

Cycle Dose Modifier™

TECHNOLOGY OVERVIEW

Introduction and Overview

Cycle Dose Modifier™ (CDM™) is a two-part mathematical process that changes the dose of a single or combination agent pharmacotherapy to achieve a specific bio-marker/s and concurrently manages the inconsistencies of Inter-Individual Variability. The bio-marker/s are generally lab-values but whatever marker is used it must be attributable to the effects of the agent/s. Markers which are commonly used to assess the efficacy and toxicity are best as prescribers are familiar with their use and the CDM™ just provides a more effective means to manage them. In the design of CDM™ while appreciating the complex nature of absorption, bioavailability, distribution, biotransformation, excretion and the kinetic processes we chose to directly link the cause (dose) to the effect (marker). (U.S. and P.C.T. Patents pending)

To accomplish this, first we expanded our paradigm of traditional pharmacodynamic dose-response relationships to a multi-dimensional model:

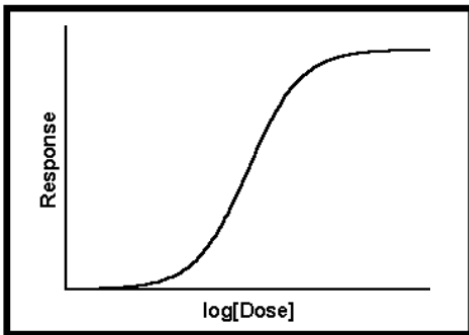


Figure 1: LDR Curve

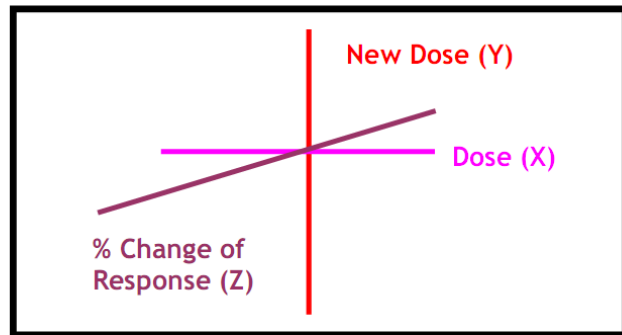


Figure 2: CDM Multi-Dimensional Model

This resulted in the first part of the CDM™ platform providing a high-level of accuracy, predicted to actual marker. Each agent and marker has a unique plane of fit. Each patient responds as expected (on the line), more than expected (above the line) or less than expected (below the line) throughout the dose continuum, see below:

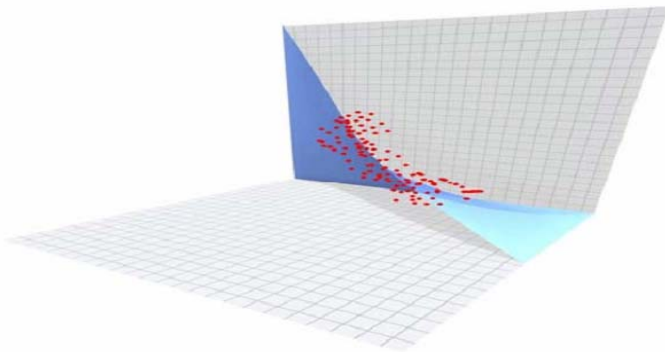


Figure 1: CDM Unique Dose-Marker Relationship

Next we used an established mathematical mechanism to quell system chaos, a Stochastic Open-Loop, and included a means to accommodate the unique characteristics of the agent/s in the therapy; the Variable Sensitivity Value™. Each patient's response is based upon a myriad of individual factors which include genomics, gender, age, disease progression, nutrition status and more; but their end-response to the dose received can only be; as expected, greater than expected or less than expected. Based upon the unique characteristics and limitations of the drug we reserve a portion of the dose to add or subtract to the dose to contain the chaotic response.

The CDM™ method has application in clinical practice and in agent development. It calculates the new dose of a drug or drugs to achieve specific values of surrogate endpoint biomarkers. These surrogate biomarkers must be directly impacted by the agent received. The biomarkers are most often lab test values; cell counts or levels of chemical analytes. They may also be other findings objective or subjective and include physical signs or pain scales or imaging studies. The biomarkers optimally are of both efficacy and toxicity and are viewed concurrently to better individualize pharmacotherapy and optimize outcome by increasing agent exposure and better manage toxic effects. CDM™ empowers the prescriber to vary the intervention and minimize toxicity without stopping therapy or maximizing agent exposure and controlling the unique characteristics of the individual patient.

