, and metadata, be made available in a structured and standardized CDISC compliant architecture. The development and evolution of a Clinical Development Plan (CDP) is a critical document and process for cost effective and efficient drug development programs. The CDP is now more important than ever with the integration of a data standardization into the CDP architecture. Recent FDA Guidance (February 2014) on Providing Regulatory Submissions in Electronic Format – Standardized Study Data and corresponding Technical Conformance Guidelines identified that a Study Data Standardization Plan (SDSP) should be submitted with an IND to outline standards to be followed throughout the course of the development program. In this paper we present a high level model for an SDSP with a specific focus on endpoints. The relationship of the SDSP to the CDP will be discussed and show that (1) it is an evolving document that should be developed during the pre-IND phase of a program and updated frequently to ensure consistency, transparency, and interoperability of all data in a program and (2) implementation will significantly aid in the maintenance and updating of important regulatory required documents like the Investigator's Brochure and Annual Safety reports.

## INTRODUCTION

Data Standardization within and across clinical development programs is now a requirement as regulatory authorities worldwide are accepting cross-referenced applications between agencies in the European Union, United States, Canada, United Kingdom, Japan, and other competent authorities throughout the world. These regulatory agencies have been engaged with the use of ICH guidance documents and harmonization of standards across development programs for many years. More over these regulatory authorities are now requiring the reporting and sharing of clinical and non-clinical data between agencies prior to and after approvals. This sharing of information and data also includes agencies and competent authorities completing cross-border manufacturing inspections to ensure quality in drug substance, drug product, and final packaging, as well as clinical site inspections.

The roadmap for molecular development of a new drug product (Figure 1) commonly followed by drug companies also provides the sequential steps in which a drug is successfully developed. The planning documentation that outlines the steps and targets starts in the discovery and feasibility stages of development when disease targets, chemistry, and pre-clinical pharmacology are all explored, and early decisions are made for Go/No-Go for further development. The goals of early planning and early drug development are to identify targets that are feasible and worthwhile pursuing, both scientifically and economically. Given the probabilities of success and the ever increasing costs for development of a new drug the best planning and early decisions will save valuable resources, and allow for more effective and efficient use of both financial and human resources for viable targets (Figure 4). The role that planning documentation plays on the regulatory processes is now more important and profound as the costs of drug development are increasing.

Early planning documentation must include the development of a viable target product profile (TPP). The TPP has long served as a gateway to the development roadmap, yet many companies still today do not fully develop the TPP prior to initiating human clinical trials. A well-developed TPP will include input from all major function that go into development and marketing of a new drug and drives the strategy for the development of the compound through development and marketing (Figure 3). The US FDA has also provided guidance on the development of the TPP[1].

Once a TPP has been developed then a well-crafted clinical development plan (CDP) may be designed and implemented to address those entities within the TPP that would make a compound successful in treating the disease target, as well as being financially viable for manufacturing and marketing. The TPP is the gateway to the Clinical Development Plan (CDP), and the CDP is the gateway to the Study Data Standardization Plan (SDSP).

