Model-based drug development applied to oncology

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Model-based drug development (MBDD) is an approach that is used to organize the vast and complex data streams that feed the drug development pipelines of small molecule and biotechnology sponsors. Such data streams are ultimately reviewed by the global regulatory community as evidence of a drug’s potential to treat and/or harm patients. Some of this information is captured in the scientific literature and prescribing compendiums forming the basis of how new and existing agents will ultimately be administered and further evaluated in the broader patient community. As this data stream evolves, the details of data qualification, the assumptions and/or critical decisions based on these data are lost under conventional drug development paradigms. MBDD relies on the construction of quantitative relationships to connect data from discrete experiments conducted along the drug development pathway. These relationships are then used to ask questions relevant at critical development stages, hopefully, with the understanding that the various scenarios explored represent a path to optimal decision making. Oncology, as a therapeutic area, presents a unique set of challenges and perhaps a different development paradigm as opposed to other disease targets. The poor attrition of development compounds in the recent past attests to these difficulties and provides an incentive for a different approach. In addition, given the reliance on multimodal therapy, oncological disease targets are often treated with both new and older agents spanning several drug classes. As MBDD becomes more integrated into the pharmaceutical research community, a more rational explanation for decisions regarding the development of new oncology agents as well as the proposed treatment regimens that incorporate both new and existing agents can be expected. Hopefully, the end result is a more focussed clinical development programme, which ultimately provides a means to optimize individual patient care.

Keywords: ADME, clinical pharmacology, in silico, model-based drug development, pharmacodynamics, pharmacokinetics


1. Introduction

Recent insights into the molecular basis of cancer have altered the landscape for cancer drug discovery and development. Advances in molecular targeted cancer therapies offer the promise of personalized medicine for cancer patients. Initial efforts have made it painfully clear that the translation of molecular insights into useful therapeutic approaches is highly complex and the success of any particular approach is far from guaranteed. Progress with molecular targeted therapies have also provided insights into the shortcomings of traditional chemotherapeutic strategies and have led to a renewed effort to define optimal dosing strategies, particularly when agents of various classes are studied in combination [1]. Likewise, traditional paradigms of drug development are not optimally suited to these new challenges and may not fully exploit the potential of new molecular advances.
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An overwhelming result of the improvements in discovery stage sciences (e.g., high-throughput screening) and the increase in oncology targets is the vast amount of data generated in industrial and academic laboratories. The use of modeling and simulation to facilitate the development of novel anticancer agents and the integration of existing agents into multimodal therapies now has clear precedents. Past examples include the evaluation of docetaxel [2-4], topotecan [5-7] and imatinib [1,8,9]. Model-based drug development (MBDD) involves the union of science-based intuition (knowledge about a target and the agents investigated to hit such targets) and techniques to describe complex biological systems (modeling and simulation methodologies) with the ultimate intention of minimizing risk to developing an agent and maximizing its clinical benefit in conjunction with other compounds.

Many agents, despite promising scientific rationale (including compelling preclinical data), have shown disappointing efficacy in clinical trials. In most cases, it remains unclear why these agents failed. Did the targeted therapy hit the target? If so, is the target or pathway not as important as postulated? If not, can the agent be used differently, against certain molecularly defined tumors, combined with other agents, or further modified and optimized for better effect? Were the dose and/or schedule optimal? Was the combination of agents studied optimal? Is there a segment of the study population that exhibited greater response or toxicity? Although such questions are often asked at the conclusion of years of investigation, they are certainly constructed from more specific questions that were or were not asked at earlier stages of drug evaluation. The vision of a MBDD paradigm is to construct quantitative expressions about target–drug activity → drug–exposure → exposure–(biomarker) response → response–(clinical)outcome relationships, so that these questions promote assumption and scenario testing prior to clinical investigation.

The authors focus this review on defining the landscape for oncology drug development, highlighting factors that differentiate oncology from other therapeutic areas. The authors define the MBDD approach and identify modeling and simulation (M&S) activities by the development of stages specific to oncology drug targets. These strategies apply to both new and historical agents as both are interwoven in current and prospective treatment modalities. Lastly, the authors illustrate the approach with previously published and recent efforts.

2. Oncology targets and drug development

2.1 Pharmacotherapy as a treatment modality

Pharmacotherapy is principally concerned with the safe and effective management of drug administration. It implies an understanding of drug pharmacokinetics (PK) and pharmacodynamics (PD) so that individual dosing guidance, when necessary, can be provided to optimize patient response within their individual therapeutic window. Many oncology drugs have a low therapeutic index. Pharmacologic and physiologic changes that occur in oncologic populations and subpopulations (i.e., elderly and pediatric) can lead to dramatic consequences such as excessive drug concentrations, unacceptable toxicity or subtherapeutic concentrations and ineffective treatment. Unfortunately, in many cases, doses are rarely adapted based on PK or PDs. However, there are means to elucidate such guidance and several prominent examples of the benefit of such approaches.

Dosing in oncological disease states has been guided by several axioms that are ultimately influenced by PK/PD relationships. First and foremost, drugs are more effective in combination and may be synergistic. Second, dosing is likely to be more effective if drugs do not share common mechanisms of resistance. Likewise, it is often beneficial if drugs do not overlap in major toxicities. Drugs should be administered near their maximum individual doses and should be administered as frequently as possible to maximize dose intensity (dose per unit time) limiting tumor regrowth. Lastly, and in summary, it is highly desirable to elicit the maximum cell kill within each treatment cycle, using the highest dose possible, repeating doses as frequently as tolerable.

Given the focus on maximizing cell kill, it is critically important to maintain therapeutic drug exposures at the site of action. As indicated previously, the PK attributes of the various drug combinations must be understood so that the dosing principles above can be maintained. Although drug clearance is the principal parameter monitored in most situations, other PK (protein, tissue and tumor binding, distribution and absorption) and PD (tolerance, receptor or enzyme modulation) processes can be influenced in one way or another by pharmacological or physiological changes within a patient or based on competition for elimination pathways. In some cases, the potential for such modifications can be projected based on the properties of the drug substance. However, most are discovered following the exploration of failed therapy.

The uniqueness of oncology is that a therapeutic drug class comes from both the standpoint of the narrow therapeutic window for many of the existing agents as well as the tolerance for toxicity. Dose finding in the past has often been guided by the maximum tolerated dose (MTD) with little additional data to judge effectiveness prior to survival-based efficacy studies. The emphasis on identifying biomarkers of drug activity and toxicity [10,11] has been a valuable addition for many new agents in development and has certainly improved the ability to diagnose prostate cancer prostate-specific antigen (PSA) [12] and prostatic acid phosphatase (PAP) [13], ovarian and breast cancer (CA 125 [14] and CA 15-3 [15]). However, the generation of biomarkers to identify specific cancer disease progression or help identify the therapeutic window within which dose selection can be optimized has not yet caught up to the expectation (Figure 1). In addition, as pharmacotherapy in oncology is multimodal, combination therapy yields temporal, composite therapeutic progressions (Figure 2), which vary across patients and by
disease stage, making treatment dynamic and very much individualized to patient response.

2.2 Critical decisions which guide compound advancement
The drug development process is long, arduous and expensive. The cost of drug development continues to increase and pharmaceutical sponsors consistently seek to gain efficiency in the underlying processes. Those companies able to maintain successful portfolios do so by making critical decisions. The decisions typically occur at key development milestones, but may also occur in reaction to an unanticipated outcome. Table 1 lists the critical decision milestones that define a new chemical entity’s (NCE’s) progression through the development path. Proof-of-mechanism, while desirable, is often undemonstrated and many drug monographs contain wording, which declares that an agent’s mechanism of action is unknown. During early stages of development thousands of drug molecules are screened for activity, safety and ‘druggability’. Druggability is a relatively new concept and refers to the characteristics of the active pharmaceutical ingredient (API) relative to the desired properties of the agent to be developed. It encompasses the physiochemical properties of the agent that dictate whether it can be compressed into a tablet or even suitable for an oral formulation, its PK properties that reveal dosing requirements, drug interaction potential and the likelihood of food effect, among other factors. Ultimately, this criterion determines the eligibility of a drug product to be

![Figure 1. Theoretical therapeutic window for oncology agents.](image1)

![Figure 2. Potential for temporal effects on the therapeutic window for oncology agents as a function of therapy duration.](image2)
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Table. 1. Critical decision stages for compound progression.

<table>
<thead>
<tr>
<th>Proof-of-mechanism</th>
<th>Establish the correlation between drug mechanism of action and the pathophysiology of the intended disease state or condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Druggability assessment</td>
<td>Determination of whether the formulation can be made consistent with market image and if the PK properties allow achievement of exposure targets</td>
</tr>
<tr>
<td>Therapeutic window definition</td>
<td>Drug therapy can be administered between an acceptable ‘window’ of drug exposure, which maximizes clinical benefit against any untoward drug action</td>
</tr>
<tr>
<td>Proof-of-concept</td>
<td>A realization of a method/idea to demonstrate feasibility – determines the effectiveness of a drug and confirms safety in patients that the drug may ultimately treat</td>
</tr>
<tr>
<td>Clinical outcome assessment</td>
<td>Assessment of change in a patient’s ‘status’ over a period of time to determine if the condition is improving, worsening or remains unchanged</td>
</tr>
<tr>
<td>Health economics and market valuation</td>
<td>Expected final performance relative to existing medicines used to treat target indications. Analysis of patient costs relative to clinical benefit and health outcomes</td>
</tr>
</tbody>
</table>

approved and marketed successfully for an indication that would yield financial gain to the sponsor. Hence, the marketplace landscape is embedded into this assessment.

