

**PREDICTING POTENTIAL CYP450 ENZYME
INHIBITION BASED DRUG-DRUG INTERACTION
DURING DRUGS PRESCRIPTION USING A
COMPUTER AID**

BY

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(Bachelor of Pharmacy Honours (B.Pharm Hons))

SUPERVISOR: PROF. T.E. CHAGWEDERA

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DR. R. CHIGWANDA

Thesis presented in fulfillment of the requirements for the of
Master of Philosophy (MPhil) Degree

**SCHOOL OF PHARMACY
COLLEGE OF HEALTH SCIENCES**



UNIVERSITY OF ZIMBABWE
2012

***DEDICATED TO MY FAMILY, PRYNET AND
TJNOTENDA M. ZVADA***

"TOGETHER AS ONE"

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ABSTRACT

Introduction: The increase in the number of drugs on the market and concomitant treatment of co-infections has increased the potential for drug interactions making it difficult for healthcare professionals to minimize the potential adverse effects of every drug. Fortunately, Medical Informatics has been evolving to match this increase in complexity in medical delivery. Pharmacoinformatics has become particularly relevant in addressing some of the undesirable effects associated with the increased practice of polypharmacy. Therefore, the major aim of this study was to develop a computer based pharmacoinformatic tool for use by clinicians and pharmacists in the prediction of *in vivo* drug-drug interactions (DDIs) using *in vitro* data.

Materials and methods: The prototypic tool was developed using Standard Query Language (SQL) database and Delphi 6.0 as the programming language. Literature sources were assembled, both as databases and symposia abstracts, original publications of drug-enzyme or drug-drug interactions for competitive and mechanism-based inhibition. Sources with validated *in vitro* methods and having the following parameters: inhibition constant (K_i); maximum enzyme velocity (V_{max}); substrate concentration needed to reach half maximal velocity (K_m); fraction metabolized by cytochrome P450 (fm) and fraction cleared by cytochrome P450 (fh), were considered. Different plasma concentrations of the inhibitor available to the enzyme site for interaction were tested with and without taking into account protein binding. The concentrations included the average maximum plasma concentration (C_{max}) and the estimated of maximum concentration of the inhibitor at entrance to the liver ($I_{in,max}$), both bound and unbound. A pilot study was carried out among 10 doctors and 10 pharmacists to test the medical relevance of the tool using a questionnaire with scores ranging from 1 (best) to 6 (worst).

Results and discussion: Various drug combinations were tested. The best predictions of *in vivo* drug-drug interactions were achieved when the concentration of inhibitor was set at the unbound maximum concentration at entrance to the liver enzymes with better overall geometric mean fold error (GMFE) values of 0.68 and overall root mean square error (RMSE) of 3.13 without considering mechanism-based inhibition (MBI). There was improvement in overall GMFE (0.49) and RMSE (1.71) for steady-state unbound C_{max} when MBI was incorporated. A preliminary evaluation of the tool by medical professionals has highly recommended application in private practice and in academia as a teaching tool, and with mixed reactions in public sector. The survey recommended that modifications be made on details captured under product composition.

Conclusion: The pharmacoinformatic tool developed during this work is likely to be well received by the medical community starting as a teaching tool. More drugs used routinely need to be added, and a high sample size evaluation of relevance and acceptability conducted. The predictive capacity of the tool had low levels of bias when the concentration of inhibitor was set at the unbound maximum concentration at entrance to the liver enzymes. However more work needs to be done to include Drug-Drug Interactions (DDIs) due to induction and irreversible enzyme inhibition or through inhibition of other enzymes not considered in this study.

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LIST OF ABBREVIATIONS

ADRs	Adverse drug reactions
AhR	Aryl hydrocarbon receptor
AIDS	Acquired immunodeficiency syndrome
ARV	Antiretroviral
AUC	Area under concentration against time curve
CDSS	Clinical decision support systems
CL	drug clearance
C _{max}	maximum plasma concentration of the drug
CPOE	Computerized Physician Order Entry
C.Q.H.C.A	Committee on Quality of Health Care in America: Institute of Medicine
CYP	Cytochrome P450
DDI	Drug-drug interactions
DNA	deoxyribonucleic acid
DSS	Decision support systems
DUR	Drug utilization review
EFV	Efavirenz
EHR	Electronic health records
EM	Extensive metabolizer
EMR	Electronic medical record
EPMR	Electronic patient medical record
f_a	Fraction absorbed from the gut
F_g	Fraction of substrate metabolized in the gut
fh	Fraction cleared by cytochrome P450

fm	Fraction metabolized cytochrome P450
f_u	Fraction of unbound drug in plasma
FMO	Flavin-like monooxygenase
GIT	Gastrointestinal tract
GMFE	Geometric Mean-fold error
HIV	Human immunodeficiency virus
HL7	Health level 7
IBM	International business machines
IC ₅₀	Drug concentration that results in half-maximal enzyme velocity
$I_{in,max}$	maximum concentration of the inhibitor in the portal vein
$I_{in,vivo}$	<i>in vivo</i> concentration of inhibitor
$I_{invivo,g}$	concentration of inhibitor available to the gut wall absorption site after an oral dose
IT	Information Technology
k_a	First-order absorption rate constant
$K_{degrad.gut}$	First order rate constant for <i>in vivo</i> gut enzyme degradation
$K_{degrad.hep}$	First order rate constant for <i>in vivo</i> liver enzyme degradation
K_{el}	First-order elimination rate constant
K_i	Inhibition constant
K_I	Inhibitor concentration at which half maximal inactivation rate is achieved
K_{inact}	Maximal inactivation rate at saturating inhibitor concentration
K_m	Concentration needed to reach half maximal velocity
LOINC	Logical Observation Identifier Names and Codes
MGH	Massachusetts General Hospital

MRI	Medical resonance imaging
MS-Acess	Microsoft Access
<i>NAT</i>	<i>N</i> -acetyl transferase
NVP	Nevirapine
PDSS	Prescribing decision support systems
PD	Pharmacodynamics
PK	Pharmacokinetics
PM	Poor metabolizer
PB	Phenobarbital
PXR	Pregnane X receptor
RMSE	The randomised mean square error
SNOMED	Systematized Nomenclature of Medicine
SQL	Standard query language
TCDD	2,3,7,7-tetrachloro-dibenzo-p-dioxin
TB	Tuberculosis
T _{max}	Time to reach peak plasma concentration
UNAIDS	Joint United Nations Programme on HIV/AIDS
VKOR	Vitamin K epoxide reductase
V _{max}	Maximum enzyme velocity
WHO	World Health Organisation
XML	Extensible markup language
USFDA	United States Food and Drug Administration

INTRODUCTION

In clinical practice, medication error is a common occurrence (Marschner, Thurmann et al. 1994; Gurwitz, Field et al. 2005) and it possibly results in different individual or collective consequences as illustrated in figure 1 below.

