

# The Integrated Early Drug Development Platform

*Oren Cohen, MD and Peter Sausen, PhD*

## **Abstract**

Is it possible to deal with the explosion of complexity in the early clinical development space? Is the traditional clinical pharmacology unit obsolete? The answers are yes and no, respectively.

The optimal engine for early clinical development in the modern era is an integrated early drug development platform.

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## **Introduction**

The landscape of early drug development has changed radically over the last decade. The norms of the past, wherein first-in-human (FIH) studies consisted of a relatively straightforward series of observations following administration of small molecules to normal healthy volunteers, have given way to exponential increases in complexity. As basic science probes deeper into the pathophysiology of disease states, experimental medicines have been discovered that modulate multifunctional biological pathways. Cases in point include inhibitors of Janus kinases, targeted to autoimmune diseases and cancers; inhibitors of histone deacetylases, targeted to cancers, inherited and acquired neuropathies and neurodegenerative diseases; and integrin inhibitors targeted to cancers and immunologic diseases. The result is less predictability of biological effects, increasing probability of undesirable off-target effects, proliferation of biomarkers as “navigational aids,” and Phase I study protocols packed with unprecedented numbers of procedures and observations. Increasingly, “umbrella” or “hybrid” study designs are proposed, wherein a single protocol may involve not only single ascending dose (SAD) and multiple ascending dose (MAD) cohorts, but also cohorts to detect the likelihood of drug-drug interactions; food effects; effects on electrocardiographic intervals; effects of age, gender and/or ethnicity; and pharmacodynamic (PD) effects in patients. In this regard, Getz and Campo documented a 53% increase in study procedures per Phase I protocol and an 82% increase in site work effort required to administer these procedures over a ten-year period (2011-2015 compared with 2001-2005)<sup>1</sup>.

Compounding the issue of biological complexity is the financial ecosystem of the biopharmaceutical industry. The cost of drug development continues to increase unabated, with current estimates reaching \$2.5B in capitalized cost per approved drug (Figure 1)<sup>2</sup>.