Over the past decade or so, anticancer drug discovery has shifted from an empirical approach, characterized by a random screening of varied compounds using high-throughput cell-based cytotoxicity assays to a more rational and mechanistic, target-based approach. The goal of this new target-based approach is to improve the efficacy and selectivity of cancer treatment by developing drugs based on the mechanism of action specific to these targets. Validated targets are generally proteins that play a vital role in malignant transformation, such as the products of the mutated genes that results in a gain of function (e.g., ras, bcr-abl), or normal receptors and signaling proteins in pathways that regulate apoptosis [16]. Some of the examples of drug development based on target-based approaches include tretinoin (all-trans-retinoic acid), which targets the promyelocytic leukemia (PML) and the retinoic acid receptor (RAR)α fusion protein in acute promyelocytic leukemia (APL) and imatinib mesilate, which targets the BCR-ABL fusion protein in chronic myelogenous leukemia and the mutated KIT (a protein-tyrosine kinase receptor specific for stem cell factor receptor) in gastrointestinal stromal tumors (GIST).

2.3 Role of modeling and simulation to facilitate model-based drug development

M&S approaches applied during preclinical drug development can provide quantitative predictions of the clinical performance of NCEs and help to better plan the early stages of clinical drug development programmes. The M&S tasks at this early stage of drug development are primarily designed to ‘learn’ about the properties of the molecule that are then ‘confirmed’ by the data generated during the early clinical drug development [17]. Table 2 lists and defines the most common M&S techniques used to construct quantitative relationships for a subsequent query. Many of these are referred to in Sections 3, 4 and 5, which describe their application in various development stages and with the case studies described. PK/PD modeling approaches are generally well-appreciated, particularly for their use on guiding trial design for oncology agents [18], but M&S activities begin much earlier in the development plan under a MBDD approach and are not limited to drug exposure and activity prediction. Table 3 shows the overlay of M&S activities across the phases of drug development and against some of the common milestones that exist for oncology agents.

From the moment a drug target is defined, assumptions regarding the optimal characteristics of viable drug candidates are formed and a target product profile is generated to encapsulate these features so that the preclinical, clinical and economic features of minimal, acceptable and superior candidates can be ranked based on the scoring of these attributes. From the moment a drug molecule is synthesized, experimental data is generated to permit assessment of the actual attributes of particular agents. Initially, these may constitute physiochemical data, which, when coupled with molecular structure alone can be used to make predictions about drug absorption, distribution, metabolism and excretion (ADME) properties. ADME properties can then be indexed against activity and/or toxicity data using a technique such as quantitative structure–activity relationships (QSAR). Likewise, as compounds advance through the various stages of development, presumably passing predefined criteria for agents of that class as well as regulatory hurdles to ensure access to human phase testing, the nature of experimental data and the resultant M&S activity evolves as can be seen in Table 3. The salient feature of the MBDD approach is that these relationships are connected in such a way that the outcomes or findings from a model-based relationship can be traced to previous models, relationships and data which were essential for proceeding to the current phase of testing.

The MBDD paradigm can, of course, be applied to any therapeutic area. For the most part the application of the MBDD approach is the same regardless of indication, but there are differences in some disease-drug targets the necessitate alteration in the types and/or nature of the underlying models. However, the use of such models to
Table 2. Modeling and simulation techniques/approaches used in a model-based drug development paradigm.

<table>
<thead>
<tr>
<th>Techniques/approach</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantitative structure–activity relationship</td>
<td>Models that correlate structural or property descriptors of compounds with activities. Physicochemical descriptors would include hydrophobicity, topology, electronic properties and steric effects and include chemical and biological assays.</td>
</tr>
<tr>
<td>Quantitative structure–pharmacokinetic relationship</td>
<td>Models that correlate structural or property descriptors of compounds with PK attributes (e.g., drug clearance).</td>
</tr>
<tr>
<td>Response surface model</td>
<td>A technique to explore the interaction of several response variables using regression modeling to provide a conclusion for optimal interactions of the response variables of a system.</td>
</tr>
<tr>
<td>Allometric scaling</td>
<td>Models that describe the relationship between PK or physiologic processes (more specifically parameters) and indices of size. Toxicology and risk assessment regularly use allometric models for extrapolation between species and for predicting biological responses in humans based on responses in a laboratory animal.</td>
</tr>
<tr>
<td>PK modeling</td>
<td>Models that explain the relationship between drug dose and exposure (of the parent compound and/or metabolites).</td>
</tr>
<tr>
<td>PB/PK</td>
<td>Models that define drug kinetics in terms of the physiology, anatomy and biochemistry of the organism and are composed of compartments, which represent body organs and tissues with body compartments are linked together by a flow network. A PB/PK model is defined by a system of deterministic kinetic equations (mass balance equations) of the amount or the concentration of the drug in the compartments as a function of time and initial dose.</td>
</tr>
<tr>
<td>PK/PD</td>
<td>A model that combines the relationship describing concentration versus time (PK) and the relationship describing effect versus drug concentration (PD) to predict the time-course of effect (activity or toxicity) versus time.</td>
</tr>
<tr>
<td>PPK</td>
<td>Models that describe the relationships between physiology (both normal and disease altered) and PKs, PDs, the interindividual variability in these relationships and their residual intraindividual variability.</td>
</tr>
<tr>
<td>Population PK (and/or PK/PD) modeling</td>
<td>Models that describe the relationships between physiology (both normal and disease altered) and PKs, PDs, the interindividual variability in these relationships and their residual intraindividual variability.</td>
</tr>
<tr>
<td>CTS</td>
<td>A technique for knowledge synthesis and exploration of possible clinical trial results based on a mathematical/stochastic model of the trial execution process, including submodels of the drug action and disease process based on the Monte Carlo simulation.</td>
</tr>
<tr>
<td>Limited sampling model</td>
<td>Models for estimating PK metrics (i.e., AUC and Cₘₐₓ) based on limited (few) samples collected post drug administration. A regression-based approach in which discrete sampling times (or windows) are evaluated relative to their predictive performance for drug exposure.</td>
</tr>
<tr>
<td>D-optimal design</td>
<td>A regression-based approach to explore the relationship between design information content and sampling location and density.</td>
</tr>
<tr>
<td>BF</td>
<td>BF is a model-based approach incorporating prior data history to improve statistical estimation involved in regulating processes during transition (i.e., when decision making is required), when applied in a clinical pharmacology setting. BF incorporates historical PK or PK/PD data into models which guide dosing.</td>
</tr>
</tbody>
</table>

AUC: Area under the curve; BF: Bayesian forecasting; CTS: Clinical trial simulation; PB/PK: Physiologically based pharmacokinetic modeling; PD: Pharmacodynamic; PK: Pharmacokinetic.
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Table 3. Modeling and simulation activities used during a model-based drug development approach for oncology agents.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Desired milestone</th>
<th>M&amp;S activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery preclinical</td>
<td>• Mechanism established</td>
<td>• Single-agent activity models</td>
</tr>
<tr>
<td></td>
<td>• Selectivity, specificity targets achieved</td>
<td>• Synergy/response surface modeling – project drug combinations</td>
</tr>
<tr>
<td></td>
<td>• Combination therapies evaluated</td>
<td>• Disease progression: define fundamental assumptions and baseline time course</td>
</tr>
<tr>
<td></td>
<td>• IV form stable; SC and oral dosage forms possible</td>
<td>• QSARPK and <em>in silico</em> modeling – predict FTIM dose, drug supply needs and desired exposure</td>
</tr>
<tr>
<td></td>
<td>• CUI favors development</td>
<td>• Generate attributes – define CUI and market potential</td>
</tr>
<tr>
<td></td>
<td>• Early toxicology acceptable</td>
<td>• Mechanistic PK/PD modeling: <em>in vitro</em> – <em>in vivo</em> prediction; tumor binding/exposure models; biomarker performance; xenograft to clinical correlation</td>
</tr>
<tr>
<td></td>
<td>• Input scenarios evaluated (dose, regimen, sequence and duration)</td>
<td>• IVIVC; IVIVE; dose-exposure scenarios simulated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Allometric modeling to confirm FTIM dose and drug supply needs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Favorable PK based on mechanism; QD dosing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PB/PK modeling to evaluate peripheral exposure targets and oral absorption</td>
</tr>
<tr>
<td>Phase I/II</td>
<td>• MTD &gt; therapeutic dose</td>
<td>• Initial PK/PD models to define dose-exposure and exposure response (considerations for PET and toxicity/AE models)</td>
</tr>
<tr>
<td></td>
<td>• Optimal dose and schedule determined</td>
<td>• Project Phase II trial designs (dose/regimen/ combination selection for Phase I/II)</td>
</tr>
<tr>
<td></td>
<td>• Low interaction potential</td>
<td>• Confirmatory PK/PD models (relevance to target population)</td>
</tr>
<tr>
<td></td>
<td>• Formulation/regimen can deliver desired exposure profile</td>
<td>• Project Phase III trial designs (based on submission strategy) via CTS; LSS (D-optimal design)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Identify potential design conflicts (non-response, adherence, ITT, etc.)</td>
</tr>
<tr>
<td></td>
<td>• Phase I window portable to Phase II</td>
<td>• Assessment of need and performance of individualized dosing strategies/designs</td>
</tr>
<tr>
<td></td>
<td>• Biomarker response confirms preclinical mechanistic studies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PoC confirmed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ‘Targeted’ populations identified</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dose selection supported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase III</td>
<td>• Phase III clinical outcomes match predictions</td>
<td>• Forecasting special or suspected varied populations (e.g., Japanese)</td>
</tr>
<tr>
<td></td>
<td>• Biomarker response confirms preclinical mechanistic studies</td>
<td>• Potential validation strategy (CTS) for bio-/Surrogate-marker</td>
</tr>
<tr>
<td></td>
<td>• PoC confirmed</td>
<td>• Cost analysis/pharmacoeconomics</td>
</tr>
<tr>
<td></td>
<td>• Favorable R&amp;D investment recovery projected</td>
<td></td>
</tr>
<tr>
<td>Phase IV</td>
<td>• Favorable and informative labeling attained</td>
<td>• Assess potential populations requiring dose modifications (pediatrics, pregnancy, etc.)</td>
</tr>
<tr>
<td></td>
<td>• Favorable R&amp;D investment recovery confirmed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• New indications defined</td>
<td>• PK/PD and CTS to evaluate new indications</td>
</tr>
<tr>
<td></td>
<td>• Product line extensions</td>
<td>• PK/PD and CTS to explore therapeutic advantages to product line extensions</td>
</tr>
</tbody>
</table>