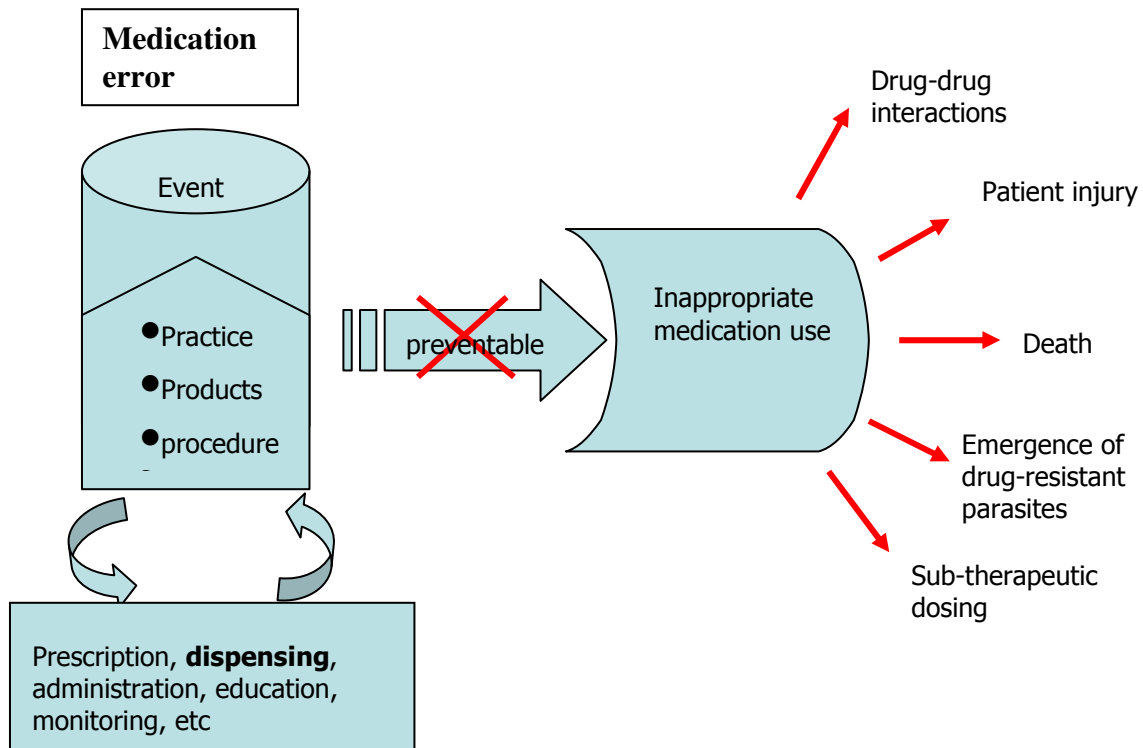


Figure 1: Illustration of medication errors and possible consequences

Studies carried out in the United States of America (USA) revealed that 44 000 to 98 000 deaths occurring annually are due to medication errors e.g., wrong diagnosis and/or prescribed drug, and of this total 7 000 of the total deaths were due to adverse drug reactions (ADRs) (C.Q.H.C.A 2000). It was also estimated that, over 350 000 ADRs occurred yearly in United States nursing homes (Gurwitz, Field et al. 2000). Again, a retrospective analysis at two London hospitals found that 11% of admitted patients

experienced adverse events where 48% were judged to be preventable and 8% led to death (Vincent 2001). All these and other findings gave a hint that the situation might be “worse” in developing nations where medical expertise, infrastructure and other major health care delivery systems are poor.

The increased demand for pharmacotherapeutic agents in infectious disease co-infections has introduced another complexity in the treatment and management of patients in resource limited nations (UNAIDS and WHO 2006). In the treatment and management of such cases, drug combinations are necessary as they help in the rapid eradication of causative pathogen, minimize emergence of drug resistant parasites and lead to quick patient recovery. However, each drug provides both therapeutic and toxic effects, thus make physicians worry about safety in the simultaneous use of many drugs. Polypharmacy predisposes patients to adverse drug reactions (ADRs) emanating from drug-drug interactions (DDIs) (Jacubeit, Drisch et al. 1990; Leape, Bates et al. 1995).

Scientifically, a number of clinically significant DDIs occur at metabolic level. Metabolic DDIs result in decreased therapeutic effect, generation of toxic metabolites due to enzyme induction or increased substrate plasma concentration above its therapeutic index to toxic levels due to enzyme inhibition. The impact of DDIs is revealed through withdrawals of mibefradil, sirovudine, astemizole and cisapride from the pharmaceutical market (Huang and Lesko 2004). Increased understanding of biochemical pathways of drug metabolism and development of *in vitro* methods to identify chemical entities that may cause clinically significant DDIs has aided in the screening for safer lead compounds at preclinical stage. Even though this is the case, drug combinations are unavoidable but some drug-drug interactions can be prevented. Recent investigations in

the use of drugs have shown that most of DDIs can be prevented through identification of compounds that have *in vitro* inhibition constant (K_i) of less than 1 μ M (Huang and Lesko 2004). These chemical entities result in clinically significant DDIs due to enzyme inhibition. Categorically, compounds with K_i value above 10 μ M were considered as weak inhibitors (USFDA 2006). Furthermore, efforts are being made to quantitatively predict the magnitude of *in vivo* DDIs using *in vitro* data. However, although very useful, these predictions are being implemented at preclinical levels of drug discovery. Therefore, it is evident that most anti-parasitic drugs were discovered and introduced on to the market without knowledge of this data and continue to be used without caution with respect to the potential for drug-drug interactions.