**Figure 1** **Roadmap from Molecular Development to Market Approval**

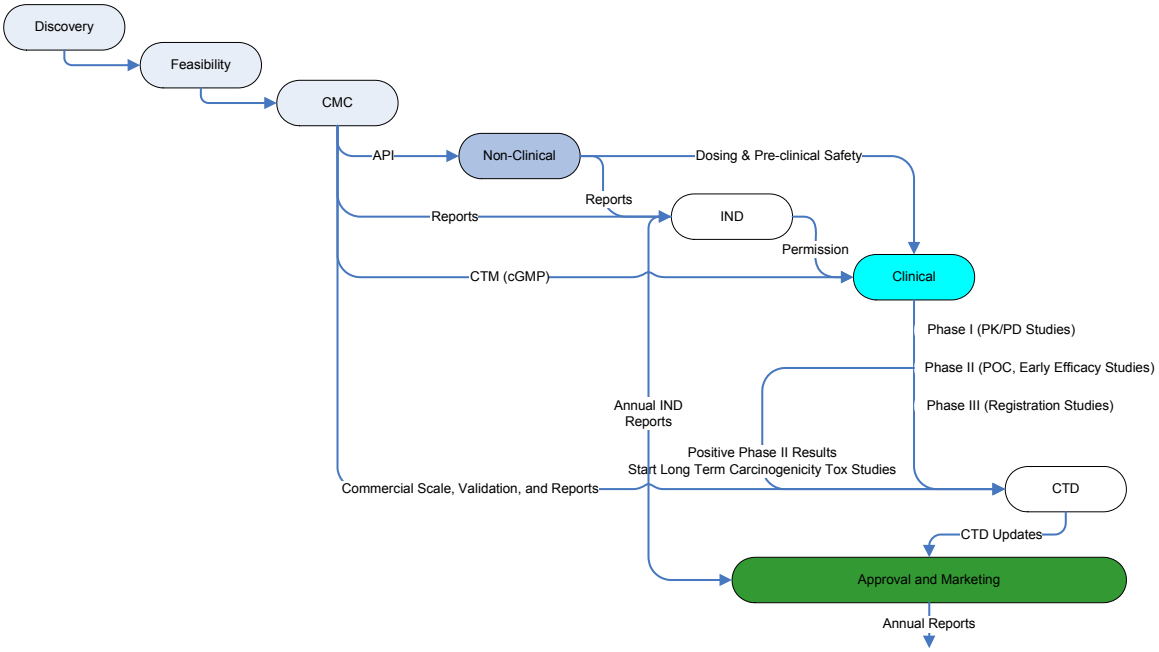
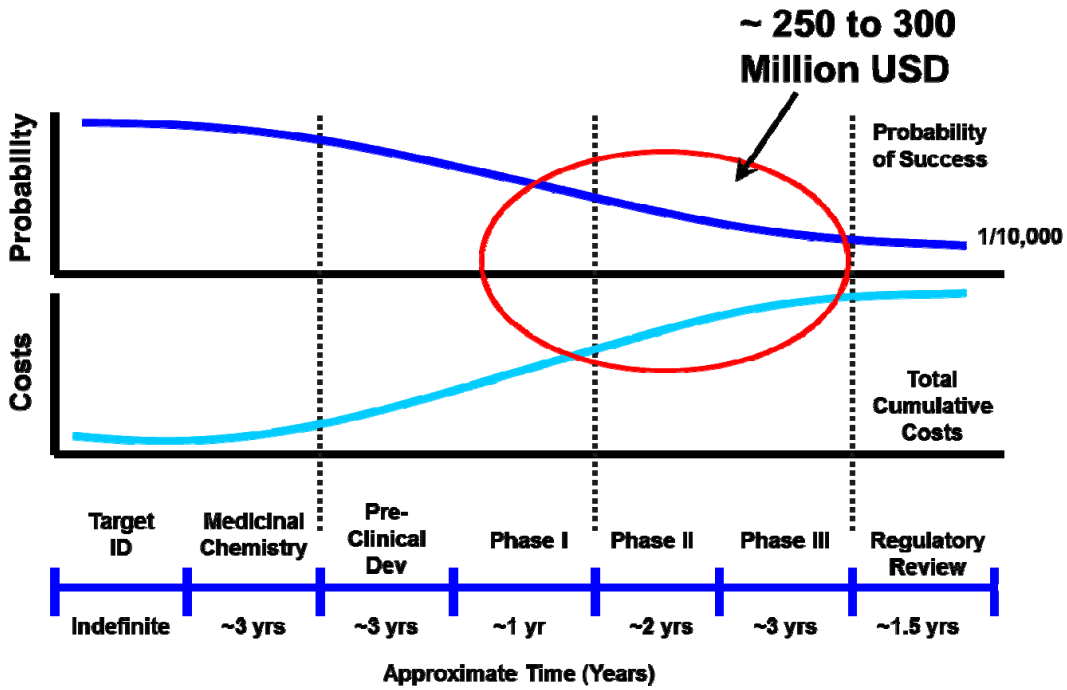
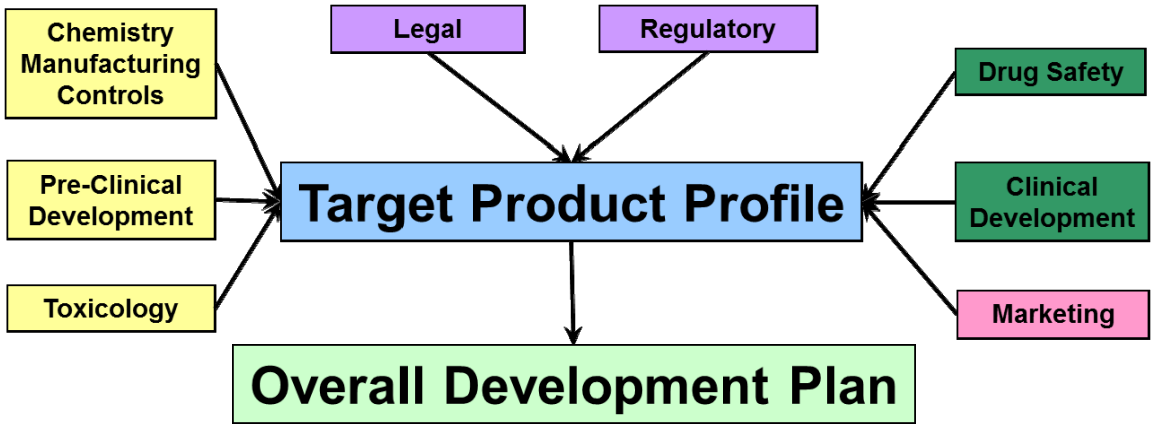