The system can attribute the effect of the agent dose on the selected biomarker response. In multi-agent treatments, each drug's contribution to the effect on the biomarker is not equal. The system identifies the contribution of the individual agent on each selected biomarker so that dose adjustment can be made more effectively; reducing the untoward effects and maintaining or increasing the desired effects (agent exposure). Unlike current practice the system allows independent 'omni directional' (increase/decrease) dose adjustment to achieve its goals.

- ❖ The product can be used:
 - For any agent with biomarkers that are impacted by its dose
 - In clinical practice by prescriber or patient:
 - As a stand-alone instrument
 - As part of an overall disease management system
 - As a means to improve the pharmaceutical agent development process
 - As part of the approved label (dose method) of a drug
 - In single or multi-agent (combination) therapies

- ❖ Clinical Practice Applications
 - Adjusts drug dose to achieve multiple biomarkers
 - Titration of dose to selected therapeutic/toxic values concurrently
 - Maximizes agent exposure
 - Recognize and manage acceptable levels of side effects
 - Reduces need for 'Rescue & Adjuvant' medications
 - Manages the sampling of lab studies (biomarkers) reducing lab costs

❖ **Pharmaceutical Development**

- **Agent (new, existing and failed drug) development**
 - **Reduces time and costs necessary to reach therapeutic goals**
 - Model transfer between species
 - Smaller study populations
 - Minimizes attrition by reducing adverse/toxic effects
 - Optimizes agent classification as a 'First-line' therapy choice
 - **Broadens ability to achieve therapeutic outcome goals by controlling and expanding dose modification opportunities**
 - **Resurrects agents with failed dosing or altered dosing profiles in single or multi-agent therapies**
- **Drug product lifecycle impact**
 - **Extends patent protection**
 - **Excludes generic market entry**

Each CDM™ is built for the drug and marker set targeted. We use 15 to 30 cases of dose (date given), marker (date sampled), new dose (date given) and new marker (date sampled) to 'build' the CDM™. Then the CDM™ is validated against that same retrospective data set for average accuracy, correlation, median and standard deviation. Only the first part of CDM™ is active in this phase of development and application. Here is a sample set of data validation on a Taxol-Gemzar mix in NSCLC looking at ANC, HgB and platelets:

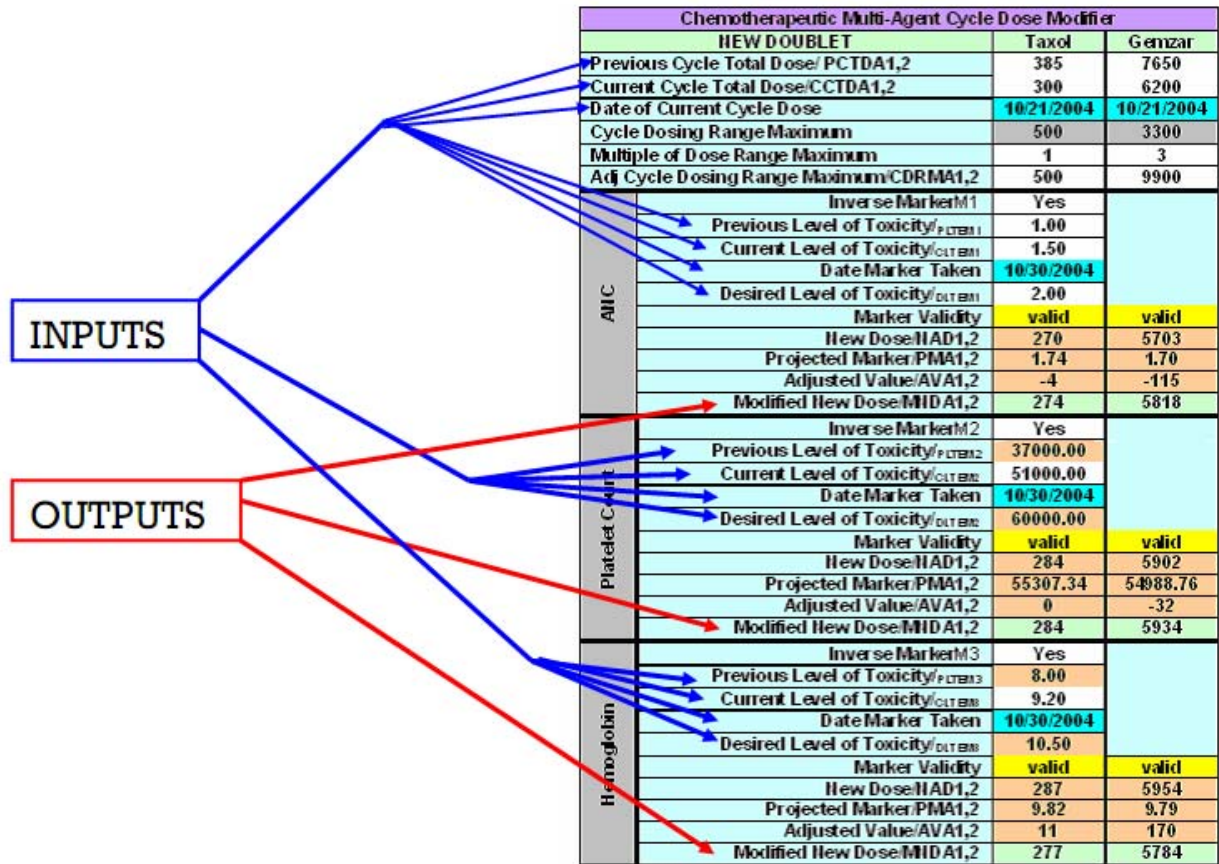
Accuracy Of CDM™ Taxol/Gemzar			
<u>N=32</u>	<u>ANC</u>	<u>Platelets</u>	<u>HgB</u>
Average Accuracy	99.34	96.84	101.84
Median	97.71	90.73	102.51
Standard Deviation	24.5	18.81	7.28
Correlation	0.92	0.87	0.88