Towards addressing this shortcoming, retrospective *in vitro* screening of anti-parasitic drugs for inhibitory and inductive effects on cytochrome P450 (CYP) was carried out in our laboratory (Bapiro, Egnell et al. 2001; Bapiro, Andersson et al. 2002; Li, Bjorkman et al. 2002; Bapiro, Sayi et al. 2005). However, there is still a big gap in clinical evaluation of some of the potential DDI that might arise in the use of various combinations of drugs in the treatment and/or prophylaxis of tuberculosis (TB), malaria, human immunodeficiency virus / acquired immunodeficiency syndrome (HIV/Aids) and other infectious diseases. Though efforts have been made to assist physicians in handling large patient data and decision making, the available computer based decision support systems like Computerized Physician Order Entry (CPOE) offer fragmented data (Cavuto, Woosley et al. 1996; Smalley, Shatin et al. 2000). In the African setting, internet connectivity is generally slow and expensive, making web-based applications unsuitable and unfriendly for many potential users.

In order to address these deficiencies in health care, the aims of this work was to develop a computer based pharmacoinformatic tool for use in the prediction of drug-drug interaction. Inhibition of cytochrome P450 (CYP) by drugs was used as the basis for predicting *in vivo* fold increase in drug (i.e. drug metabolized by the inhibited CYP isoenzyme) exposure after oral drug administration. Published *in vivo* data of drug-drug interaction between particular drug combinations were incorporated to validate the prediction. The acceptability of the pharmacoinformatic tool was assessed among 10 doctors and 10 pharmacists in Zimbabwe

1. REVIEW OF LITERATURE

1.1 Historical perspective of Information Technology

The introduction of Information Technology (IT) came with the promise of helping to make decisions, manage scarce resources, increase efficiencies, reduce workload, and increase work productivity in all sectors. Information Systems researchers and technologists have built and investigated Decision Support Systems (DSS) for more than four decades, and these systems evolved early in the era of distributed computing (Keen and Morton 1978).

In the medical community, healthcare is an information-dependant profession and profoundly affected by technological changes. In practice, physicians spend around 38% of their time charting in the medical record while other healthcare professionals spend more than this amount of time gathering, analyzing and sharing information (Smith 1998). Appreciable efforts were made in the early 1990s to harness the success in the Information Technology into the medical sector. The term “Medical Informatics” became popular in the clinical environment.

1.1.1 Early years

Information storage and data manipulation methods were employed as early as the turn of the century by Dr. John Shaw Billings, the Surgeon General of the Army and founding editor of the Index Medicus (Collen 1986). In 1890, Dr. Billings postulated an

electromechanical device that would tabulate the census automatically through the use of punch cards. With the improvement by Herman Hollerith, a government statistician, fifty-six Hollerith machines were used to process census information for 62 million people in 1890. In 1896 Hollerith established International Tabulating Machines which became International Business Machines (IBM) in 1924. These were widely used in the business community (Coiera 1994).

The late 1960s marked the origin of the widely used term 'informatics'. A Russian Scientist coined the term "informatika" and defined it as 'The discipline of science which investigates the structures and properties, not specific content, of scientific information' (Collen 1986). Even though, not much work was done in the medical sector, the popular term 'medical informatics' had its origin which dates back to this early time. Francois Gremy is credited with coining the term "informatique medical" in the 1960s, translated to medical informatics (Coiera 1994). It was defined as the informational technologies which are concerned with patient care and the medical decision making process. The first appearance of medical informatics broadly defined to include "biomedical informatics" as well as "health informatics" as a term "informatique medicale" (Coiera 1994). However, the art of terminology did not bring development or realization in the medical environment.

The end of 1960s was also associated with development of a model-oriented DSS or management decision system became practical. Peter Keen and Charles Stabell pioneered the work, and claimed that the concept of decision support evolved from the theoretical studies of organizational decision making done at the Carnegie Institute of Technology during the late 1950s and early 1960s where Massachusetts Institute of Technology was the center of the research work (Keen and Morton 1978). The earlier bit of technology

filtering into the medical field was in 1967. Massachusetts General Hospital (MGH) used a two-way microwave technology system to provide emergency care and medical attention to the travelers and employees at the airport. Nurses who were available used electronic transmission equipment to send assessment findings, x-ray and microscope images, electrocardiograph readings, vital signs and other pertinent data to MGH physician (Collen 1986; Coiera 1994). In a similar event, development and implementation of DSS also found its way in the Indian Health Service, the Department of Health, Education and Welfare and NASA which conceived and engineered a program to provide healthcare on the Papago Indian reservation where appreciable health care services were provided to natives (Bashshur and Lovett 1977). These technological intervention marked the integration of IT in the medical circles.

The beginning of 1970 was associated with promotional events especially in the business field. Journals began to publish articles geared on management decision systems, strategic planning systems and decision support systems. For example, apart from Scott Morton and colleagues, Ferguson and Jones discussed a computer aided decision system in the journal *Management Science* in 1969 (Sprague 1980). In the late 1970s, both practice and theory issues related to DSS became subject at academic conferences including the American Institute for Decision Sciences meetings e.g., the conference on DSS in San Jose by 1977. At the same time, a number of researchers and companies had developed interactive information systems which used data and models to help managers analyze semi-structured problems (Sprague 1980; Volpp and Schwartz 1994). All these efforts were made during those early stages and anticipated benefits can make one postulate that, development and implementation of these systems was mainly done by business minded people followed by the health sector.