drive compound progression, articulate and challenge assumptions and defend decision criteria is still the focus of the approach. Specifically, the availability of biomarkers at early stages, particularly when they can be transitioned into the patient setting is valuable in the discrimination of active doses as well as the definition of the therapeutic window. This is the case for many cardiovascular agents particularly those that target the vascular space. In contrast, CNS-mediated targets (for example, depression, dementia and Parkinson’s disease) rely on psychometric scales, which are often imprecise and have no correlation with preclinical markers. Similarly in oncology, although biomarker exploration is increasing, most of those defined to date are prognostic for disease status and do not necessarily track drug actions. This presents challenges to drug developers from the standpoint of biomarker development, the assignment of exposure targets based on preclinical pharmacology data and the development of
models that satisfy mechanistic versus empirical plausibility.

Table 4 lists examples of M&S applications in the development/investigation of oncology agents. Whereas this list is neither comprehensive nor prototypical, it does illustrate the diversity of recent applications across many classes of oncology agents consistent with a MBDD paradigm. Rombout et al. provide a thorough review of the application of M&S strategies used during the development of anticancer agents [19]. One of the many benefits of the approach is the ability to examine clinical study designs prior to conducting a trial (clinical trial simulation). Figure 3 shows a typical trial simulation schematic for an oncology agent. Many of the model compartments are actually quantitative relationships that are defined based on preclinical and/or pooled Phase I/II data, which approximate the time dependencies on drug actions. Likewise, knowledge regarding the intended patient population can be obtained from previous trials with the same or related agents and the impact of filtering criteria (placebo, drop-out, inclusion–exclusion criteria) evaluated.

3. Discovery and preclinical development

During the preclinical phase of the drug development, the PK/PD properties of candidate molecules are generally compared. In addition, potential relationships among dose, concentration, efficacy, and/or toxicity are modeled, which eventually helps in the selection of the doses chosen for early clinical testing. In oncology specifically, the evaluation of dose input, sequence with other agents and duration of input (e.g., short, intermittent or continuous infusions) are essential for later phase testing. Thus, one of the deliverables of M&S at this stage, is to project the Phase I dose based on the preclinical, biopharmaceutical and PK/PD properties of the

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>M&amp;S activity</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA alkylating agents</td>
<td>Cyclophosphamide</td>
<td>BF [121]</td>
<td>Individual dose adjustment to reach target exposure</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide</td>
<td>PPK [56]</td>
<td>Described effects of autoinduction on ifosfamides disposition</td>
</tr>
<tr>
<td></td>
<td>Busulfan</td>
<td>PPK [70]</td>
<td>Recommendation of adjusted weight-based doses in children &lt; 12 kg</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Methotrexate</td>
<td>PPK [122]</td>
<td>Serum creatinine and age explained variability in clearance</td>
</tr>
<tr>
<td></td>
<td>Pemetrexed</td>
<td>PPK [72,73]</td>
<td>Renal function affected drug clearance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PK/PD [74,75]</td>
<td>Supported folic acid and vitamin B12 administration to manage neutropenia</td>
</tr>
<tr>
<td>Topoisomerase inhibitors</td>
<td>Irinotecan</td>
<td>PK/PD [64]</td>
<td>Irinotecan hematologic toxicity profiles predicted using a general PK/PD model developed using other oncology agents</td>
</tr>
<tr>
<td>Topotecan</td>
<td>PPK [6]</td>
<td>Development of limited-sampling strategy for clinical monitoring</td>
<td></td>
</tr>
<tr>
<td>Antimitotics</td>
<td>Paclitaxel</td>
<td>PPK [77]</td>
<td>Individual predicted AUC from sparse sampling scheme was a predictor of granulocytopenia and survival</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>CTS [2]</td>
<td>Dose intensification would not benefit patients with high baseline α1-acid glycoprotein</td>
<td></td>
</tr>
<tr>
<td>Podophyllotoxins</td>
<td>Etoposide</td>
<td>LSM [124-127]</td>
<td>Development of limited PK sampling model to predict etoposide AUC</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Epirubicin</td>
<td>PPK [128]</td>
<td>Performed simulations to support fixed doses based on AST levels</td>
</tr>
<tr>
<td>Target-specific agents</td>
<td>Capecitabine</td>
<td>PK/PD [76]</td>
<td>Systemic exposure was poorly predictive of safety and efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PB/PK [37]</td>
<td>Activation by dThdPase, elimination by DPD and blood flow rate determine 5-FU production in tumor tissue</td>
</tr>
<tr>
<td>Oblimersen</td>
<td>RSM [129,130]</td>
<td>Using response surface modeling, the authors identified the concentration region where maximum synergy or antagonism was achieved at varying concentrations of cytotoxics used in combination with oblimersen</td>
<td></td>
</tr>
</tbody>
</table>

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NCE and to establish the concentration–effect relationship of the NCE in animals. This is generally achieved using a combination of M&S approaches, including population analysis of preclinical data, allometric scaling to predict human PK and empirical efficacy scaling can be used to project the anticipated human dose and/or dosing regimen for Phase I studies.

As with other therapeutic areas, the discovery/preclinical stage is focused on identifying target activity metrics and screening compounds against established, often mechanism-specific assays. In oncology, the activities during preclinical stage include the molecular characterisation of models along with an appreciation of the PD and PK properties of compounds defining both toxicity and antitumor efficacy [20]. Different PD models can be used to examine the influence of exposure-time and drug concentration on drug effect \textit{in vitro}, which can be subsequently used for optimizing regimens considered during \textit{in vivo} testing. Such models might also be useful in providing insights into mechanisms of drug action.

The preclinical program in oncology usually involves \textit{in vitro} evaluation of compounds from chemical libraries for antitumor effect against various cell lines. Clinical potency can be estimated from preclinical models, which can be used to further screen candidate drugs. The preclinical system can either be an \textit{in vitro} or an \textit{in vivo} system; for example, myeloid colony-forming unit progenitor cell systems (CFU-GM) may be used for estimating relative potency of different drugs [21]. These models are used during the preclinical drug development to rank compounds and optimize the experimental designs, allowing consistent savings in terms of both resources and time.

