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Assessing Risk in Oral Drug Development Programs

Pharmatek's Drug Development Risk Assessment Scorecard



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What Is The Scorecard?

The following white paper provides a quantitative approach to assessing risk in oral drug development programs with respect to Chemistry, Manufacturing, and Controls (CMC) activities. Pharmatek's Drug Development Risk Assessment Scorecard allows managers to get a dashboard view of critical areas in their specific drug development program. Once the components of risk are understood, strategies can be implemented to mitigate some of this risk going forward.

Pharmatek's Drug Development Risk Assessment Scorecard defines 8 key categories where project managers can evaluate the risk associated with their project. These 8 categories, along with a brief definition, are provided below.

Category	Definition
BCS Classification	BCS I (soluble and permeable), II (not soluble but permeable), III (soluble but not permeable), or IV (not soluble or permeable).
API Supply	Quantity and quality of research, non-GMP, and GMP batches of API. Timing of API availability is key. Considerations: form (crystal/amorphous), polymorphs?
API Stability	Stability in solid state (oxygen, moisture, light, heat) and in solution (aqueous pH range). Stability-indicating analytical method required.
Highly Potent/Cytotoxic	APIs characterized as highly potent or cytotoxic require special handling, limiting vendor selection and increasing development costs. Use Pharmatek, Merck, Safebridge, or other qualified banding system.
Dosage Strength	Proposed dosage strength for FIM. Anything outside the range of 1mg to 250mg may require additional formulation considerations.
Formulation	What is proposed FIM dosage form?: PIC, PIB, dry blend, or solubility enhancing formulation. Staged development approach vs. final formulation?
Quality of CMC Leadership	Source of CMC strategies to support all development needs such as quality, timing, scientific scope, and cost.
Timing	The development timeline leading to the proposed IND filing date.

Scoring

Each category is given a numeric score of 0, 1, or 2, based on its assessed risk to the drug development program using the following scale.

- 0 – Low Risk
- 1 – Standard Risk
- 2 – High Risk

The risk score for each category is summed to generate a Total Score. The Total Score is then used to quantitatively assess the Overall Project Risk for any given drug development program using the guideline below. A high risk score is not uncommon, and will benefit from the de-risking strategies provided below.

<u>Total Score</u>	<u>Overall Project Risk</u>
0-4	Low
5-8	Standard
9-16	High

Using The Scorecard

There is clearly a level of subjectivity involved when assigning a Risk Score for a given category. The following table summarizes two hypothetical oral drug development programs with all categories scored '0' or all categories scored '2' to help frame the evaluation.

Category	Low Risk (all scored '0')	High Risk (all scored '2')
BCS Classification	BCS Class I	BCS Class IV
API Supply	Same batch of 2kg available for non-GMP and GMP development and FIM. Impurity profile leaves room for error upon further scale up. Crystalline material with single polymorph.	Only 200g of research batch available for development (produced in-house). Non-GMP and GMP batches made by different suppliers (offshore for non-GMP, US for GMP). GMP API available less than 1 month before CTM manufacture.
API Stability	Stable at room temperature and 40°C without desiccant in clear glass bottle. Stable in aqueous solution from pH 1-9.	API is hygroscopic and degrades when stored for 1 month at 25°C as a solid. Light sensitive. Degrades in water.
Highly Potent/Cytotoxic	Not classified at HP/C. (Pharmatek Band 2, Merck Band 2, Safebridge Band 2, or below)	Requires special handling as a HP/C compound. (Pharmatek Band 3, Merck Band 3, Safebridge Band 3, or above)
Dosage Strength	All dosage strengths between 5 mg and 50 mg	Dosage strengths below 1 mg or above 250 mg for single unit
Formulation	PIC or simple dry blend in capsule	Liposome, emulsion, amorphous dispersion, or melt granulation
Quality of CMC Leadership	In-house CMC professional (or consultant), experienced with phase appropriate approach to IND process	No CMC experience (i.e. discovery chemist or clinical background only). Only experienced in Phase 3/Commercial drug products. Consulting firm recommends work that isn't phase appropriate.
Timing	Development timeline \geq 9 months	Development timeline \leq 3 months

De-Risking a Drug Development Program

The most common approaches used to mitigate risk in a drug development program are described below, along with the corresponding Risk Categories that each action may impact. Based on over 12 years of experience as a pharmaceutical CDMO and working with 100's of different drug candidates, it is our opinion that the most effective way to reduce the total project risk, short of altering the compound itself, is to ensure a CMC professional skilled in early phase drug development is contributing to the project. The Overall Project Risk should be considered along with many other factors for a drug development program, including the therapeutic indication.

Action	Risk Category	How Risk May Be Reduced
Alter Salt Form or Physical Form of API	BCS Classification	Improve solubility, target BCS I
	API Supply	Easier synthesis, reduce impurities, reduce batch size by increasing solubility/bioavailability
	API Stability	Crystalline form may improve stability
	Dosage Strength	Improved solubility may reduce dosage strength and risk of side effects
	Formulation	Improved solubility may reduce time, cost, and complexity of formulation development
Extend Timeline	API Supply	Representative API available for development work, ideally the GMP batch of API intended for CTM
	Timing	Allow time buffer for unexpected scientific results
Increase Investment	API Supply	Make a single GMP batch for development and CTM
	Quality of CMC Leadership	Improve strategic direction of development program
	Timing	Meet objectives by performing work in parallel
Improve Quality of CMC Leadership	API Supply	Identify options to improve solubility, quality, and manufacturing of API
	API Stability	Identify stable polymorph or salt form
	Dosage Strength	Minimize dosage strength through improvements in API solubility and understanding of clinical design
	Formulation	Identify the most efficient approach to achieve clinical objectives while balancing: cost, time, bioavailability, ease of manufacture, stability, and scalability
	Quality of CMC Leadership	Improve strategic direction of development program and provide perspective and guidance on each Risk Category described in this Scorecard
	Timing	Prioritize CMC activities in a phase appropriate manner, reducing time, cost, and risk associated with the drug development program

For further information on Pharmatek's Drug Development Risk Assessment Scorecard, or for help scoring your own compounds in development, please contact Pharmatek at scorecard@pharmatek.com.