1.1.2 1980s

The beginning of 1980 evidently marked the seething through of IT into the medical community even though major events were occurring in the business environment. The term “nursing informatics” was first used and defined by Scholes and Barber in 1980 in their address to the MEDINFO conference in Tokyo (Marin 2005). They defined it as “the application of computer technology to all fields of nursing; nursing services, nurse education, and nursing research”. During early times of this period, academic researchers developed a new category of software to support group decision-making (Huber 1982).

1.1.3 1990s - to date

Much of health related work occurred in the late 1990s to date. This period was associated with development and integration of a number of useful DSS. However, most of the attention was paid to the adoption of computer-based patient records (CPR). The use and adoption of Clinical Decision Support Systems (CDSS) was one of the successful implementation of IT in the clinical community. However, even though most of the CDSS are based on current best practices, the entity responsible for determining and translating the best practice guidelines into actionable rules varies between tools and countries. This makes the CDSS appear useless and fragment if not incorporated into most Electronic Patient Medical Record (EPMR). Objections, criticism and loss of confidence also marked the development of CDSS in the 1990s. As the best way forward and succumbing to pressure from technological success such as pharmacogenomics, most

of the CDSS were developed to match personalized health care. The following are some of the examples of the developed CDSS.

a) Bilitool clinical decision support system (www.bilitool.org)

This tool is an example of a web-based tool that requires manual entry of laboratory data and other patient information by the clinician or consumer. The algorithm is based on best-practice guidelines of the American Academy of Pediatrics to assess risk of complications and aid in management of a single physiologic condition in newborns, hyperbilirubinemia. The tool is independent of patient data repositories and electronic health records (EHRs). The logic-based rule uses age and levels of bilirubin as variables. The tool produces a result with risk stratification and provides recommended follow-up based on that risk. It provides useful information to the clinician at the point of care where the testing is often done. However, Bilitool can be inconvenient to clinicians who must alter their natural workflow, access the tool on the web, and manually re-enter information that may already be present in the patient's record or EHRs. Again, it is difficult to use this type of tool in developing countries where internet access is rather expensive, and very slow.

b) WarfarinDosing clinical decision support system (www.warfarindosing.org)

WarfarinDosing is a useful analytical CDSS tool. It uses a computational algorithm to help clinicians determine a proper therapeutic anti-coagulant dose. This CDSS tool integrates pharmacogenomic test information with other patient information to aid in deriving the correct dose of warfarin, an anti-coagulant medication that is commonly associated with bleeding complications. The tool obtains general information, including sex, age, weight, height, smoking habits and liver disease; genetic information such as

cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase (VKOR C1-1639/3673) genotypes; and medical information such as laboratory tests for coagulation function. The algorithm produces an estimated therapeutic dose result as well as suggestions for specific observation for certain high risk scenarios. Under routine clinical practice, successful implementation of this kind of tool, considering that CYP2C9 enzyme inhibition might shift an individual's phenotypic status from Extensive Metabolizer (EM) to Poor Metabolizer (PM), is difficult. Besides, DDIs should be incorporated into the software if it is to be used worldwide.

c) SafeMed clinical decision support system (www.safe-med.com)

SafeMed is an active CDS tool that is able to obtain necessary medical information from clinicians or any other medical information system. Its software is Extensible Markup Language (XML) web based and platform independent. The software consists of three performance improving components: SafeMed Imaging, SafeMed Pharma, and SafeMed Quality. SafeMed Imaging assists clinicians in identifying the most appropriate imaging test based on the level of effectiveness, cost, and side effects relative to the patient. SafeMed Pharma automatically and continuously checks current and prescribed medications for possible adverse drug reactions, efficiency, and cost-effectiveness comparison. SafeMed Quality is an active data accumulation process that checks for shortcomings in medical care as well as potentially harmful therapies. The logic-based rules are derived from best practice guidelines and are maintained and updated by SafeMed. Messaging and alerting is highly integrated into the providers EPMP system. However, this kind of tool does not provide a list of possible drug alternatives or the best action to optimize therapy.

d) PointOne Clinical Systems (www.pointonesystems.com)

PointOne Clinical Systems is an active platform-based system that uses genetic and family history information found in EHR, medical claims, lab tests, health assessments and a web-based family history questionnaire. This CDSS system serves to assist clinicians in identifying patients at high risk for certain diseases, and apply appropriate screening and risk reduction strategies. The system includes data capture tools, risk stratification algorithms, integrated reporting, care guidelines, and educational material for clinicians and patients. A patient-specific report from evidence-based guidelines is generated for the clinician, which includes an annotated family pedigree and patient risk stratification based on logic, analytical, and integrated algorithms. However, apart from the limitations highlighted under the above software, it exists as a stand-alone software application which is not integrated into workflow of the EHR.

e) TheraDoc (www.theradoc.com)

TheraDoc, is a stand-alone CDS platform-based tool that can be actively connected to the clinician's EHR to provide automated access to historical and current patient information. It is able to provide active surveillance that recognizes changes in patient conditions, adverse events, and threats to patients' safety. TheraDoc applications include: Infection Control Assistant, Antibiotic Assistant, Clinical Alerts Assistant, and Adverse Drug Event Assistant. TheraDoc is developed independently from the EHRs but the software platform is able to interface with EHR systems utilizing health information technology standards such as health level 7 (HL7), Logical Observation Identifier Names and Codes (LOINC), and Systematized Nomenclature of Medicine (SNOMED). This interoperability allows TheraDoc applications to accumulate data from the EHR, apply logic-based algorithm rules, and present messages within the workflow of the physician.

Algorithms used by the TheraDoc software are developed and maintained by specialty advisory boards that are responsible for knowledge review to assure information and rules are current and accurate. This tool shares the same limitations as SafeMed.

1.2 Overview of progress made in health care delivery

Various drug co-administration approaches are employed in this medical environment to achieve better efficacy and reduced emergency of drug resistant parasites. Although multiple drug therapy has several advantages among them the simultaneous treatment of many ailments and achievement of better outcomes for problematic diseases such as HIV/AIDS, it brings with it an increased risk for DDIs based ADRs (Jacubeit, Drisch et al. 1990). The ADRs were reported to be one of leading causes of morbidity and mortality in health care (Lazarou, Pomeranz et al. 1998).