Due to the financial and logistic limitations to clinically evaluate all possible drug combinations, different drug combinations of older (cytotoxic) drugs and new anticancer drugs are evaluated using \textit{in vitro} modeling approaches [22] such as response surface modeling during the preclinical stage of oncology drug development [23]. The authors have identified synergistic interactions using MTT assays (\textit{in vitro}) between G3139 (active agent in the oligonucleotide Bcl-2 inhibitor oblimersen sodium) and cytotoxic agents, for example, etoposide based on response surface modeling (Figure 4) during preclinical investigations of combination therapy with G3139 and cytotoxic agents (projecting antitumor effect). The zero-interaction response surface for the drug combinations was generated using a variation of the Loewe additivity equation. Using this approach, the authors were able to identify the region where maximum synergy/antagonism was achieved at varying concentrations of drugs used in combination. These model-based approaches are aimed at identifying more safe and effective drug combinations and elucidating the rationale for such combinations. There are several published examples demonstrating the effects of combination therapy using a model-based approach. For example, trastuzumab and tamoxifen were evaluated in both \textit{in vitro} and \textit{in vivo} models of breast cancer, which indicated that this combination represented a promising treatment strategy [24]. Some of the questions that need to be answered during this stage of the drug development process are: i) what are the parameters that

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**Figure 3.** Schematic for a clinical trial simulation model used to project study outcomes based on drug-, patient- and design-specific factors.
The prediction of human PK from preclinical data is essential to reduce the evaluation of compounds with poor PKs in the human phase of testing. The common practice is to estimate PK parameters from observed plasma data by empirical approaches, such as non-compartmental analysis (NCA) or a simple compartmental model of the data. There are several examples in the literature where such approaches have been applied, although limited examples exist where a population-based approach has been applied during the preclinical stage of drug development. Rouits et al. used non-linear mixed effects modeling approaches to evaluate the linearity of CPT-11 PK and the influence of the schedule of administration in mice [32]. Although these models may have some use and pragmatism, PK/PD modeling is progressing from an empirical, descriptive discipline into a more mechanistic science that can be applied to all stages of drug development [33].

M&S methodologies can be used to capture uncertainty and use the expected variability in biopharmaceutical and PK/PD data generated in preclinical species for projection of the plausible range of clinical dose based on exposure–response (antitumor and toxicity) relationships; clinical trial simulation can be used to forecast the probability of achieving a target response in patients based on the information obtained in the early phases of development [17,34]. Preclinical studies are based on certain assumptions, including: i) the relative efficacy and potency observed in the in vitro systems and the studied animal species, given the projected uncertainty, is predictive of the relative efficacy and potency later observed in humans and ii) allometric scaling most often provides a reasonable estimate of the clearance of the compound in humans. Inter-species scaling, based on allometric relationships, have been used to bridge preclinical and clinical PK information by prediction of drug clearance and the volume of distribution. For the purposes of estimating starting doses in humans, the human clearance and volume of the NCE is projected with uncertainty based on allometric scaling of the clearance values obtained in different animal species. The prediction from animal species (e.g., rat) to human can be further improved by scaling by the relative drug potency between rat and human myeloid cells in vitro, in addition to accounting for species differences in PKs, for
example, in protein binding and the formation of metabolites [21]. Physiologically based approaches might be more useful in cases where allometric scaling fails, mostly for active processes, such as metabolism and transport.

Physiologically based PK models (PB/PK) offer a more scientific approach to help rationalise the 'first into human' decision-making process [33]. PB/PK models are increasingly being used in preclinical drug development to enhance the understanding of the complex interactions of biological and physiological parameters that affect drug behaviour at the molecular level in multiple physiological compartments [35]. These models provide several benefits, including: i) the prediction of plasma (blood) and tissue PK of drug candidates prior to in vivo experiments; ii) supporting a better mechanistic understanding of PK properties, as well as helping the development of more rational PK/PD relationships from tissue kinetic data predicted and, hence, facilitating a more rational design during clinical candidate selection and iii) extrapolation across species, routes of administration, duration and timing of drug input and dose levels [36]. These models are also used to screen potential clinical candidates from the pool of compounds in drug discovery [34]. For cytotoxic drugs, PB/PKs model can be used to identify factors that govern the dose-limiting toxicity in gastrointestinal tissue and antitumor activity. The developed PB/PK model can also be applied to human cancer xenografts in rodents, which could be used further to plan clinical development strategies from preclinical data. Mechanism-based population PK/PD models can be applied to several important milestones during oncologic drug development such as candidate selection, first-in-man studies, prodrug and formulation development, dose finding and schedule optimization, assessing influence of modifying agents, drug combination studies, subgroup identification and feedback individualisation [18,21]. There is an increasingly greater number of examples in oncology, where the PB/PK model has been successfully used during the preclinical stage. Tsukamoto et al. has shown that the PB/PK model integrating biochemical parameters in vitro (enzyme activity and tissue binding) was suitable for describing the PKs of capecitabine in human xenograft models. They also demonstrated that the 5-FU total exposure in tumor tissue at the effective dose for human cancer xenograft models was comparable with that at the clinical dose in humans [37]. In another example, Baxter et al. described the PB/PK model for monoclonal antibodies in human tumor xenografts in nude mice, which could potentially be used to scale antibody PKs from mouse to man [38].

During the preclinical stage of drug development, biomarkers are used to assess target activity and/or safety thresholds and, ultimately, as a means of bridging the transition from preclinical to clinical studies [39,40]. Preclinically, biomarkers can facilitate the selection of animal models and of lead compounds tested in those models. They can also aid in the demonstration of the mechanism of action from both in vitro and in vivo models. Some biomarkers evaluated in this manner, such as those that measure apoptosis or signaling pathways, can be used to quantify the effects of anticancer drug combinations and subsequently to predict optimum clinical treatment regimens. Biomarkers such as PSA are being used routinely to monitor the treatment response of prostate cancer in animal models [41]. One of the recent advances that promises to shorten the preclinical drug development process for oncology agents is the incorporation of positron emission tomography (PET) into early drug studies to identify non-invasive disease specific biomarkers as PK/PD end points, so that the best candidate can be selected for clinical development. Non-invasive molecular imaging probes have been successfully used to detect tumor hypoxia for Hsp90 molecular chaperone inhibitor 17AAG, as well as the development of SR-4554 [42]. Likewise, such techniques yield rich data from which quantitative models can be derived and used to define activity targets and screen development candidates.

4. Phase I/II

In the oncology setting, there is seldom a clear distinction between the design and conduct of Phase I and Phase II studies. Unlike most therapeutic areas, Phase I oncology trials are usually performed in the target population. The principal goals of Phase I/II studies are to describe safety and toxicity, pharmacologic behavior and to define an optimal and safe dose and schedule for subsequent efficacy studies. The design and analysis of Phase I/II oncology studies are particularly well suited to a population-based approach, as these studies are generally conducted in patients with metastatic cancer, who are being treated with a combination of therapeutic agents. Typically, PK and PD data are pooled across studies for analysis via non-linear mixed-effects modeling. This modeling effort is vital as the first step to learn about the PK characteristics and quantify the variability of the NCE in human subjects.

The transition from preclinical to clinical drug development most often resides in setting an optimal starting dose in humans. There is no gold standard yet for estimating the initial dose for oncology phase-I dose escalation trials. Generally, the starting dose of a cytotoxic agent is calculated as one-third of the toxic low dose (TDL) expressed as mg/m2 in a large animal species (either dog or monkey). Collins et al. used a pharmacologically guided dose escalation (PGDE) approach defined as one-tenth of a dose (expressed in mg/m2) that is lethal to 10% of non-tumor bearing mice (LD10) [43]. Recently, there has been a shift to transform the starting-dose calculation from an empirical approach to a more mechanistic pharmacokinetically and pharmacodynamically driven one. Gallo et al. used physiologically based PK models derived from preclinical data and then scaled it to humans to predict human tumor carboplatin, topotecan and temozolomide concentrations [44]. These efforts have focussed on tumor-based PK/PD relationships, which provide a rationale means to select the most efficacious drug dosing...
regimens [30,44]. It has also been suggested that PK/PD models describing the hematologic toxicity time profile may be useful for dose escalation decisions [21]. Simulations to explore various dose escalation scenarios could be predictive of likely hematologic toxicity outcomes in response to the proposed escalation schemes.

Historically, much of the efforts put forth in modeling analyses for oncology agents have been focused on characterising and explaining the variability in PKs. Numerous examples exist to illustrate this point: melphalan clearance is somewhat higher in males than in females and decreases with decreasing creatinine clearance [45], variability in epirubicin clearance could be attributed to sex and also to age in women [46], carboplatin clearance in children is related to weight and serum creatinine [47], mild-to-moderate renal insufficiency has no effect on gemcitabine PKs [48].

More recent modeling studies have focussed on investigating patient specific genotypes in order to identify the effects of genetic polymorphisms on the disposition of chemotherapeutic agents. The association of cytochrome P450 (CYP)2D6 polymorphism and ifosfamide PKs was investigated using a mixed-effects modeling approach [49]. The effects of CYP2C8, CYP3A4, CYP3A5 and ABCB1 polymorphism on paclitaxel PKs have also been investigated using the same approach [50]. Although results for both of these studies demonstrated that no influence on drug disposition was apparent for the enzyme polymorphisms studied, several examples outside the oncology setting have shown genetic factors to be significant predictors of drug disposition. A recent study of cyclophosphamide pharmacogenetics used a mixed-effects modeling approach to demonstrate that patients with the CYP2B6 G516T variant had a higher cyclophosphamide clearance than wild-type patients [51]. Such studies for oncology agents are warranted to explain the substantial interindividual variability in PK and PD that may be attributed to genotype for these agents.

