Drug Development Plan

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Clinical Plan

Element	Items
Knowledge and Resource Plan	• What knowledge is required to move the project forward at each stage? • What resources beyond people (CROs, CMOs, labs, vendors distributors)? • Who will be a full-time employee to the project? • What services will be outsourced? • Who will internally manage the outsourced services? • What outside personnel/consultants will be needed? • When will each of these resources be brought into the project? • Are there gaps in knowledge because the plan is being formulated before a particular resource is available? • How is the risk of the unknown being managed? • How will knowledge be documented?

Target Product Profile	• The TPP forms the basis of engagement (particularly early engagement) with regulatory bodies. Guidance suggests the following items be included in the TPP (Guidance for Industry: Target Product Profile — A Strategic Development Process Tool, Draft 2007).
	• Labeling concept:
	  ○ Indications and Usage
	  ○ Dosage and Administration
	  ○ Dosage Forms and Strengths
	  ○ Contraindications
	  ○ Warnings and Precautions
	  ○ Adverse Reactions
	  ○ Drug Interactions
	  ○ Use in Specific Populations
	  ○ Drug Abuse and Dependence
	  ○ Overdosage
	  ○ Description
	  ○ Clinical Pharmacology
	  ○ Nonclinical Toxicology
	  ○ Clinical Studies
	  ○ References
	  ○ How Supplied/Storage and Handling
	  ○ Patient Counseling Information
	• Proposed promotional claims

TPP—Additional Items	Important to consider in drafting the TPP • Pharmacology: PK, PD, mechanism of action, expected side effects

	• Description of target population: demographics, comorbidities, disabilities, comedications, possible segmentation (based on clinical criteria, biomarkers, and diagnostics). Want to focus on patients most likely to benefit from treatment.
Market Analysis	Market analysis appears twice in this document (within the Clinical Plan and in the separate Commercial Plan; it's important to both items) • Status of competition (the present) • Pipeline drugs of competition (the future) • Competitive analysis: use your favorite tools (wedge analysis, value curve, weak signals, SWOT...); goal is to find out how market share will be gained and how you plan to compete—critically, what are the characteristics of your product necessary for success
Regulatory Path	There is a separate Regulatory plan—this is a condensed one that hits the key points • Are accelerated paths available (orphan, breakthrough...)? • Is scientific advice needed? • What products have followed this path successfully (or not successfully)? • This is a good time to review Guidances, approval documents of similar drugs, regulatory advisory committee notes
Nonclinical and Clinical Trial Plans	• Outline of each nonclinical and clinical trial (Phase 1 to 3): study objectives, trial design, clinical hypotheses, criteria for success, key endpoints and measures (for safety, efficacy, pharmacodynamics, pharmacokinetics, surrogate markers, biomarkers, patient reported outcomes...), subject populations, inclusion/exclusion criteria, number of subjects, treatment duration, treatment follow up. • At an early stage, the details of later trials will be thin, but they can be valuable for exercises like high level budgeting and planning. • Post approval: Phase IV (comparison versus competitors to support economics and reimbursement, new formulations, or special populations (pediatric)), follow up commitments to regulatory agencies, pharmacovigilance requirements
Timeline and Budget	• Elements: nonclinical and clinical, CMC, development of biomarker and diagnostic assays, fund raising, publications, milestones, decision points (Go/No Go) • Budget is high level for longer lead items and more detailed for ones coming soon
Marketing	• Publications and presentations
Risk Management	• Risk rank the elements of the program and focus risk management on high scoring items (using FMEA). • Consideration of problems experienced by similar programs and how those problems were managed.
Rolling Review	• As more pre-clinical/clinical data becomes available, the clinical plan should be revised and expanded. Checking back with stakeholders about changes in the plan is important. Focus groups, patient and family organizations, and disease organizations can be helpful both in terms of advice and often funding.