Tools like CPOE and bar coding systems have demonstrated tangible benefits in the healthcare system (Ghebhart 1999; Bates, Cohen et al. 2001). The extend of reducing the medication errors through the use of electronic medical records (EMRs) as well as DDI screening software that quickly detect and alert the user to potentially fatal drug interaction has been recognized in the medical arena. However, these technological interventions have some limitations. The fragmentation of healthcare delivery system results in incomplete records. Even though drug interaction support was in place, this fragmentation of routine work flow resulted in some medical practitioners not utilizing the decision support that was optimally incorporated (Cavuto, Woosley et al. 1996; Smalley, Shatin et al. 2000). The benefits of this technological advancement have not yet

been fully realized in developing countries where healthcare delivery system efficiency is low.

The evolution of proteomics, pharmacogenomics and other fields of pharmaceutical biotechnology offer a wide scope for utilization in drug-drug interaction predictions. Scientists can predict the magnitude of drug interactions through the use of in vitro data, and disseminate their findings to medical practitioners in order for them to explain therapeutic failure in some instances. Inefficient information handling results in medication errors due to incorrect diagnosis, cumbersome assessment strategies and inappropriate problem statements (Eddy 1993; Ghebhart 1999; Marin 2005). In order for medical personnel to cope up with the rapid increase in medical information, it is time for the development and implementation of interactive electronic tools that will assist them in decision making during their routine work, in a way that provides continuous and comprehensive data.

Rapid new information explosion and advances in all fields linked to medical community has resulted in the creation of huge volumes of data. However, to keep abreast of revolutionary and evolutionary changes is extremely challenging. Clinical data gathering and decision making has been eased by the advent of Electronic Medical records EMRs and efficient CDSS in combination. However problems like epidemics of diseases of infectious origin brought unrest to the Health Care sector with most affected nations being developing countries.

1.2.1 Electronic Medical Record (EMR)

Electronic health record (EHR), computer-based medical record, electronic medical record (EMR), electronic patient record and computer-based patient record all refer to basically the same concept: a digitalized record of a single person's encounters with the healthcare delivery system. An Electronic Health Record (EMR) is a medical record or any other patient profiles relating to the past, present or future physical and mental health, or condition of a patient which resides in computers which capture, transmit, receive, store, retrieve, link, and manipulate multimedia data for the purpose of providing health care and health-related services. Even though the first applications were during 1960s (Collen 1986), most of their applications and improvements are still underway

With the start of the 21th century, the EMRs market started to flourish.

Advantages of current EMR over paper record

- The EMR has huge capacity for storing data in small space. The data can be retrieved almost instantaneously and this gives time to health care practitioners for other medically relevant tasks and patient care activities rather than spend time on data retrieval.
- EMRs improve effective time for patient and doctor physician interactions instead of repeatedly narrating the same information such as medical history.
- Instantaneous availability of patient's medical history, treatment regimes and current health status in routine and emergency clinical situations foster reduction in medication errors
- Data retrieval for epidemiological and statistical evaluation can be quickly accessed and pertinent measures taken to improve community health.

- There is data security through utilization of backup files in case of emergency. Furthermore this information can only be accessed by authorized personnel.
- They provide clinical alerts, expert systems and reminders which are valuable for optimum healthcare delivery. For example, laboratory data that fall outside normal range can be routinely flagged to focus clinician's attention on results worth considering. Computer generated reminders of appropriate length of stay for with a particular diagnosis often reduce the median length of stay in a hospital. Warnings and alerts gives the decision support and potentiates initiation of risk reduction measures by the physician.
- An EMR provides distinct and quick identifying information for each patient, and identifiers to locate the digital record among any number of other records
- Networked computers with EMR enable data to be accessible from remote sites to many people at the same time other than an individual to be in a specific location. This data can only be accessed by authorized personnel
- EMR provides more accurate and capture of financial charges and billing efficiency. This is advantageous, though, it is not a priority for clinicians, but it gives them time for care provision. Accurate and timely billing also reduces confusion between the patient and health care providers. Again, Linking the documentation of procedure with the needed services is likely to reduce the burden of charge capture to clinicians, making it more accurate

Limitations to timely implementation of EMR in the medical field

- Confidentiality, privacy and security of information are serious concerns to be addressed carefully. Since functions that allow the physicians to edit data in cases of errors, patients fear that their data may be handled in the same way.

- Startup costs for hardware, software, installation, maintenance, increases technical personnel and future upgrades are often high especially in low income earning nations. It is therefore important to start by preparing less costly but effective spreadsheets that allows a practice to calculate initial and annual operating costs.
- EMRs offer static data without the ability to offer relational databases during use. This makes EMRs inapplicable for teaching purposes.
- Most physicians want to hit the therapeutic target with highest accuracy. The EMRs appear to be an improvement in the data storage and manipulation without additional information on the best way to optimize therapy.
- Cost of the software is one of the barriers of their implementation in developing countries.

1.2.2 Decision making process in the medical field

In developed countries, physicians' decisions control between 70% and 80% of all health care dollars spent (Eddy 1993; Volpp and Schwartz 1994) and many strategies to influence or control physician decision making have been advocated. These strategies include education, peer review with feedback, administrative interventions, financial incentives and penalties, critical pathways, and nationally derived guidelines (Greco and Eisenberg 1993).

Irrational prescription of drugs as a result of poor decision making is a common occurrence in clinical practice (Marschner, Thurmann et al. 1994). The cost of such irrational drug use is enormous in terms of both scarce resources and the adverse clinical consequences of therapies that may have real risks but no objective benefits. Drug

utilization review (DUR) is the process by which the quality of drug prescribing is measured by organizing important predetermined criteria (Marschner, Thurmann et al. 1994). In developing countries the cost of drugs is a major concern to both physician and patient. Analysis of indication-related drug prescription patterns is of particular interest with regard to the rising costs of the health service. This is also reflected in the higher costs of drugs, especially Anti-retrovirals (ARVs). Widespread concern has been expressed about the inappropriate use of antimicrobials (Srishyla, Rani et al. 1994). Inappropriate and irrational use of antimicrobials can lead to microbial resistance to the commonly used antimicrobials.