In addition, there are several reported studies in the literature where an integrated population PK and/or PD model has been developed during Phase I/II studies to elucidate the relative contributions of parent and metabolite to the pharmacologic and toxic effects of anticancer therapy. The population PK model describing the disposition of irinotecan and its metabolites has been reported by several investigators [52-55]. Population PKs of ifosamide and its 2- and 3-dechloroethylated and 4-hydroxylated metabolites in resistant small-cell lung cancer patients has been reported in the literature [56]. In this example, the PKs of ifosamide was described by concentration-dependent autoinduction and clearly showed that fractionation of the dose of ifosamide resulted in an increased exposure to 2-dechloroethylifosamide. These models are useful in predicting the time course and inter-individual variability of characterised substances.

PK/PD models developed at this stage are also important in characterising the effect of drug–drug and drug–disease interactions that might be expected to perturb the PK/PD relationships of the drug. Population PK model suggested a mutual drug–drug interaction between cyclophosphamide and thiopeta, most likely due to induction of thiopeta metabolism with time [57]. In another study, a population-based approach was used to evaluate the PKs of paclitaxel when it was concomitantly administered with the P-glycoprotein (P-gp) inhibitor, zosuquidar trihydrochloride. The model clearly showed an increase in paclitaxel exposure, which can most likely be attributed to P-gp inhibition [58]. The same authors have also shown an increase in doxorubicin and doxorubicinol exposure in the presence of zosuquidar hydrochloride [59]. This approach has also been used to show that there is no significant PK interaction between 5-fluorouracil and oxaliplatin [60].

Efforts to estimate the relationship between the exposure and magnitude of myelosuppression have used a variety of empirical models (e.g., linear, log-linear, logistic regression and E-max). Using mechanistic PK/PD models, it is possible to appropriately assess both the impact on PK interaction as well as the PD (potential efficacy or toxicity) of the combination. A key minimum objective of these early PK/PD studies is to verify the in vivo biological activity of the drug against the in vivo intended target and to ensure that the action on the target is of suitable intensity and duration with respect to the dosing interval. However, parameters from these mechanistic models are generally not available when analyzing clinical data and, thus, more simplistic semi-mechanistic models of myelosuppression to optimize anticancer therapies are becoming increasingly popular among the scientific community. These models use the whole concentration-time profile and not a summary variable of exposure (empirical models) as input to the model.

Myelosuppression is the most frequent toxicity in response to chemotherapy. Much of the effort in developing PK/PD models has been focussed on describing myelosuppression in response to chemotherapy [61]. Models of chemotherapeutic-induced neutropenia have been reported for indisulam [62] and topotecan [63]. Friberg et al. have reported a semi-mechanistic approach of modeling chemotherapy-induced myelosuppression that partitions the model into drug specific parameters and system parameters that are generalizable across chemotherapeutic agents [64]. This model was developed from patient data resulting from docetaxel, paclitaxel and etoposide administration. The model was then applied to myelosuppression data resulting from irinotecan, vinflunine and DMDC administration. Application of a generalisable model across a variety of chemotherapeutic agents would be beneficial for the investigation of myelosuppression in clinical development. Likewise, a simulation approach for study design, dose escalation studies in Phase I could be useful to limit the probability of patients experiencing severe myelosuppression. Discrete event simulation (DES) is a mechanism used to study trial performance and efficiency. The approach decomposes study event into a set of logically separate processes that autonomously progress through time. Each event occurs on a
specific process and is assigned a logical time (a timestamp). Recently, DES has been used to investigate dose escalation/de-escalation and stopping rules based on the frequency of dose-limiting toxicity (DLT) occurrence in pediatric oncology trials [65]. The classic Phase I oncology trial design was decomposed into a series of discrete time events (accrual/enrolment, evaluation and/or time to DLT or inevaluability) with outcome probabilities (DLT or inevaluability) assigned to each subject based on historical data from Phase I pediatric oncology trials. The probability of DLT occurrence was correlated with the trial cohort and varied distributions were used to simulate/assign the discrete time elements. Metrics for study efficiency (time to reach MTD, time to complete various trial designs and the number of patients necessary to complete the trial) were defined and compared for the classic 3+3 design [65].

Models constructed during Phase II drug development are typically used to guide the decision-making process for advancement to Phase III studies. The primary use of these models has been to support dose selection for large-scale Phase III efficacy studies. Likewise, knowledge of drug input and timing (dose, duration and sequence of various treatment regimens) is incorporated into both Phase II trial designs. Subsequently, the design and evaluation of proposed Phase III studies can be based on models developed in Phase II [66]. As there is no straightforward method to conduct sample size calculations to appropriately power a Phase III study, PK/PD simulation lends itself as a valuable tool for the assessment of the impact trial design factors and study conduct variances on study outcomes. The number and distribution of plasma collection time points, the number of doses and dose range, the number of patients included (total and subpopulation), the effect of compliance and/or dropouts on statistical power and the clinical efficacy/outcomes are all aspects of the trial that may be addressed by simulation. The actinomycin case study reported in this paper describes an example of a modeling and simulation approach to trial design in oncology.

Predicting Phase III outcomes based on models developed in Phase I/II has also recently been advocated [67,68]. This methodology allows for the investigation of probable trial outcomes for a particular design before incurring the time and expense of a large-scale Phase III trial. For example, a simulation study has been described that compared body weight-adjusted and fixed doses of darbepoetin and the effects on hemoglobin levels [69]. Simulations showed that for patients weighing 45 – 95 kg, the impact of the fixed dose was insignificant, with a minor weight effect present outside this range. Simulation studies to examine trial outcomes have also been described for docetaxel [2]. A higher docetaxel dose (125 mg/m² versus 100 mg/m²) demonstrated no advantage in treating patients with high baseline α1-acid glycoprotein levels who exhibit a shorter time-to-progression and death. Based on the result of these simulations, the decision was made to forego the Phase III trial.

Despite the advantages of using a rigorous modeling and simulation effort during the Phase I/II drug development stage, the full potential of this approach has not been fully realised [18,21,70]. Traditional, well-defined markers of clinical success in the oncology arena include overall survival, response rate, time to disease progression and disease-free survival. These markers are often examined in a modeling context using statistical models such as survival and time-to-event analysis. However, recent efforts in Phase I/II trials have concentrated on the evaluation of novel biomarkers that would be indicative of pharmacological activity of a chemotherapeutic agent. Molecular targeted agents afford the opportunity to use biological markers as measures of efficacy. For these agents, the primary end-point used to measure the dose–effect relationship is likely to be biological rather than toxicity, depending on whether a biological end-point is achieved at a non-toxic dose [71]. Thus, for molecular targeted drugs, the maximum therapeutic effect may be achieved at doses that are well below the MTD. For example, imatinib mesilate’s therapeutic effects result from the inhibition of BCR-ABL tyrosine kinase activity. However, it also inhibits other receptor tyrosine kinases. If inhibition of other tyrosine kinases is responsible for one or more of its toxicities, then the dose–response relationship for toxicity may not parallel the dose–response relationship for BCR-ABL inhibition because of the differing affinities of the receptor for the drug [16]. Although drug development by way of a biological marker approach would not be likely to replace traditional methods, it will be an important adjunct. Modeling and simulation approaches incorporating well-defined and appropriate biomarkers will facilitate the development of oncological agents as this approach would circumvent some of the problems with traditional end-points, such as long follow-up periods and the confusing of multiple treatments. Not only would this model-based drug development paradigm support the decision process while developing a potential oncology candidate, but also assists in identifying candidates, which may prove to be unsuccessful before incurring the time and expense of conducting a Phase III trial.

Pemetrexed is an example of an oncology agent whose Phase II clinical development has significantly benefited from a model-based drug development approach. Pemetrexed is an antimetabolite that inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFRR) and glycaminide ribonucleotide formyl transferase (GARFT). The initial pemetrexed population PK model was reported by Ouellet et al. [72]. PK data from four Phase II studies was pooled for the analysis with the objectives of characterising pemetrexed PKs and to estimate the effects of demographic factors that may be relevant predictors of variability in pemetrexed PKs. Pemetrexed PKs was described by a two-compartment model. Creatinine clearance, body weight, alanine transaminase and folate deficiency were demonstrated to have a significant impact on pemetrexed clearance.
A second pemetrexed population PK analysis was reported by Latz et al. that pooled data from 10 Phase II studies [73]. The goals of this analysis were similar to the previous study, with an additional objective of providing individual Bayesian estimates of PK parameters for the development of a PK/PD model to describe pemetrexed induced neutropenia. Renal function was again identified as an influential covariate for clearance. This study suggested that pemetrexed dose adjustments might be warranted based on an individual patient’s renal function.

A population PK/PD model to describe neutropenia in patients has also been reported [74]. The objectives of this analysis were to describe the time course of the neutropenic response to pemetrexed and to identify any demographic factors that explain variability in the neutropenic response. The data set used for the modeling consisted of eight Phase II trials. The response was described by a semi-mechanistic physiological population PK/PD model that estimated baseline neutrophil count, mean transit time and a feedback parameter. The analysis supported that estimated baseline neutrophil count, mean transit time and a feedback parameter. The data set used for the modeling consisted of eight Phase II trials.