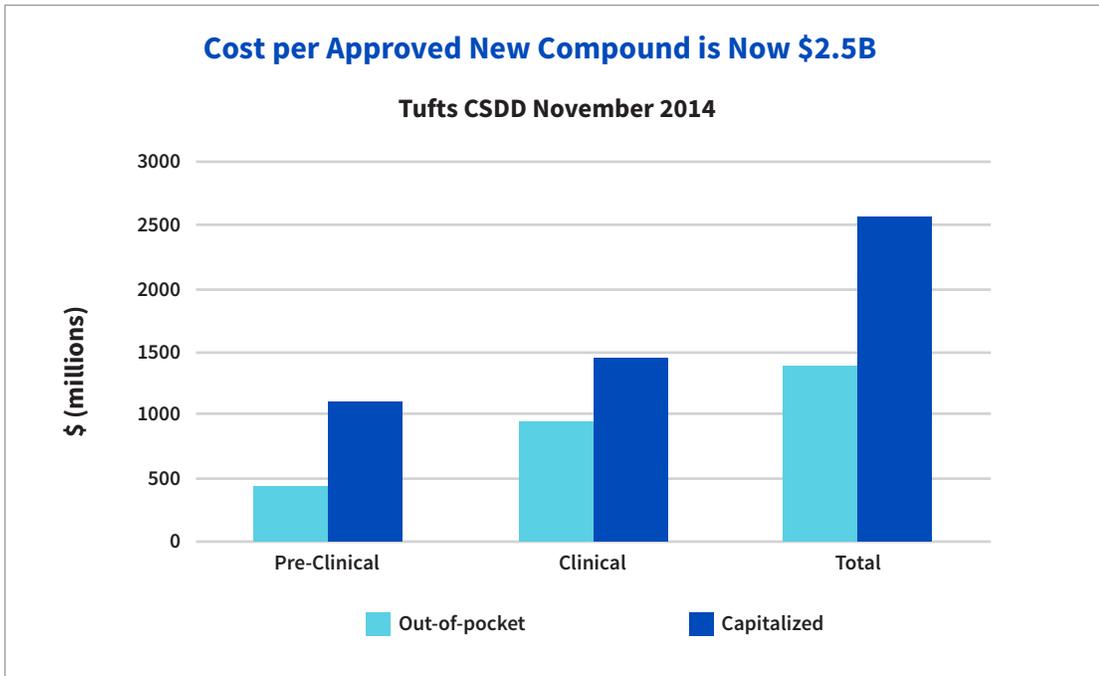


Figure 1. Drug development costs

Despite increasing investment and higher development costs, productivity has remained flat, with an overall approval rate for compounds entering Phase I clinical trials of <10%. As a result, the internal rate of return for large pharma's late stage pipeline continues to decline (Figure 2)<sup>3</sup>.

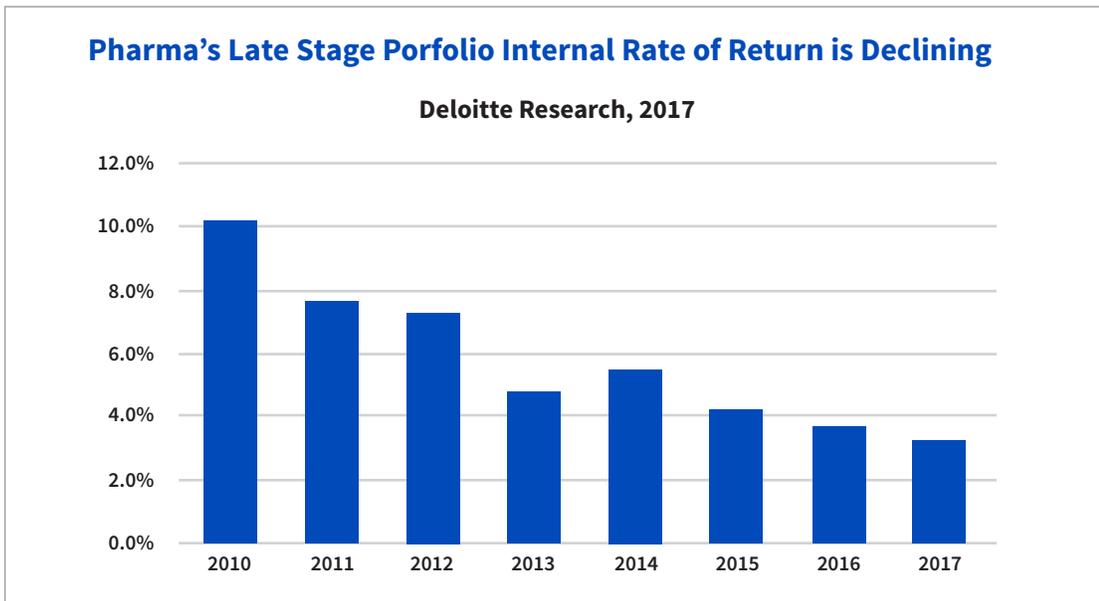


Figure 2. Large pharma pipeline internal rate of return, 2010-2017

Furthermore, the relative depletion of large pharma's early stage pipeline has disproportionately positioned venture-backed biotechnology companies as the suppliers of innovative candidate drugs to the industry. Increasingly, the goal of the biotechnology companies in early phase drug development is to develop data that may result in the sale or partnering of an asset. In the past, the goal was to understand as fully as possible the pharmacologic properties of an experimental drug. Does the drug distribute to the target space or tissue? Does it have a sufficiently wide therapeutic index? Does it interact with its target as anticipated, and does this interaction lead to the predicted biological effects? There is clear evidence that inability to adequately answer these questions in the earliest phases of clinical development results in very high failure rates in Phase II and III<sup>4</sup>. The challenge for the biotech companies is to generate enough data on a limited budget to position the asset for partnership or sale whilst also reducing risk of failure in later development.