A prescription by a doctor may be taken as a reflection of physicians' attitude to the disease and the role of drug in its treatment. It also provides an insight into the nature of the health care delivery system. Average number of drugs per prescription is an important index of the scope for review and educational interventions in prescribing practices. A study on prescribing patterns from Zimbabwe once reported a mean number of 4 drugs per paediatric patient (Nhachi, Kasilo et al. 1992).

1.2.3 Interactive databases and decision support systems

Decision support systems often come separate to EMRs or other databases. If this function is added it does not cover all the relevant and required aspects. The decision support systems often have failed mainly due to incompleteness of data. On the other hand, EMRs do not provide timely consultative and decision support to the physician. This is therefore rather static data unless it is linked to other databases such as MEDLINE, PubMed, Drugdex, etc. There are numerous reasons why more CDSS are not

in routine use. Some require the existence of an electronic patient record system to supply their data, and most institutions and practices do not yet have all their working data available electronically. Others suffer from poor human interface design and so do not get used even if they are of benefit.

Much of the initial reluctance to use CDSS simply arose because they did not fit naturally into the process of care, and as a result using these tools required additional effort from already busy medical personnel; as in developing countries which are highly short staffed. It is also true, but perhaps dangerous, to ascribe some of the reluctance to use early systems upon the technophobia or computer illiteracy of healthcare workers. If a system is perceived by those using it to be beneficial, then it will be used. If not, independent of its true value, it will probably be rejected.

EMRs, in conjunction with interactive databases, should provide:

a) Alerts and reminders. In real-time situations, an expert system attached to a patient monitoring device like an electrocardiograph or pulse oximeter can warn of changes in a patient's condition. In less acute circumstances, it might scan laboratory test results, drug or test order, or the EMR and then send reminders or warnings, either via immediate on-screen feedback or through a messaging system like e-mail. Reminder systems are used to notify clinicians of important tasks that need to be done before an event occurs. For example, an outpatient clinic reminder system may generate a list of immunizations that each patient on the daily schedule requires.

b) Diagnostic assistance. When a patient's case is complex, rare or the person making the diagnosis is simply inexperienced, an expert system can help in the formulation of likely diagnoses based on patient data presented to it, and the systems understanding of illness

stored in its knowledge base. Diagnostic assistance is often needed with complex data, such as the electrocardiograph, where most clinicians can make straightforward diagnoses, but may miss rare presentations of common illnesses like myocardial infarction, or may struggle with formulating diagnoses, which typically require very high levels of expertise.

c) Therapy critiquing and planning. Critiquing systems can look for inconsistencies, errors and omissions in an existing treatment plan, but do not assist in the generation of the plan. Critiquing systems can be applied to physician order entry. For example, on entering an order for a blood transfusion a clinician may receive a message stating that the patient's haemoglobin level is above the transfusion threshold, and the clinician must justify the order by stating an indication, such as active bleeding. Planning systems on the other hand have more knowledge about the structure of treatment protocols and can be used to formulate a treatment based upon a data on patient's specific condition from the EMR and accepted treatment guidelines.

d) Prescribing decision support systems (PDSS). After diagnosis, the second important clinical task is the prescription of medications, and PDSS can assist by checking for drug-drug interactions, dosage errors, and if connected to an EMR, for other prescribing contraindications such as allergy. PDSS are usually well received because they support a pre-existing routine task, and as well as improving the quality of the clinical decision, usually offer other benefits like automated script generation and sometimes electronic transmission of the script to a pharmacy.

e) Information retrieval. Finding evidence in support of clinical cases is still difficult on the Web, and intelligent information retrieval systems can assist in formulating

appropriately specific and accurate clinical questions. Furthermore, they can act as information filters by reducing the number of documents found in response to a query to a Web search engine. These systems can assist in identifying the most appropriate sources of evidence appropriate to a clinical question. More complex software 'agents' can be sent to search for and retrieve information to answer clinical questions, for example on the Internet. The agent may contain knowledge about its user's preferences and needs, and may also have some clinical knowledge to assist it in assessing the importance and utility of what it finds.

f) Image recognition and interpretation. Many clinical images can now be automatically interpreted, from plane X-rays through to more complex images like angiograms and medical resonance imaging (MRI) scans. This is of value in mass-screenings, for example, when the system can flag potentially abnormal images for detailed medical attention.

1.3 Xenobiotic Metabolism

Xenobiotics are foreign molecules that the human body is constantly exposed to. In response to this chemical insult, the human body has enzymes systems to metabolise these chemicals through the use of such systems as cytochrome P450s, epoxide hydroxylase, glutathione S-transferase, UDP-glucuronosyl transferase, N-acetyltransferase, alcohol dehydrogenase, sulfotransferase and cysteine conjugates that facilitate their removal from the body (Guengerich 1990).

Due to their lipophilic nature, most drugs, however, need to be modified structurally to facilitate excretion. These modification processes are called drug metabolism. Drug

metabolism is a detoxification function the human body possesses to defend itself from environment hostility. Figure 2 below highlights how a drug moves within the body.