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**5. Phase III**

The primary goal of Phase III clinical studies is to show efficacy and safety in a larger patient population representative of the target population. Phase III studies are typically not as well controlled as Phase I and Phase II trials, with a widely varying patient population that may include patients of various disease states, additional medical conditions not associated with oncology, patients administered numerous concomitant medications, differing radiotherapy treatments and broadly different demographic factors. These trials are performed after data collected in Phase I and Phase II suggest effectiveness and safety. Another necessity of the Phase III stage is to gather the appropriate efficacy and safety information to provide dosing guidance and product label specifications.

The Phase III process provides further opportunity to evaluate the relevance of a given biomarker to a chemotherapeutic agent’s pharmacologic action. Given the large-scale nature of the Phase III study, this point in the development process usually provides the necessary data to either confirm the ability of a proposed marker to function as a surrogate for efficacy/safety or to demonstrate little or no clinical use of the biomarker.

As a wide patient diversity is studied in Phase III trials, this affords the opportunity to retrospectively study any special populations and patient demographics that may influence drug disposition. For example, within the hundreds or thousands of patients dosed in a Phase III trial, a small portion may show characteristics of renal impairment ranging from mild to severe. For a drug that is eliminated via the renal route, the disposition of the chemotherapeutic agent in these patients may be compared with those patients with normal renal function. Based on the model developed from the Phase III data, inferences can be made regarding the magnitude of the renal effect and what dose adjustments may be necessary in this population. If an additional trial is deemed necessary to study the special population, simulation efforts may be used to not only design the trial, but also to predict the trial outcomes and determine the probability of a successful trial.

Phase III studies also afford an opportunity to examine the clinical response to a chemotherapeutic agent in a large population of patients. Population PK/PD modeling is the preferred method of analyzing PK/PD data arising from these studies due to the sparse sampling designs used in Phase III studies. For example, capecitabine exposure has been determined using a population PK model developed from data collected in two Phase III studies in colorectal cancer patients [76]. Exposure metrics were then explored as predictors of efficacy and safety for logistic regression and time-to-event analysis. Results from the study showed that exposure to capecitabine and its metabolites were generally not predictive of outcomes. A population PK analysis of paclitaxel in endometrial cancer patients has also been performed to predict individual patient exposure from sparse PK samples [77]. It was found that survival and granulocytopenia were predicted by paclitaxel AUC.

Another goal of the Phase III trial may be to learn the necessary PK and PD properties to individualize chemotherapy to the particular patient. The narrow therapeutic index, combined with the lack of appropriate surrogate markers of toxicity or response, adds to the empiricism in the administration of cancer chemotherapy. In addition, the PKs of cancer chemotherapy agents is highly variable between patients. However, recent studies have established relationships between systemic exposure to cancer chemotherapy and both response and toxicity. These relationships have been used to individualize chemotherapy dose administration a priori and a posteriori. Drugs which can be individualized based on their PKs include methotrexate [78-80], busulfan [81-83] and carboplatin [84-86]. Other examples of anti-neoplastic agents, which may eventually be individualized based on their PKs are mercaptopurine [87], fluorouracil [88-90], etoposide [91,92] and topotecan [93,94]. Population PK/PD modeling has played a large role in defining individualized dosing metrics for all of these drugs.
Model-based drug development applied to oncology

The FDA’s accelerated development and review process was introduced in 1992 as a means to expedite the drug development process for those indications that are of a serious or life-threatening nature for which no therapy exists. Included in this mechanism would also be drug candidates that would provide significant benefits relative to existing therapies. A surrogate end point may be used in place of a traditional, well-defined end point to demonstrate efficacy. This surrogate must be further evaluated in post marketing studies in order to verify the clinical benefit of the drug. Modeling and simulation approaches may be instrumental in the decision-making process for drug development in the case of accelerated approval. Capecitabine, imatinib and topotecan are examples of drugs that were approved under the accelerated approval programme which contain information in the product label pertaining to population PK modeling. These analyses have been limited to characterising PK and the contribution of demographic factors to variability. Little data is available at present on the use of a surrogate marker in a modeling and simulation approach to accelerated approval, but this will likely change based on ongoing activities at many pharmaceutical sponsors and the ongoing and collaborative work of the FDA and the National Cancer Institute (NCI).

6. Regulatory communication and impact

As pharmaceutical sponsors and clinical investigators explore treatment modalities which may offer advantages to existing oncology therapies, an important partner in this endeavour is, of course, the regulatory community. In the US the FDA has taken an active role in this process and have formed collaborations, developed tools and established communication pathways with the drug industry in the hope of providing better cancer drugs to patients sooner. Specifically, in 2003, under an agreement between the FDA and the NCI, the two agencies initiated a plan to share knowledge and resources [201]. This agreement is intended to broaden existing programmes and to create additional joint programmes between these two Department of Health and Human Services (HHS) agencies. NCI believes that the timely and considered application of science across the continuum of discovery, development and delivery, will optimize and accelerate the delivery of safer, more efficacious, drugs to patients. In addition, the FDA has created a ‘tools’ website [202], which contains a variety of information related to cancer and approved cancer drug therapies. Although still at the pilot stage, the intention is clearly to promote communication and education regarding novel therapies and oncology disease biology. Most importantly, the FDA is considering the creation of a library of drug/disease models that could eventually be used by industry to simulate and design clinical trials [203]. A disease model for oncologic indications will certainly have to address the hundreds of different diseases that can arise from virtually any tissue or organ in the body and despite sharing similar properties of local invasion and distant spread may exhibit different causative factors, natural history of disease, method of diagnosis and treatment modality. A drug/disease model that accommodates such diversity would likewise by the funnel of any MBDD platform [95].

Two case studies are described in the subsequent section. Both illustrate the MBDD paradigm from different starting points with respect to their development and continued use as anticancer agents vital to their respective indications. The docetaxel experience is more well-known regarding the historic perspective and broad base of clinical application. Actinomycin D is a work in progress for a drug which has been investigated for > 50 years without the benefit of a modern drug development plan.

7. Case study: docetaxel

The history of the research and development of the prototype taxanes paclitaxel and docetaxel is well known particularly given the natural origin of their discovery. Docetaxel was first synthesised in 1986 following the identification of the compound in the needles of the European Yew tree in 1981. By 1990 Phase I studies had been initiated followed closely by Phase II and III studies in 1992 and 1994, respectively [96]. The first regulatory approval from the US FDA came in 1996 for locally advanced or metastatic breast cancer. Additional approvals ensued following the demonstration of survival benefit in various target populations. Table 5 lists the major milestones in the discovery and development of docetaxel. It also lists many of the concurrent M&S activities conducted in support of docetaxel’s development. Many of the M&S analyses were in fact used in the decision making and subsequently submitted as part of the regulatory transactions with FDA in support of label claims and in response to targeted questions regarding activity and especially safety. An interesting aside is that several of these efforts were championed by scientists outside the sponsor company (initially Rhône-Poullenc Rorer) and the composite data including in vitro activity, IVIVC and clinical outcome data are continually used by other companies seeking to make the next generation taxanes [97], evaluate their product’s performance when added to a regimen including docetaxel or comparing safety and/or efficacy results with docetaxel.

Much of the early phase testing was not published, but included PK and PK/PD model-based analyses to support dose selection for human phase testing (personal communication). These studies and family of models then became the starting point for Phase I study designs. Six human trials were conducted to support Phase I [96]. These studies [98-103] characterised the safety and PK of docetaxel administered intravenously at different infusion lengths (1, 2, 6 and 24 h) up to 5 days and were consistent in defining the MTD between 80 and 115 mg/m². The primary dose-limiting adverse effect was neutropenia, whereas mucositis was the dose-limiting toxicity when docetaxel was administered over a longer duration [96]. Based on the Phase I results, the recommended dose for Phase II testing
was 100 mg/m². Whereas population-based PK analyses were initiated to partition sources of variation from the pooled Phase I data [104], the Phase II data were used to explore exposure–response relationships with the intention of understanding how to manage patient toxicity to docetaxel [105]. Several population-based PK and PK/PD analyses were published [5,104,105] along with one of the earliest, detailed examples of population PK model building and validation [106]. With respect to the PKs alone, it was learned that interpatient variability is related primarily to body surface area and hepatic function. Clinically, this information was extended to recognize that patients with impaired liver function are at increased risk of serious adverse effects (febrile neutropenia, severe infections, severe stomatitis and toxic death) during docetaxel therapy at 100 mg/m², which could be reduced by adjusting the dose to 75 mg/m².