Given these circumstances, is it possible to deal with this explosion of complexity in the early clinical development space? And is the traditional clinical pharmacology unit obsolete? The answers are yes and no, respectively.

As described below, the optimal engine for early clinical development in the modern era is an integrated development platform (Figure 3).

### The Integrated Early Clinical Drug Development Platform

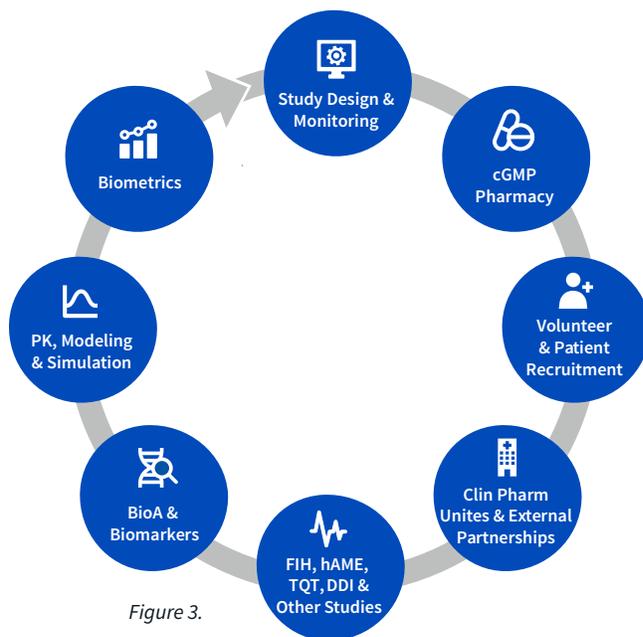


Figure 3.

#### Target product profile - Start with the end in mind.

Success of a drug candidate is directly linked to the thorough planning of the whole drug development paradigm. Starting with the end in mind, with a focus on the patients and the overall market, allows for well-thought-out and detailed study plans to be put in place. The clinical development plan will allow focus on the dosing regimen, the patient population, the detail of the complex clinical protocols and what is needed from early clinical development to support this. The clinical plan itself will support the optimization of a detailed and relevant nonclinical plan to ensure rapid entry into the clinical FIHetting with the right studies conducted at the right time.

Historically, work has been outsourced in a transactional, study by study, approach where dedicated specialists supported individual studies and there may have been little input between functional areas to design and integrate plans. There has been a big shift in industry working practices over the last 10 years, driven by detailed and collaborative planning within project teams linking up all stages of drug development. This has been a vital approach to enable biotechnology companies to design the right studies to “de-risk” their molecules, meet their clinical goals and move quickly and efficiently through early clinical development to enable the sale or partnership of their asset at an early stage.



## Study design and medical monitoring

Success begins with a well-designed study protocol that enables a limited number of questions related to fundamental pharmacology to be answered. It is impossible to overstate the importance of establishing the drug's exposure and safety and tolerability profile. This can be a challenge with the plethora of hydrophobic molecules in the pipeline. Unanticipated plateaus in exposure may demand assessment of food effect or new formulation. Expertise in pharmacology and study design is therefore a key success factor.

Once a study is "in flight," an experienced medical monitor can be the difference between progressing or killing a compound inappropriately. Isolated increases in levels of ALT or CPK, or QT interval may or may not be harbingers of existential threats to a compound's viability. Thoughtful adjudication, taking into account the clinical data as well as the mechanism of action and the preclinical profile is essential.



## cGMP pharmacy

Clinical pharmacology units must have a pharmacy capable of adequate control of clinical trial supplies. However, the ability of that pharmacy to manufacture clinical trial drug product according to current Good Manufacturing Practice [cGMP] (i.e. producing a product driven by controls that lead to safe and high quality investigational drug product) on site is a tremendous benefit. An on-site cGMP pharmacy can provide timely, appropriately-scaled quantities of fully formulated clinical trial product far more quickly and at a fraction of the cost compared with expensive manufacture of far larger lots by contract manufacturing organizations (CMOs). In addition, the stability testing required is significantly reduced, saving time and cost. This customized and nimble solution for each protocol's needs, while complying with regulatory requirements, represents a significant enhancement over production at an independent CMO.