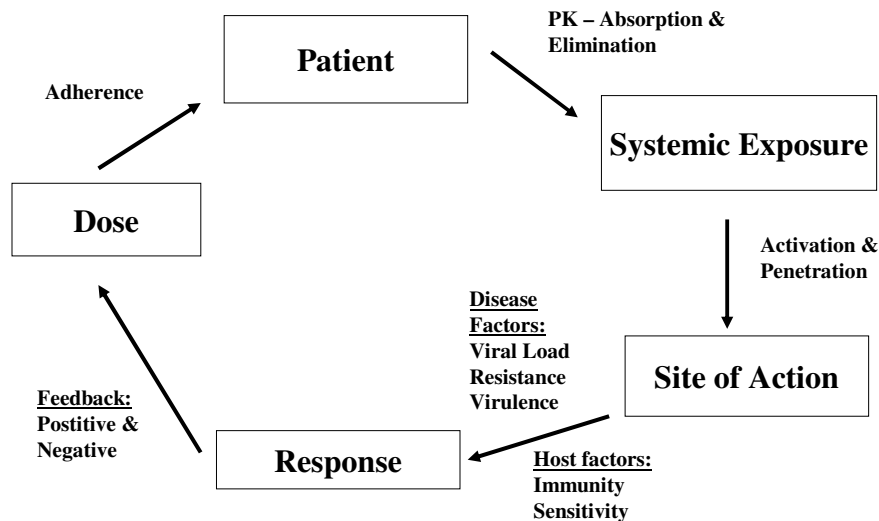


Figure 2: Overview of how a drug moves around the body and elicits responses

However, drug developers often face the dilemma that a potential drug is either metabolized/excreted from the body too fast, that the drug cannot reach its therapeutic effect, or too slow, that it resides in the body for a long time in turn causing side effects. The study of drug metabolism, therefore, serves primarily two purposes: to elucidate the function and fate of the drug, and to manipulate the metabolic process of a potential drug.

The liver is the primary site for metabolism. Liver contains the necessary enzymes for metabolism of drugs and other xenobiotics. These enzymes operate through two metabolic pathways: Phase I (functionalization/defunctionalization reactions) and Phase II (biosynthetic reactions) metabolism (Goldstein and Faletto 1993). Some typical examples of Phase I metabolism include oxidation and hydrolysis. Phase II metabolism

involves the introduction of a hydrophilic endogenous species, such as glucuronic acid or sulfate, to the drug molecule. Drugs are usually lipophilic substances (Oil-like) so they can pass through plasma membranes and reach the site of action. Drug metabolism is basically a process that introduces hydrophilic functionalities onto the drug molecule to facilitate excretion (Okey 1990). When the drug molecule is oxidized, hydrolyzed, or covalently attached to a hydrophilic species, the whole molecule becomes more hydrophilic, and is excreted more easily. Drugs often undergo both Phase I and II reactions before excretion. The Phase I reaction introduces a functional group such as a hydroxyl group onto the molecule, or exposes a preexisting functional group, and Phase II reaction connects this functional group to the endogenous species such as a glucuronic acid (Okey 1990; Goldstein and Faletto 1993). The modified drug molecule may then be hydrophilic enough to be excreted.

Although liver is the primary site for metabolism, virtually all tissue cells have some metabolic activities. Other organs having significant metabolic activities include the gastrointestinal tract, kidneys, and lungs (Goldstein and Faletto 1993). When a drug is administered orally, it undergoes metabolism in the gastrointestinal track (GIT) and the liver before reaching systemic circulation. This process is called first-pass metabolism. First-pass metabolism limits the oral bioavailability of drugs, sometimes significantly e.g., triazolam, chlorpromazine, aspirin, metoprolol, and many others. Drug- interactions

Nearly 50% of xenobiotics administered to humans have failed due to lack of adequate efficacy, including unsatisfactory pharmacokinetics such as poor bioavailability. Up to 40% of drug candidates have failed because of safety issues in earlier phase (DiMasi 1995) and one of these is adverse DDIs. In recent pharmacotherapy, multi-drug therapy is commonly used especially in malaria, TB and HIV/Aids diseases as detailed in the

previous sections. The most common DDIs are caused through CYPs, and inhibition of these enzymes accounts for nearly 70% in all reported cases. Recent withdrawals of mibefradil, sirovudine, astemizole and cisapride were due to DDIs (Huang and Lesko 2004).

Of all the CYPs, the CYP3A4 accounts for about 50% metabolism of available drugs on the market (Chiba, Jin et al. 2001). Drug-drug interactions are divided into pharmacodynamic (PD) and pharmacokinetic (PK) interactions. PD drug-drug interactions are associated with altered pharmacological effect of drug when administered in combination with other drug(s) e.g., synergistic occurrence of side-effects or antagonism of PD effect (like antagonistic antiviral effect between zidovudine and stavudine). PK drug-drug interactions are associated with inappropriate plasma concentrations of drugs. Changes in plasma concentrations can be the result of inadequate absorption, transport, metabolism or elimination. For example, in HIV therapy, a considerable number of drug-drug interactions occur during transport via p-glycoprotein or metabolism by isoforms of the cytochrome P450 enzyme system (Piscitelli and Gallicano 2001).

The following sections highlight mechanisms that describe a variety of drug interactions.

1.3.1 Genetic polymorphisms in metabolizing enzymes

The genes coding for major metabolizing enzymes, Cytochrome P450s, UDP-glucuronyl transferases, *N*-acetyl transferases (*NAT*) and others have been shown to exhibit genetic polymorphism. These differences can result in other people lacking the enzyme hence experiencing exaggerated pharmacological effects of drugs whose elimination is mainly through the affected enzyme. Two *N*-acetyltransferase isozymes, *NAT1* and *NAT2*, are

polymorphic (Wormhoudt, Commandeur et al. 1999) although *NAT1* has previously regarded to as non polymorphic. They catalyze both *N*-acetylation (usually deactivation) and *O*-acetylation (usually activation) of aromatic and heterocyclic amine carcinogens. Epidemiological studies suggest that the *NAT1* and *NAT2* acetylation polymorphisms modify risk of developing urinary bladder, colorectal, breast, head and neck, lung, and possibly prostate cancers (Hein 2000; Lilla, Verla-Tebit et al. 2006). Associations between slow *NAT2* acetylator genotypes and urinary bladder cancer and between rapid *NAT2* acetylator genotypes and colorectal cancer are the most consistently reported. The *NAT2* genes partition individuals into rapid, heterozygous intermediate and homozygous slow acetylators. It is responsible for the metabolism of isoniazid which is used in the treatment of tuberculosis. In individuals who are slow acetylators, there is increased risk of hepatotoxicity because considerable amount of isoniazid will be converted to its toxic metabolite by CYP2E1. Efavirenz (EFV) and nevirapine (NVP) are metabolized by cytochrome P450 2B6 (CYP2B6). Allele 516 G>T (Gln172His) is associated with diminished activity of CYP2B6 isoenzyme and may lead to differences in drug exposure. CYP2B6 516TT was found to be associated with greater plasma and intracellular exposure to EFV, and greater plasma exposure to NVP (Rotger, Colombo et al. 2005). Intracellular drug concentration and CYP2B6 genotype were predictors of EFV neuropsychological toxicity. Therefore CYP2B6 genotyping may be useful to complement an individualization strategy based on plasma drug determinations to increase the safety and tolerability of EFV.