**Figure 2** **Incremental Development Costs for a Drug Development Program**




**Well-designed TPP, CDP, and SDSP documents that evolve throughout the lifecycle will help to reduce costs and increase probability of Success**

**Figure 3** **Target Product Profile and Development Planning Entities**




## CLINICAL DEVELOPMENT PLAN CDP)

The CDP is a unique, integrated roadmap, or blueprint, for the clinical development of a compound. The CDP will identify key "Go/No Go" decision points and regulatory milestones along the development pathways. The CDP is also an integrated, comprehensive document that is updated frequently at milestone development points to define the steps, activities, regulatory information, competitor information and goals for the compound. In draft guidance issued by the US FDA the addition of study data standardization was added to the CDP[2,3] to be delivered at the filing of an IND.

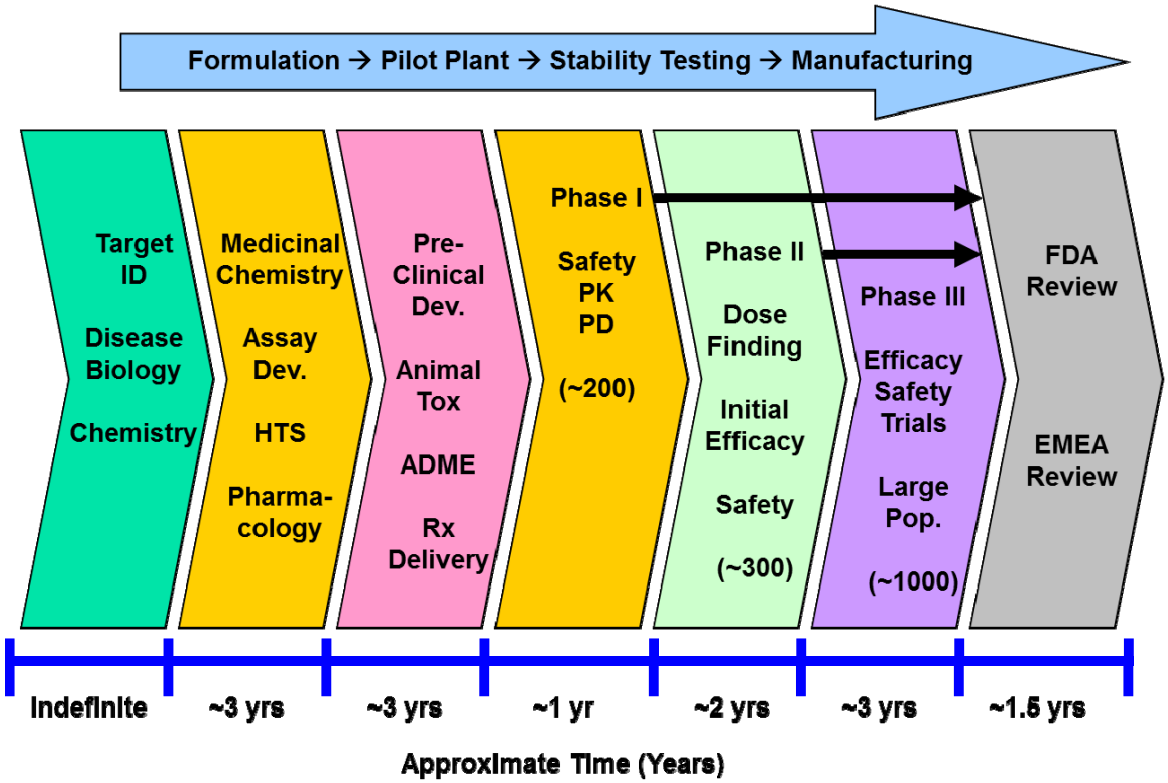
The CDP is identified in regulatory documents as required in an Investigational New Drug (IND) application in Item 4 (General Investigational Plan), where details for the initial testing in human subjects is identified and laid out, as well as general plans for development post one year. It is clear from the CDP guidance documentation for filing an IND that the CDP should be updated frequently at millstone points in the development cycle. This evolution of the CDP now also includes the integration of the study data standardization plan (SDSP)[2, 3, 4, 5], starting at the filing of the IND and evolving throughout the life cycle development of a compound (Figure 4).

