1. EXECUTIVE SUMMARY

Executives who manage pharmaceutical pipelines sometimes use the static-shaped model described in this critique from AstraZeneca's executives:

> "The [static-shaped pipeline] hypothesis was simple: if one drug was launched for every ten candidates entering clinical development, then doubling or tripling the number of candidates entering development should double or triple the number of drugs approved. However, this did not happen; consequentially, R&D costs increased while output – as measured by launched drugs – remained static." (Cook et al. 2014, p. 419)

Table 1 illustrates a static-shaped pipeline model. The model estimates the number of compounds needed in each phase based on attrition rates. The model assumes the attrition rates are invariant, unaffected by the criteria for evaluating and advancing compounds through upstream gates.

Stage	Success Rate (throughput)	Attrition Rate	Number of projects required for one success
Phase I	70%	30%	6.11
Phase II	40%	60%	4.27
Phase III	65%	35%	1.71
NDA	90%	10%	1.11

Table 1: A common pipeline model, in which attrition rates, and thus a pipeline's shape, is immutable.

Pipeline Physics LLC

Gary J. Summers, PhD
President & Founder
gary.summers@PipelinePhysics.com

705 Powers Ferry Road SE, #315
Marietta, Georgia 30067
www.PipelinePhysics.com
503-332-4095

Intuition, theory, and empirical evidence suggest drug development is not a static-shaped pipeline.

- **Intuition**: Suppose managers relax the criteria for advancing compounds from phase II to phase III. Phase II's attrition rate decreases, but compounds with poor prospects advance downstream. Phase III's attrition rises.

- **Theory**: Each phase of clinical trials samples the same patient population, so the phases' results are positively correlated. Nonzero correlation implies that advancement decisions made upstream affect attrition rates downstream.

- **Empirical evidence**:

    - Over a thirteen year period, Eli Lilly's experts produced well-calibrated subjective probabilities for predicting technical success (Andersen 2011). Imagine ranking these compounds by their estimated probabilities, with the most likely to succeed at the top. Now choose projects by selecting down the ranking. Advancing more compounds increases phase III's attrition.

    - Ringel et al. (2013) identified various factors that predict success in phase III trials and in the NDA-process. The best predictor was upstream attrition rate. Companies with high attrition upstream had lower attrition downstream.

If real pipelines are not static-shaped pipelines, how do they behave? This study models the preclinical phase, phase I, and phase II with signal detection theory, and from these models, it produces a Bayesian model of drug development pipelines. It tests the model with pipeline data, collected from multiple large pharmaceutical companies, and then it performs the following analyses:

- Estimates the quality of compounds in each phase.

- Estimates each phase's (1) ability to distinguish marketable compounds (safe and effective) from unmarketable ones, (2) false-positive and false-negative rates and (3) percent of evaluated compounds that are marketable.

- Identify areas of excellence and opportunities for improvement. For example, if phase I's safety evaluation does not adequately distinguish marketable from unmarketable compounds, the study will identify the problem.

- Evaluates efficacy, safety, market value, scoring models, and common metrics (such as NPV, ROI, bang-for-the-buck or expected value) to identify the metric with the highest resolution.

- Performs a sensitivity analysis to identify opportunities to reduce development costs and raise productivity by 10-20%, or more.
- Identifies the optimal pipeline shapes for minimizing cost and maximizing profit. Compares these optimal values to a company's strategic and financial goals to see if the goals are feasible.
- Provides decision tools and an analysis of current practices to help executives better shape their companies' pipelines.
- Benchmarks industry best practices.

The study produces a simulation as well, so executives can experience and practice managing Bayesian pipelines.