The understanding of exposure–response relationships was then used examine dose optimization with docetaxel. A series of clinical trial simulations [2] were initiated to test whether a specific subset of adult patients with non-small-cell lung cancer might benefit from dose intensification. PK and PD models for time to progression, death and drop-out were developed and validated with the

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**Table 5. Development milestones for docetaxel relative to modeling and simulation activities that facilitated development and regulatory acceptance.**

<table>
<thead>
<tr>
<th>Date</th>
<th>Milestone</th>
<th>M&amp;S activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960</td>
<td>NCI creates program to screen plant species for new anticancer drugs</td>
<td></td>
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<tr>
<td>1962</td>
<td>Samples collected from the Pacific yew tree</td>
<td></td>
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<tr>
<td>1963</td>
<td>Anticancer activity in samples of the Pacific yew tree bark documented</td>
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<tr>
<td>1971</td>
<td>Active ingredient identified leading to isolation of paclitaxel, the first taxane</td>
<td>Many QSAR studies/analyses conducted in support of back-up program</td>
</tr>
<tr>
<td>1981</td>
<td>Researchers in France examine European yew tree</td>
<td></td>
</tr>
<tr>
<td>1986</td>
<td>Discovery of docetaxel, a taxane drug derived from needles of the European yew tree</td>
<td>Predclinical ADME studies conducted; initial PK models developed</td>
</tr>
<tr>
<td>1989</td>
<td>Human studies of docetaxel begin</td>
<td>Human PK models developed</td>
</tr>
<tr>
<td>1993</td>
<td>Laboratory research shows that docetaxel is 2 – 4 times as potent as paclitaxel due to an increased ability of docetaxel to bind to tubulin</td>
<td>Patient PK/PD models developed; exposure–response with target toxicities explored.</td>
</tr>
<tr>
<td>1996</td>
<td>Docetaxel approved by FDA (locally advanced or metastatic breast cancer)</td>
<td>Population PK models developed and submitted with the NDA [104,106]; clinical use and pharmacoeconomic models developed [131]</td>
</tr>
<tr>
<td>1999</td>
<td>Docetaxel approved by FDA as second-line treatment for locally advanced or metastatic non-small-cell lung cancer</td>
<td>Pooled Phase I PPK [5]</td>
</tr>
<tr>
<td>2002</td>
<td>Docetaxel approved by FDA as first-line treatment for non-small-cell lung cancer in combination with cisplatin</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Clinical trial in patients with metastatic breast cancer failing prior chemotherapy shows median survival advantage of docetaxel over paclitaxel (15.4 months versus 12.7 months)</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>Docetaxel approved by FDA as treatment for patients with androgen-independent (hormone-refractory) metastatic prostate cancer, in combination with prednisone</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>Docetaxel, in combination with doxorubicin and cyclophosphamide, is FDA-approved for the adjuvant (supplemental) treatment of operable node-positive breast cancer</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>Docetaxel continues to be tested in ongoing clinical trials for treatment of other cancers</td>
<td>QSAR models developed for next generation taxanes [97]</td>
</tr>
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use of Phase II data from 151 patients with non-small-cell lung cancer. The simulation process was evaluated by comparison of the original Phase II data with the predicted results. Simulations were undertaken for the evaluation of whether a Phase III trial of two different dose of docetaxel in these patients would result in improved survival. In the simulated Phase III trial, although median survival was slightly longer in the 125 mg/m² docetaxel group than in the 100 mg/m² group, the difference was significant in only 6 of 100 trials. Hence, given the small likelihood that a meaningful difference in clinical outcomes would actually exist, the simulation was the basis for not conducting such a trial. Much of the evolved modeling effort, particularly the relationships which describe docetaxel exposure versus toxicity are described in the drug monograph (package insert,) which confirms both the value the sponsor company (now sanofi-aventis) and the FDA place on this information.

As mentioned previously, the progression of models that characterise various facets of docetaxel as a medicine continue to benefit drug development. In an effort to inform the next generation of taxanes, biochemical analyses for a series of 20 butitaxel analogs, paclitaxel and docetaxel were used to build two- and three-dimensional quantitative QSAR models to investigate the properties of docetaxel as a medicine particularly the relationships which describe docetaxel exposure versus toxicity are described in the drug monograph (package insert,) which confirms both the value the sponsor company (now sanofi-aventis) and the FDA place on this information.

As mentioned previously, the progression of models that characterise various facets of docetaxel as a medicine continue to benefit drug development. In an effort to inform the next generation of taxanes, biochemical analyses for a series of 20 butitaxel analogs, paclitaxel and docetaxel were used to build two- and three-dimensional quantitative QSAR models to investigate the properties associated with microtubule assembly and stabilisation [97]. Comparative molecular field analysis (CoMFA) models built using steric and electrostatic fields and hologram quantitative structure–activity relationship (HQSAR) modeling of this same data were used to examine the ability to predict activity outcomes based on structural features. Results are promising and may be indexed with models predicting safety indices to project the therapeutic window of development compounds prior to clinical evaluation. Hence, although not part of a modern MBDD paradigm, docetaxel remains an excellent example of the MBDD concept applied to an oncology agent, which continues to be used to treat patients and has been explored as an adjunctive or comparative agent.

8. Case study: actinomycin D

Actinomycin D is a member of the antibiotic class of antineoplastic agents (actinomycins) produced by the Streptomyces species of fungus. Actinomycins were first discovered in 1940 [107] and actinomycin D was first isolated and introduced into the clinical oncology setting in 1954. During its initial clinical evaluation it was studied in patients with gestational choriocarcinoma and in primary Wilms’ tumor in combination with surgery and radiotherapy. Actinomycin D is one of the older chemotherapy drugs, having gained approval from the FDA in 1982. Actinomycin D is presently used in the treatment of several childhood sarcomas including Ewing's sarcoma, rhabdomyosarcoma, soft tissue sarcomas and Wilms tumor.

Based on the origin and era of actinomycin D's discovery and clinical evaluation, now-standard physiochemical and preclinical evaluation were not performed in a comprehensive manner. Despite its ongoing use in the above-mentioned childhood sarcomas, much information is still lacking. Unfortunately, the pediatric patient has been the recipient of this ignorance as patient management on actinomycin D is a continual dilemma. At the root of this problem is the unknown ignorance as patient management on actinomycin D is a continual dilemma. At the root of this problem is the unknown relationship between dose and exposure. At present, dosing guidance provided by the drug sponsor cites an adult dosage of 500 μg daily i.v for a maximum of 5 days. The dosage for adults or children is recommended not to exceed 15 μg/kg or 400 – 600 μm² meter of body surface daily based on the 5-day intravenous regimen. The only guidance for dosing special populations recommends that the calculation of the dosage for obese or edematous patients should be on the basis of surface area in an effort to relate dosage to lean body mass. Unfortunately, none of the dose information/guidance provided in based on the PKs of actinomycin D.

As a result, close clinical evaluation and monitoring of patient response to actinomycin D is critical to maintain adequate therapy and only partially successful in managing patient care. Toxic reactions following actinomycin D administration are frequent and may be severe, limiting in many instances the amount that may be administered. Deaths have been reported as well. The severity of toxicity varies markedly and is only partly dependent on the dose used. One hypotheses yet untested would be that the time course and/or severity of such reactions more closely correlates with individual patient exposure. Again, formal guidance provided in the package insert states that the dosage of actinomycin D varies depending on the tolerance of the patient, the size and location of the neoplasm, and the use of other forms of therapy. It further advises that it may be necessary to decrease the usual dosages suggested when additional chemotherapy or radiation therapy is used concomitantly or has been used previously. An additional concern is that a wide variety of single agent and combination chemotherapy regimens with actinomycin D are used. Because chemotherapeutic regimens are constantly changing, dosing and administration mandates direct supervision of physicians familiar with current oncologic practices and new advances in therapy often without the benefit of anticipated drug interaction potential.

In 2002 the Children's Oncology Group (COG) suspended three active protocols for the treatment of children with rhabdomyosarcoma after four actinomycin-associated deaths from hepatotoxicity. Despite this event, actinomycin D is an integral component of rhabdomyosarcoma and Wilms’ tumor therapy and pediatric oncologists continue to administer the drug despite the gap in knowledge. Following the award to the COG through the NCI in September of 2004, U10 CA098543-0251, ‘actinomycin-D/vincristine exposure–response characterisation in children with cancer,’ a comprehensive strategy to identify critical factors that define the therapeutic window for these agents in children.
has been undertaken. The original proposal contains four projects, one of which has the objective of simulating exposure–response and ultimately clinical outcomes resultant from the assembly of models that define dose–exposure, exposure–response and response–outcome relationships for various trial designs. Infants under the age of 12 months are known to exhibit higher toxicity rates than older children administered equivalent body-weight adjusted doses of actinomycin D. Likewise, it is not known at present if this higher toxicity rate is due to dispositional differences in developing infants. Elucidating these potential differences in actinomycin PKs would be a key aspect in providing dosing guidance in this population.

Given the limited knowledge of actinomycin D PKs, a model-based approach to designing such a study would be feasible. The objectives of the modeling exercise conducted by the authors' laboratory were to: i) construct a population PK model to describe actinomycin D disposition in children and young adults; ii) perform clinical trial simulations incorporating parameter uncertainty for the design and evaluation of a prospective large-scale actinomycin trial in pediatric cancer patients and subsequent sensitivity analysis; and iii) perform simulations to calculate the number of subjects under the age of 1 year old required to reliably estimate a clinically meaningful change in clearance. Hence, the application of the MBDD approach in this setting is based on the needs assessment regarding the ‘unknowns’ which have confused the ability to manage patient pharmacotherapy. The approach is focussed on prioritisation of the available (albeit limited) prior information to construct models exploring the relationships of interest (e.g., exposure-toxicity) and guide targeted experimentation when critical to model assumptions.