Elements of the CDP will include a discussion of the development of the compound for:

- Clinical Pharmacology and pharmacokinetics (Phase I)
- Dose forms / dose definition (Phases I and II)
- Proof of Concept for Efficacy (Phases I and II)
- Safety Monitoring and Reporting (All Phases of development)
- Efficacy Endpoints and Variables (Phases II and III)
- Statistical Plan (All Phases of development)
- Clinical Trial Supplies (Packaging, blinding, logistics)
- Pharmaco-economics, Epidemiology
- Market Access and Clinical Effectiveness endpoints and strategies (All Phases)
- Regulatory strategy and key regulatory milestones

The CDP is NOT just a list of studies, fixed over a specific time frame, or the activities of a single individual within a sponsor organization. Lastly, the CDP is not an easy or simple exercise to complete. This document evolves over the lifecycle of the program, and well developed CDP documents are updated at least on an annual cycle, often timed with annual reporting or Investigator brochure updates.

**Figure 4** **Phased Development and Decision Support Stages for a New Chemical Entity**




Standardized study data fits into the CDP across the entire development program (Figure 4) and an integrated SDSP into the CDP process will allow for a comprehensive data package that should in theory aid in the review cycles, and shorten the submission cycles for a sponsor. The CDP and SDSP should each consider in an integrated manner such things as:

- Requirements identified and imposed on previous products developed in a class,
- Safety issues and safety endpoints,
- Efficacy endpoint definition and methods for computation and analysis of these endpoints,
- Drug exposure,
- Number and type of studies needed to meet regulatory approvals (e.g. are hepatic or renal impairment studies needed),
- Regulatory hurdles and milestones (e.g. planned meetings thresholds for safety and efficacy, etc.)

The importance of standardized study data, integrated into the clinical development lifecycle and CDP is the subject of an FDA position statement on the importance and requirement for standardized study data.

## FDA POSITION STATEMENT OF STANDARDIZED STUDY DATA

The US FDA issued on September 13, 2013 a position statement that clearly articulates the position for the collection and submission of standardized study data[6]. That position statement (reproduced below), along with the guidance documents for standardized study data[2,3] and the respective US FDA CDER[4] and CBER[5] data standards resources pages for sponsors provides the most up-to-date requirements for adherence to the implementation of data standards. Sponsors should not consider this optional, or draft: They should consider this to be binding and a requirement for any drug application starting in 2014. Early implementations of data standards will results in cleaner, more valuable clinical data for a development program. Sponsors who fail to adopt early implementation of CDISC compliant standardized data across a program will end up at key submission milestones spending significant financial resources, and time, to move their data into a standardized architecture.