An on-site cGMP pharmacy may be able to manufacture non-sterile dosage forms like API in a bottle, oral solutions and suspensions, tablets and capsules (high volume capsule fill), as well as sterile dosage forms like sterile injections and infusions from material sterilized on site.



## Volunteer and patient recruitment

Recruitment of full cohorts of normal healthy volunteers is essential to the efficient conduct of early phase clinical trials. A multi-pronged approach is necessary to build a robust database of volunteers, including multi-media advertising, call centers, community outreach, a digital presence (i.e. web portal), social media and other methods. When external sites are utilized for recruitment of patients or special populations, similar methods may be applicable. In either case, assessment of feasibility in the context of study design and inclusion/exclusion criteria is key. Sophisticated search strategies may also be useful. For example, the Labcorp clinical research organization has access to Labcorp clinical laboratory data, which can be used to locate clusters of patients with particular laboratory findings and overlay this information with locations of partner investigative sites.



## Clinical pharmacology units and external site partnerships

Clinical pharmacology units remain foundational to the conduct of early phase clinical trials. Before a study can be conducted, approval must be obtained from the relevant regulatory authority and institutional review board or ethics committee. Thorough medical and scientific review from within the clinical pharmacology unit should be undertaken as well, with the Principal Investigator taking ultimate responsibility for study conduct. Appropriate measures should always be taken to keep volunteer safety as the highest priority. In this regard, implementation of a "just culture"<sup>5</sup> and using methodologies such as failure modes and effects analysis to anticipate and mitigate risk may be particularly beneficial. An example of this approach is sentinel dosing, wherein two volunteers are dosed ahead of the remaining cohort in higher risk FIH studies to avoid near-simultaneous exposure of a larger cohort as happened with disastrous consequences in the TeGenero trial<sup>6</sup>.

Units should be purpose-built and staffed for the efficient collection of precision data from human subjects in Good Clinical Practice-compliant fashion. Adequate processes and training are critical for the reproducible collection of data across a broad spectrum of study types and designs as well as for the protection of the health, safety and well-being of volunteer study subjects. Emergency carts must be stocked with supplies that are necessary to deal with any situation that may arise during the course of a drug trial, such as anaphylaxis, seizures, respiratory distress and abrupt changes in heart rate or rhythm and blood pressure. Clinical pharmacology units are ideally located within minutes of a medical center with an emergency room and intensive care unit for the rare cases where transfer is necessary.

Other essential elements of an effective clinical pharmacology unit include nursing stations with telemetry capability, designated areas for meal preparation and distribution, screening, informed consent administration and volunteer recreation.

Increasingly patients are being included in early clinical studies to gain important information regarding the safety and pharmacodynamics (PD) profile of a drug in the intended population. These study designs are particularly useful in generating proof of principle data and adding value to an asset. To support this, external investigative sites are often needed to conduct clinical pharmacology studies in special populations and patients. Examples include specific patient populations, such as rheumatoid arthritis (RA), asthma, nonalcoholic steatohepatitis (NASH), HIV infection and others. Additionally, studies in hepatic-impaired and renal-impaired populations are needed prior to submission of a new drug application (NDA).



### Clinical pharmacology study types

Clinical pharmacology units should be adept at conducting a variety of study types, including: FIH SAD; MAD; bioavailability (BA); bioequivalence (BE); thorough QT (TQT); drug-drug interaction (DDI); and food-effect (FE). Some specialized units have the capability to perform human absorption, metabolism and elimination (hAME) studies using radiolabeled drug. Fundamental to all of these study types is the precisely-timed collection of blood or other biological specimens (spinal fluid, urine, bile, feces, etc.) for analysis of drug concentrations in order to characterize the pharmacokinetics [PK] properties of the drug.