Figure 2: CDM in Chemotherapy Doublet with Three Primary Markers

As we built CDM™ we became aware of the need to validate the biomarkers in terms of its validity and latency as related to the timing of the dose received and the timing of marker sampling. Our clinical experience has taught us that often markers are sampled and dose adjustments made when the marker is not fully reflective (mature) of the dose received which adds considerable chaos to the system. We are able to control this by integrating limits defining the time, minimum and maximum from receiving the dose that the marker is valid to make dose changes into the system. These data have distinct

limits of validity that must be adhered to. In addition this mechanism controls unnecessary lab costs.

Sample CDM™



We chose to utilize MS Excel® as it is a ubiquitous software program that prescribers are generally familiar and comfortable with.

Proposed Projects

Clinical Practice Application Overview: ONCOLOGY

Cancer therapy is costly in lives, quality of life and dollars. As more therapies that are effective are introduced and physician acumen improves, the condition is being treated more like a chronic disease. The cost of chemotherapy is immense at about \$15B last year and another \$12B for adjuvant and rescue therapies to manage the adverse effects of the primary agents in the U.S. alone. Patients often are unable to continue to receive therapy due to adverse events and the toxic

effects of the agents. Therapy is regularly given well past the time it may be effective; often to within days of their death resulting in a reduced quality end of life, increased cost of treatment and the need for substantial supportive adjuvant and/or rescue agents

Particularly as the patients condition erodes. The inappropriate continuation of curative therapy results in the delay of initiation of palliative therapy resulting in increased anxiety and pain as end of life ensues. Additional costs of multiple ongoing laboratory studies, physician fees and nursing care add further to these substantial volumes. Therein resides our opportunity in utilizing both of our technologies; CDM™ and PrognostiCheck™ to specifically improve the treatment and management of cancer patients.

We have proposed a collaborative strategy to investigate the potential of using our CDM™ dosing technique in an Oncology practice area to MD Anderson in Houston and they have accepted the initial premise and we are presently developing the protocol.

Oncology Clinical Practice Applications for CDM™

- Increased chemotherapy agent exposure for improved therapeutic effect
- Reduced adverse events and need for costly adjuvant and rescue therapies
- Reduced lab studies
- Dose increase and decrease of individual agents
 - Presently all agents in a multi-agent therapy are reduced (only) in unison
- Preferred formulary and regimen focus
- Prescriber attention opportunity
- Value of accumulated experience and knowledge base

Clinical Practice Application Overview: HEPATITIS C

There is a growing number of patients with HCV genotype I characterized as 'non-responders' in that they fail to demonstrate a 'Sustained Viral Response' (SVR) to the initial pharmacotherapy combination of Ribavirin and Pegylated Interferon. This pool in the U.S. alone exceeds 250K patients and is growing at a rate of 50K annually. Recent publication of a study in Europe that used a 'High-Dose Ribavirin' demonstrated a 100% SVR with accompanying profound anemia. Dose management was especially challenging in the trial as the PK model used was not effective at maintaining the desired levels; neither of ribavirin concentration nor in controlling the toxic anemia.

We wrote to the study PI captured their attention with CDM™ and after presenting our technology to Roche and executing an NDA we were just given data from Roche to build

a CDM™ for Ribavirin dosing as it relates to hemoglobin. This first step will build towards a combination agent CDM™ in which high-dose Ribavirin and the needed erythropoietin will be given together from the initiation of therapy to maintain needed concentrations, control anemia and attain SVR.