The position statement is clear regarding implementation and adherence to CDISC compliant data standards:

> *FDA recognizes the investment made by sponsors over the past decade to develop the expertise and infrastructure to utilize Clinical Data Interchange Standards Consortium (CDISC)[1] standards for study data. The submission of standardized study data enhances a reviewer's ability to more fully understand and characterize the efficacy and safety of a medical product.*
>
> *The Prescription Drug User Fee Act (PDUFA V)[2] Performance Goals state that FDA will develop guidance for industry on the use of CDISC data standards for the electronic submission of study data in applications. In the near future, FDA will publish guidance that will require study data in conformance to CDISC standards.[3]*
>
> *FDA envisions a semantically interoperable and sustainable submission environment that serves both regulated clinical research and health care. To this end, FDA will continue to research and evaluate, with its stakeholders, potential new approaches to current and emerging data standards. FDA does not foresee the replacement of CDISC standards for study data and will not implement new approaches without public input on the cost and utility of those approaches.* (FDA Position Statement: September 13, 2013)[6]

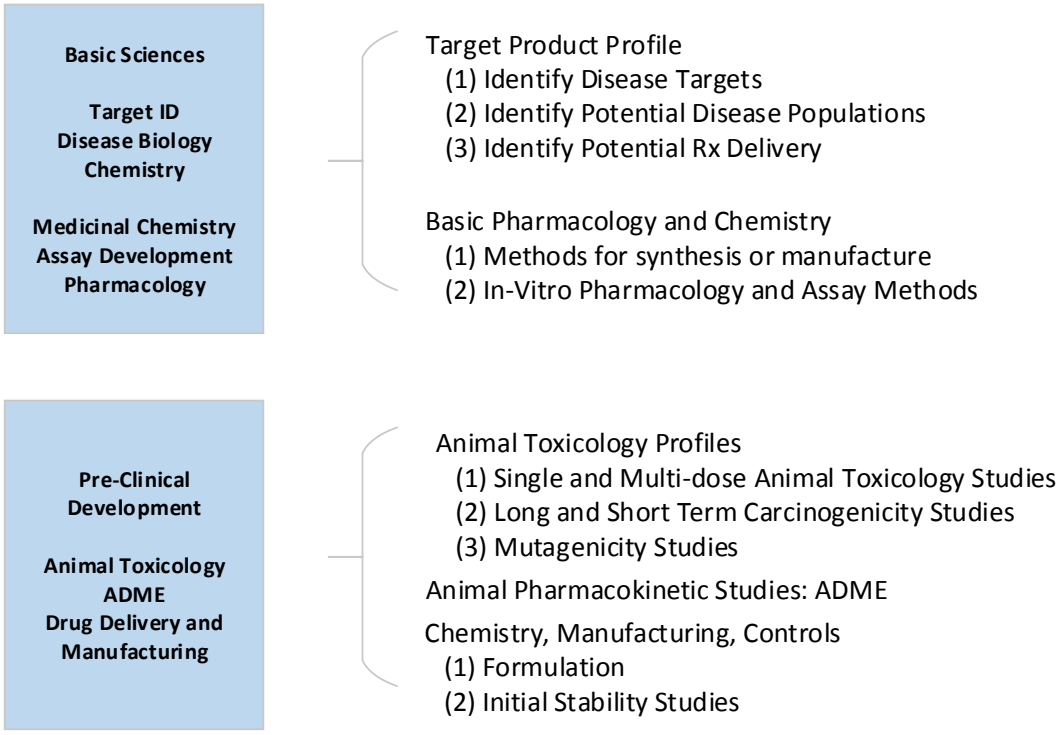
## STUDY DATA STANDARDIZATION PLAN (SDSP)

The SDSP has been identified as an important project for development of a standardized template as a guide for industry. The PhUSE CSS Working group for Optimizing Data Standards has initiated a project for development of an SDSP template and examples for industry to consider as part of the CDP processes[7]. The SDSP team is made up of industry representatives and FDA Liaisons. One key element of the SDSP will be the standardization and harmonization of endpoints assessed in trials across the development program. In the rest of this paper we focus on what these endpoints are and provide some considerations for standardization and harmonization across a CDP.

## EARLY PRE-CLINICAL DEVELOPMENT

Early development includes initiating the TPP and identifying those endpoints associated with pre-clinical toxicology and ADME programs (Figure 5). These endpoints are implemented with the CDISC SEND data standard.

**Figure 5 Early Development Planning Documentation Prior to Clinical Development Plan**



## PHASED CLINICAL DEVELOPMENT ENDPOINTS

The FDA Guidance on standardized study data is primarily focused on the implementation of CDISC standards (SDTM, ADaM) across a phased development program[2,3]. However, implementation of the CDISC SEND data standard into the SDSP for pre-clinical development has benefits that allow for transparency and transition of data between the pre-clinical and clinical programs that will aid significantly with development.