### Bioanalysis and biomarkers

Specimens collected for bioanalysis must be delivered (either on-site or shipped) to a laboratory capable of precise determination of drug concentration (and potentially metabolites) in the relevant biological specimen (e.g. plasma). This is generally performed using a combination of liquid chromatography and mass spectrometry for small molecules or a variety of mass spectrometry-based techniques for large molecules.

Biomarkers are an increasingly important component of the integrated development platform. As noted above, the biological complexity being targeted by current drug candidates can make it difficult to assess whether a biological effect is induced consistent with the drug's purported mechanism of action (i.e. a PD effect). This principle is illustrated vividly by early clinical trials in Alzheimer's disease, which may include quantitation of biomarkers in cerebrospinal fluid in order to validate a drug's mechanism of action and potentially gain early insight into potential therapeutic effect (e.g. Beta Amyloid 38 (A $\beta$ 38), A $\beta$ 42, Soluble Amyloid Precursor Protein alpha (sAPP $\alpha$ ), Soluble Amyloid Precursor Protein beta (sAPP $\beta$ ), Amyloid precursor protein intracellular domain (AICD), Acetylcholinesterase (AChE), soluble neuregulin-1 (sNRG-1), cerebrospinal fluid (CSF) tau and phosphorylated tau (ptau) 181).



### Pharmacokinetic and pharmacodynamics analysis, modeling and simulation

Analysis of bioanalytical data enables determination of the PK properties of a drug, including its concentration in plasma during absorption, distribution, metabolism and elimination phases. Key parameters, including half-life, volume of distribution, the maximal concentration and the time to reach this concentration, the area under the time vs concentration curve (AUC) and others can be calculated.

Modeling and simulation of PK data can be useful in a variety of settings. Clinical drug-drug interaction potential can be modeled with a physiologically based PK (PBPK) approach, using inputs including doses and formulations of drug, physiochemical properties, protein binding, permeability, and the presence of relevant enzymes and transporters. These simulations can be valuable in the design of clinical studies and can even be useful in order to justify the need not to perform interaction studies. Models can also be built that allow prediction of human efficacious doses, thus aiding in FIH study design by linking the PK to the PD and better understanding the therapeutic window. Simulations can even be used to optimize formulation and to better understand the variability in larger populations to adjust dosing strategies based on different covariates. It has been estimated that a model-based approach can save upwards of \$97 million per NDA<sup>7</sup>.



### Biometrics

Data must be carefully and precisely collected during the conduct of a clinical trial. Data points that are questionable or ambiguous must be queried and resolved. Data are then compiled in a database and flow into tables, listings and figures created by statistical programmers in accordance with protocol specifications. Statistical analyses are performed according to the protocol's statistical analysis plan, and finally, a complete study report is written that summarizes the conduct and all findings from the study. Organizations that excel in biometrics should be able to provide rapid access to data and data visualizations, and interim reporting to enable rapid decision-making. In addition, the organization should be proficient with Analysis Data Model (ADaM), which defines the data standards that support clinical trial statistical analyses and traceability between analysis results, analysis data and data represented in the Study Data Tabulation Model (SDTM).

## The integrated drug development platform

Drug development is a complex and challenging pathway to navigate. In today's environment with ever more complex drugs and drug targets, it is essential to think beyond the four walls of a traditional clinical pharmacology unit in order to optimize early clinical development. An integrated development platform, including the resources, experience, expertise and infrastructure necessary to design and execute early clinical studies is an effective way of mitigating risk. A multidisciplinary team that understands the market and the molecule can devise a regulatory strategy and an early clinical development plan that aims to efficiently determine whether or not a drug candidate should continue to be developed. Effective use of the integrated platform allows for efficient determination of whether or not the drug achieves sufficient levels in the relevant physiologic compartment, whether it interacts with its intended target as anticipated, and whether it has any unanticipated or otherwise untoward biological effects. Increasingly, this requires not only strong clinical pharmacology expertise, but also access to biomarker testing and project management staff that can guide a protocol seamlessly from cohorts of normal healthy volunteers in a clinical pharmacology unit to cohorts of patients at multiple investigative sites.

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