Intellectual Property Plan

Element	Items

Intellectual Property	• List of planned patents (US and international), including:
	  ○ Structure and method of synthesis/cell synthesis
	  ○ Purification
	  ○ Formulation, delivery, and device

	○ Dosing ○ Diagnostic testing and biomarker • Assessment of patent landscape and identification of any patents that could be blocking • Outline of key claims and data required to support claims; plans to collect data; timing of patent filings

Regulatory Plan

Element	Items
Regulatory Plan	• Regulatory path for each regulatory authority under consideration (FDA, EMA, UK, Japan, etc.): ○ Plan for filing dates, including country specific review cycles ○ Plan for preparation of briefing documents with maximization of the use of a single CTD, preventing a proliferation of versions by region ○ Region specific issues, such as characteristics of study populations; plan for alignment with clinical test sites • How similar drugs faired (approved or not) on selected paths; any new regulatory requirements • Timeline of submissions (IND, NDA, etc.), responses, and other meetings (pre-IND, end of Phase 2) • Plan for each meeting: outlines of questions to regulators and goals for meeting • Key studies, trial endpoints, and data that regulators will need to see at each stage, with potential agency concerns • Options for acceleration: fast-track, breakthrough, orphan • Lifecycle issues: additional indications, new dosage strengths and forms; plans for entry of competing products/biosimilars • Plan for presentations and publications of study data

Nonclinical and CMC

Element	Items
Nonclincial	• Selection of CROs and laboratories; negotiate contracts; audits • In vitro studies: lipophilicity, pKa, stability, solubility, metabolic stability, hepatic clearance, protein binding, plasma and GI stability • In vivo studies: PK profile, bioavailability, metabolization, excretion, GLP studies, C14 labeled studies • Drug and placebo supply: ○ May be difficult to deliver drug product manufactured for humans to in vivo test subjects—think about dose scaling, method of administration. ○ Will drug product be compounded on site or shipped to the site? ○ How will the quality of the drug product be tested? ○ How will placebo be formulate, compounded, and dosed? • Where and how will be radiolabeled active be synthesized and how will it be tested? How long is it stable? • How will radiolabeled drug product be prepared (spiked into drug product prepared elsewhere or will the CRO prepare the labeled drug product from labeled active and unlabeled active and excipients)? • How will data be managed?

CMC	• Plans for drug product supply and placebo (if required)
	• Plans for:
	  ○ Selection of vendors, manufacturers, laboratories, and distributers; negotiation of vendor agreements/contracts; audits
	  ○ Raw materials specification and testing
	  ○ Drug substance manufacture (synthesis or cell synthesis)
	  ○ Assessment of manufacturing parameters of drug substance and drug product (stability during manufacture (light, pH, oxidants, heat), powder properties (solubility, wetability, hygroscopicity, density, blendability), compatibility and stability with excipients
	  ○ Compatibility of manufacturing properties with intended dosage form and route of administration
	  ○ Formulation development
	  ○ Drug product manufacture, release, labeling, and shipping/distribution
	  ○ Reference standards
	  ○ Stability and degradation testing and assays
	  ○ Analytics of drug substance and drug product
	  ○ Drug substance and drug product specifications
	  ○ Scale and scalability of manufacture
	  ○ Scheduling of manufacture and release
	  ○ Plan for clinical manufacture and commercial launch in all markets
	  ○ Cost of goods (particularly as project reaches commercial stage)
	  ○ Supply chain robustness; alternative and backup vendors, suppliers, and manufacturers
	• CMC risk: stability, intended formulation and procedure for delivery, ability to supply the market, risk mitigation strategies

Commercial Plan

Element	Items
Commercial	• Market analysis is also discussed above in the clinical plan. • Need to develop a plant to get rapid adoption by prescribers and patients; develop favorable opinions from opinion leaders and stakeholders (patients, physicians, medical organizations, insurers...) • Should be continuously engaged with stakeholders throughout the drug lifecycle • Competitive landscape: existing products and company's product, as well as future pipeline products are compared for: effectiveness, side effects, cost, patient satisfaction, physician satisfaction... • Consider: how to differentiate product, what data to collect, how to differentiate based on healthcare economics, what other markets might exist for drug (other diseases) • Net present value calculation for product within each market; this is important in partnering discussions and as the company considers selling the rights to market in certain regions