Prior to initiating human clinical trials the CDP and the integrated SDSP should address an endpoint strategy that identifies key safety and potential efficacy endpoints and assessments for standardization. This concept is phased in across the development program (Figure 4) and also includes evolution and updates of endpoints as more knowledge is acquired throughout the program.

Information carried forward from the pre-clinical program that allows for standardization of endpoints includes elements associated with animal PK and PD endpoints that are also collected in human trials. The standardization and harmonization of these endpoints between pre-clinical and clinical trials allows for examination of animal data relative to human data (referred to as allometric scaling) to study potential starting doses or refine doses base on safety information acquire in either animal studies or human studies (Figure 5, Figure 6).

### PHASE I Endpoints

Phase I endpoints requiring standardization include safety, pharmacokinetic, pharmacodynamic, and early efficacy or surrogate endpoints (Figure 6) to be evaluated for proof of concept. In Table 1 we provide an initial list of the types of typical endpoints to be standardized across a phase I program that would be carried throughout the entire lifecycle. The list is not exhaustive and needs to be addressed on a program by program basis at each stage of the development cycle and each regulatory milestone.

In phase I studies particular emphasis should be placed on ensuring the standardization of the pharmacokinetic endpoints for the development program. Clear identification of the parameters to be computed (e.g. Cmax, AUC, etc.) allows for harmonization in later phases of development where the same parameters may be collected to support PK/PD assessment and PK/Efficacy or PK/Safety analyses. Early implementation of these standards will allow for transparent and efficient analysis of these relationships as they are implemented in the CDP.

**Table 1 Endpoint for Data Standardization in Phase I.**

| Data to be Standardized | Domains | Endpoints (Variables) |
|---|---|---|
| Safety Endpoints | SDTM.AE | Adverse events, treatment emergent Ae's, AE's of special interest. Identification of the common coding dictionary and version to be implemented. |
| | SDTM.VS | Vital Signs, with list of key vital signs to be assessed, coding (VSCAT, VSTESTCD, VSTEST) to be implemented. |
| | SDTM.LB | Safety Laboratories, with list of key laboratory assessments to be assessed and coded (LBCAT, LBTESTCD, LBTEST). Particular emphasis should be placed on identifying the standardized references and units across a program to be implemented. |
| | SDTM.CM | Medications, with identification of the versioning of the appropriate drug dictionary to be implemented across the program. |
| | SDTM.EX | Exposure (dosing information) nomenclature and coding is key for standardization early in the phase I program. |
| | SDTM.EG, or SDM.CV | Cardiac and electrocardiogram assessments. |
| Pharmacokinetic Endpoints | SDTM.PP | Pharmacokinetic parameters to be computed should be identified and standardized for presentation (PPCAT, PPTESTCD, PPTEST). This is important for matching with animal PK parameters to complete allometric scaling exercises is needed. |

| Data to be Standardized | Domains | Endpoints (Variables) |
|---|---|---|
| Early Efficacy POC Endpoints | Various SDTM Domains<br>Various ADaM datasets | Identify initial and key proof of concept efficacy or pharmacodynamic endpoints, appropriate coding dictionaries for the endpoints, methods for computations and analysis, validation methods, as well as standardizing the naming conventions for the endpoint (SDTM: --CAT, --TESTCD, --TEST: ADaM: PARCATy, PARAMCD PARAM). Ideally also identify an analysis dataset naming convention to be applied across the development program for the endpoint. |

### PHASE II/III Endpoints

Phase II and Phase III endpoints requiring standardization include efficacy, market access, clinical effectiveness and continued use of safety and PK/PD endpoints from the phase I program. Following the logical completion of a Phase I program, which is also a regulatory milestone, the CDP and SDSP should be updated to reflect key learnings, new variables, new assessments and endpoints to be examined in later stage development studies, and introduction of variables and endpoints for evaluating market access and clinical effectiveness (Figure 6).