Distribution studies of actinomycin D in rat, monkey and dog had shown that equivalent doses based on body surface area (BSA) of 0.6 mg/m$^2$ result in nearly equal tissue exposures in the three species [108]. This work was expanded further to characterise the distribution and kinetics of actinomycin D in the beagle dog using a flow-limited PB/PK model [109]. Early published human actinomycin D PK studies consisted of actinomycin D in three adult cancer patients at a dose of 15 µg/kg [110] and two doses in children of 0.75 mg/m$^2$ (n = 1) and 1.5 mg/m$^2$ (n = 1) [111]. More recently, Veal [112] has published preliminary PK results in children receiving actinomycin D. This limited data represented the prior information on dose–exposure relationships with actinomycin D.

Initially, PB/PK models were constructed from physiologic data in children with the actinomycin D PK scaled from the beagle. Specifically, mean parameter values for organ blood flows (Q) and organ volumes (V) and actinomycin D specific PK data from the respective animal models were used to construct pediatric PB/PK models [113,114]. Intersubject variability around physiologic parameters (e.g., partition coefficients, etc.) was assumed to incorporate a measure of precision around the predicted exposures. This model agreed well with the pediatric data obtained in pilot studies ongoing at The Children’s Hospital of Philadelphia [115] and will be revisited on historical toxicity data from previous clinical trials that can be mined and indexed to dose and demographic subgroups.

Additional population PK models were developed from actual pediatric PK data recently made available. PK data (33 patients from the United Kingdom Children's Cancer Study Group, UKCCSG) were provided by Veal et al. [112]. This data (165 plasma concentration observations) were collected from children aged 1.58 – 20.3 years receiving actinomycin D as part of their standard chemotherapy (doses of 0.7 – 1.5 mg/m$^2$). A three-compartment model with first-order elimination was chosen as the structural model for the data. The population PK data was analysed using non-linear mixed-effects modeling. Actinomycin D and vincristine PK parameters were allometrically scaled by body weight, normalised to a weight of 70 kg [116].

The final population PK model was used to simulate new studies. Simulations incorporated uncertainty in the parameter estimates by probability density functions for all model parameters. The uncertainty in parameters was implemented as intertrial variability. From these distributions, 500 sets of population PK parameters were simulated [116]. The 500 parameter sets and the final population PK model were used to simulate 500 replicate data sets for a preliminary clinical trial construct. The original PK model was then fitted to each replicate data set and the bias and precision in parameter estimation was evaluated for a given trial design. Deficiencies in the trial designed were then identified and iteratively refined until a construct was identified that produced minimal bias for all PK parameters, particularly total drug clearance and the volume of distribution in the central compartment (Figure 5).

The simulation study yielded a final design consisting of 200 patients, which will be randomised to one of two sampling schemes. Once the study design was defined, a hypothetical age effect was incorporated using a power model to describe the possible maturational changes in clearance for children < 1 year old [116]. The results from a simulation study that included 20 subjects below the age of 1 were used to construct sample size curves over the range of possible clearance values. From the sample size analysis, it was concluded that 50 subjects under the age of 1 would be required to detect a 30% change in clearance in children under the age of 1 (Figure 6). Simulations performed to confirm this sample size showed that CI could be accurately estimated in children under 1 year old.

A feasible and informative trial design was identified for an actinomycin and vincristine clinical trial in pediatric cancer patients. The results of this effort have been incorporated into a prospective trial protocol to be conducted through the COG’s Phase I Consortium. PK, safety and clinical response data will be evaluated with the existing mixed-effects model and the final population PK analysis derived from this study.
will be used to revise actinomycin D labeling. Whereas the effort has been uniquely focussed on deriving dosing guidance for pediatric patients, the MBDD approach applied in this setting has also facilitated experimentation which has enhanced the overall information content on this important agent. Sensitive and specific analytical methods were developed for use in pediatric populations [115,117,118], information on metabolism and protein binding [115] and methodologies to enhance patient enrolment [115] were developed as outcomes of the MBDD approach in that they removed uncertainty in the respective models that they are used in (PK and trial design models, respectively). This example should also highlight the notion that this approach is confined to a big Pharma budget as all of this research is funded by the NIH [119].

9. Conclusion

The term ‘model-based drug development’ has been used to refer to the approach of constructing quantitative relationships to define and explore key decision criteria that constitute development milestones or key hurdles for a development compound. The approach has received the endorsement of the FDA [120] and the global regulatory community [70] and is various stages of implementation at many large Pharma companies. Oncologic drug targets offer and excellent application to this approach. The application of models in oncology has been a necessity for some time given the toxicity of many of the drug classes, the severity of the indications and the status of the patients. Given: i) how poorly characterized some of the older agents are; ii) the

Figure 5. Bias and precision in parameter estimation from final trial design based on evaluation of 500 replicate data sets generated from 500 sets of PK parameters simulated from a population PK/PD model for actinomycin D. Individual parameters from the population model are shown on the x-axis.

V1: Central compartment volume of distribution; V2: Peripheral compartment 2 distribution volume; V3: Peripheral compartment 3 distribution volume.

CL: Systemic clearance; OMCL: Intersubject variation in CL; OMV1: Intersubject variation in V1; Q2: Intercompartment 2 clearance; Q3: Intercompartment 3 clearance; OM V1: Intersubject variation in V1; OM CL: Intersubject variation in CL.
reality of multimodal strategies to treat the variety of cancer types; and iii) the heterogeneity of the various patient populations, a MBDD paradigm must, of course, accommodate existing agents for which there is often sparse data or limited bridging of translational information. This presents an additional challenge to pharmaceutical sponsors as they must often ‘back-fill’ information gaps for historical agents developed when development programs, particularly for oncology drugs, were less comprehensive.

10. Expert opinion

Aspects of MBDD, particularly those pertaining to M&S approaches and techniques, have been a part of drug development for some time [19]. The FDA’s Critical Path document [204] and NIH Roadmap [70] were important for the public recognition of what is clear to many – the next generation of medicines will require more rigorous preclinical and clinical investigation. Consumer tolerance is low with respect to adverse effects and adverse drug reactions appreciated for the first time after the drug is marketed (especially when there was safety signals identified early in development). Hence, scientific and ethical accountability are not only called into question post approval, but examined critically along the drug development pathway as never before. The potential for post marketing litigation has also raised corporate awareness regarding record-keeping and likewise decision making.

Therefore, MBDD in addition to its obvious use as a drug development paradigm, provides a mechanism to examine the traceability of drug development decisions. One would assume that good science needs no conscious. However, the vast amount of data generated in support of NCEs, the data and knowledge gaps regarding historic agents and the complexity of modern disease targets provides a challenge to the brightest scientists. The MBDD approach necessitates multidisciplinary project teams and, more importantly, demands new skill sets to be nurtured. The Critical Path document clearly identifies clinical pharmacology as an essential discipline for the future given that dose finding has

Figure 6. Power sample size analysis required to detect a 30% change in clearance in children under the age of 1 based on trial simulation model. Individual curves for 70, 80 and 90% power shown. The x-axis refers to the actual difference in actinomycin clearance between children < and ≥ 1 year of age.
been poorly performed in many regulatory submissions and is often the culprit when drugs are removed from the market. Most important is that the clinical pharmacology discipline evolves to appreciate and exploit the quantitative techniques that MBDD relies on. The additional challenge to drug developers seeking to ‘sell’ this approach is to maintain the focus on improving the information content of the NDA. There are obvious economic gains to be made in development efficiency both from the standpoint of omitting less informative as well as redundant trials where model-based approaches can be relied on. However, these same models can and have been used to skip Phase II/A/B trials based on presumed acceptable risk: benefit and the desire to accelerate Phase III trials. This is contrary to the sentiments of the Critical Path document and can only be viewed as a void in the ability to defend a proposed dosage and/or regimen.

The molecularly targeted mechanisms that define many present oncology pipelines necessitate a much greater dependence on informatics approaches. Despite this feature, there remains a reluctance to connect gene- and cell-based results to in vivo data. Some of this reluctance is due to poor correlation between xenograft models and clinical data. However, quite often, the reason is also due to experimental conditions that are neither accurately defined nor standardized, or poor experimental designs that prohibit data pooling required for generalizations across molecular entities. The root cause in most cases is that investigators are comfortable with making decisions regarding discrete experiments and unwilling to invest the time to understand how experimental data can be linked especially if it involves a challenge to established experimental methods. A major hurdle in the extension of MBDD to early development phases will be the appreciation of these factors and the ‘leap of faith’ required to change preclinical decision making. This is essential to delivering on the promise of translational medicine as well given that many among the academic medical research community are participating in oncology-based research in close collaboration with the pharmaceutical industry.

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43. PEREZ-RUIXO JJ, ZANNIKOS P, OZDEMIR N et al.: Effect of CYP2D6 genetic polymorphism on the population
pharmacokinetics of tipifarnib. 


Expert Opin. Drug Discov. (2007) 2(2)
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Websites

National Cancer website (2003).

http://www.fda.gov/cder/cancer/index.htm
FDA oncology tools website (2006).


http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html
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