Also following the completion of the initial Phase I studies a major update to the investigators brochure (IB) is often times implemented prior to Phase II/III studies. Often times sponsors will also hold end of phase I meetings with regulatory authorities to discuss development results to date, Phase II plans for dose finding studies and initial assessments of clinical efficacy (proof of concept). Standardized safety and PK data will significantly aid in the updating processes for the IB and submitting information and data to this regulatory milestone.

The disease target and TPP will identify the specific efficacy endpoints that will house standardized data in the SDTM model. For instance development of a new antibiotic will require the use of the objective endpoints collected in the microbiology SDTM domains, and for oncology studies will require the use of the objective endpoints in the tumor domains. Herein we focus on those efficacy endpoints that are more subjective in nature such as those assessments associated with standards for inclusion in the FA (Findings About) or QS (Questionnaire) domains. These subjective efficacy data are important to identify early on in the CDP and SDSP processes for standardization.

A regulatory milestone and key point in the development and evolution of the CDP and SDSP is the end of phase II meeting, completed prior to moving into registration Phase III studies. We are of the opinion that this is the point in the development cycle when the CDP and SDSP is fully mature and all of those standards to be implemented for harmonization of data have been identified and promulgated across the program. This is also the time in the development cycle (Figure 1, Figure 4) when the key “Go/No go” decision should be made to initiate Phase III registration trials. An adequately developed CDP will have this decision point embedded into the decision tree, with a robust assessment of the clinical safety and potential efficacy of the compound. Also it is at this stage that the SDSP will have identified those key efficacy variables to be carried forward into the Phase III program, with information on the methods for collection, derivation of endpoints, and analysis methods to be applied in the target population for the Phase III program. It is rare, and often times a mistake, to assess new efficacy endpoints in Phase III that have not been previously studies and validated in a Phase II program, or a companion development program.

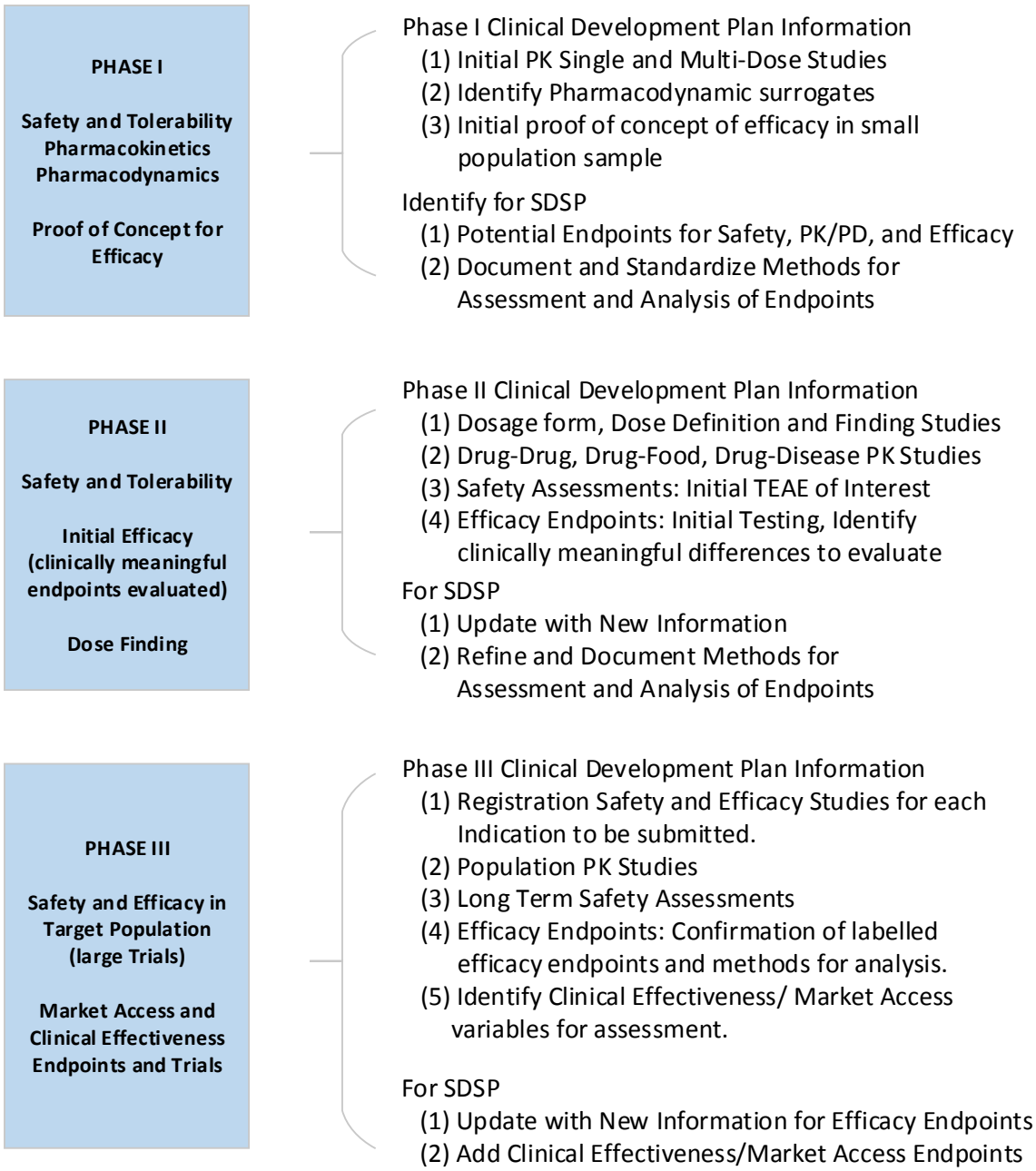
To many Phase III programs fail because of inadequate planning, insufficient time in exploratory Phase II studies, and a rush to achieve a positive result. This rush is often driven by financial decisions and the availability and commitment of precious capital for drug development. However, early and adequate planning with particular emphasis on developing a TPP and CDP that outline a strategy for development, with specific details on the endpoints needed for labeling of the drug can reduce the failure rate in Phase II and III studies, allow for earlier “Go/No Go” decisions, and provide regulatory authorities with mandated standardized data to review early in the development lifecycle.

With the introduction of Proof of Concept Studies in Phase I and early Phase IIa development programs the implementation of the SDSP becomes more important to allow for harmonization of these data across the program.

**Table 2 Clinical Endpoints for Data Standardization in Phase II/III.**

| Data to be Standardized | Domains | Endpoints (Variables) |
|---|---|---|
| Clinical Endpoints | SDTM.FA | Objective clinical findings with lists of key endpoints for each clinical assessment. . Identification and standardization of the FACAT, FASCAT, FATESTCD, and FATEST standards is ideal. |
| | SDTM.QS | Questionnaires or QOL Instruments with list of key endpoints and assessments for each instrument. Identification and standardization of the QSCAT, QSSCAT, QSTESTCD, and QSTEST standards is ideal. |
| Efficacy Endpoints | Various ADaM datasets | Identify efficacy endpoints for analysis, methods for computations and analysis, validation methods, as well as standardizing the naming conventions for the endpoint (SDTM: --CAT, --TESTCD, --TEST: ADaM: PARCATy, PARAMCD PARAM). Ideally using the same naming conventions from the Phase I POC program for the endpoint. |

**Figure 6** **Phased Clinical Development Planning Documentation**



## CONCLUSION

In this paper we have attempted to introduce the Clinical Development Plan (CDP) as a significant and important planning document that is a required regulatory document. With the introduction of required data standardization (CDISC SEND, SDTM, and ADaM) for submission of data, and guidance that early standardization planning at the time of the IND application is now required sponsors have the opportunity to spend more time early in the development process to standardize data and save significant financial resources by early implementation of these standards.

The development, and ongoing maintenance, of a Clinical Development Planning (CDP) is a critical document for cost effective and efficient development programs. The CDP is developed from information in the Target Product Profile, and the Study Data Standardization Plan (SDSP) is developed in concert with the CDP at the time of the filing of an IND or an IMPD.

Standardization of safety, efficacy, pharmacokinetic, pharmacodynamic, market access and clinical effectiveness endpoints is an evolving process throughout the development lifecycle as new information is collected and data are evaluated. Endpoints will be continuously assessed for relevance to the safety and efficacy of a product, and with this evaluation comes implementation of data standards to ensure harmonization of endpoints across the development program. Failure to standardize the data architecture and metadata for endpoints early in the development lifecycle may easily lead to the chaos in the submissions and review cycle, which is very expensive and an ineffective regulatory strategy in modern drug development.

## REFERENCES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