1.3.2 Drug food/nutrient interaction

Generally, administering oral medication along with food or at a mealtime is a convenient manner of drug dosing. However, drug interactions can occur that modify the activity of the drug (decrease or increase drug effects) or impair the nutritional benefit of certain food. The most commonly observed type of drug-food interaction affects drug absorption. Food can decrease a drug's rate of absorption and/or decrease the extent of absorption of numerous drugs. Examples of drugs whose absorption is decreased when taken with food include penicillin, tetracycline, erythromycin, levodopa, phenytoin, and digoxin and those whose absorption increases when taken with food include itraconazole (Crounse 1961; Melander, Danielson et al. 1977). With some drugs, this food-drug interaction may be utilized to achieve higher serum drug levels or to use lesser amounts of drug per dose. Generally, these interactions have an insidious onset and may not be clinically evident except for failure to achieve the therapeutic goals of therapy or loss of disease control. Continuous long-term monitoring of patients is needed when drugs and food must be taken together.

1.3.3 Enzyme inhibition

Inhibition of CYP enzymes accounts for about 70% of all reported cases of DDI (Chiba, Nishime et al. 1995). There are quite a number of drugs that inhibit the activity of CYP450 isoenzymes e.g., ketoconazole, ritonavir and quinidine. Inhibition of CYP450 activity results in diminished clearance of substrate drug hence higher and/or toxic levels of substrate drug. Apart from the drawback highlighted above, enzyme inhibition can be useful if you want to boost the therapeutic level of a certain drug but care has to be taken in order to avoid accumulation of the boosted drug to toxic levels. For example, Kaletra

which is a product of Abbott is a combination of two protease inhibitors, ritonavir and lopinavir. Ritonavir was included to boost the plasma concentration of lopinavir through inhibition of CYP3A4 which extensively metabolize lopinavir (Oldfield and Plosker 2006). Enzyme inhibition has been described in detail in the following sections.

Inhibition of enzyme is divided into reversible and irreversible mechanisms.

a) Reversible inhibition

This mechanism occurs when the inhibitor binds to the enzyme through non covalent interactions. Maximal response is attained unlike in irreversible mechanism described in the following sections. This mechanism can further be divided into competitive and non-competitive.

- I. Competitive inhibition. This mechanism occurs when the inhibitor and substrate compete for binding sites with concomitant increase in Michaelis-Menten constant (K_m) and a decrease in maximum rate of metabolism (V_{max}) (Fig. 5; Fig. 6). Increasing the substrate concentration overcomes the inhibition, for example interaction between orally administered ketoconazole and midazolam (Copeland 2000; Madan, Usuki et al. 2002).
- II. Non-competitive inhibition. This mechanism occurs when the inhibitor binds to the site other than the site where the substrate binds. Uncompetitive inhibition occurs when the binding of substrates results in orientation of the enzyme which results in inhibitor binding.

b) Irreversible inhibition. Irreversible inhibitors rely on the catalytic function of the CYP450 cycle, and metabolism of the inhibitor is a prerequisite (Murray and Reidy

1990). The formation of more inhibitory species from non-inhibitory species, metabolic intermediates that turn the CYP450 into non-functional metabolic site has been associated with sulphur-containing compounds, and protease inhibitors like ritonavir forming a stable complex between the CYP450 and the metabolic intermediate. Involvement of haem and apoprotein turnover in the catabolic process is associated with abnormal drug pharmacokinetics (Murray and Reidy 1990).

Cyclopropylamines and olefins are some of the autocatalytic inactivators of CYP450 (Testa and Jenner 1981). Their biotransformation by CYP450 to radical intermediates that alkylate the prosthetic group of the enzyme results in functionally inactive enzyme. Administration of mechanism-based inactivators substrates cause biological activation of chemical oxidation, and prolonged flavin-like monooxygenase (FMO) depression occurs (Murray 1987).

1.3.4 Enzyme induction

Exposure to enzyme inducers results in sub-therapeutic concentrations of the enzyme's substrates due to increased activity of the metabolizing enzyme. Co-administration of rifampicin with CYP450 substrate results in substantial decrease in substrate plasma concentration. For example, oral midazolam systemic exposure is decreased by 96% when subjects are pretreated with rifampicin 600 mg per day for five days (Backman, Olkkola et al. 1996). However, increased enzyme activity can also be utilised in administration of pro-drugs. For example, codeine is metabolized by CYP2D6 to morphine. The ultrarapid metabolism of codeine has been found to be associated with opioid intoxicification (Gasche, Daali et al. 2004).

Induction mechanism can be divided into the following:

a) Enhanced CYP450 activity. Induction of CYP genes generally occurs at the transcriptional level and is mediated by receptors such as pregnane X receptor (PXR) and aryl hydrocarbon receptor (AhR). PXR is a major determinant of CYP3A4 (Lehmann, McKee et al. 1998) and CYP2C9 genes induction activities (Chen, Liang et al. 2004) due to xenobiotic administration. However, CYP1A has not been reported to be induced by any marketed drugs at their therapeutic doses, and its mechanism of induction has been studied extensively (Whitlock 1999). The CYP1A enzymes are regulated by AhR, and prototypical AhR ligands are planar, hydrophobic, and halogenated hydrocarbons, for example, 2,3,7,7-tetrachloro-dibenzo-p-dioxin (TCDD) (Denison and Nagy 2003). Therefore, this discrepancy among species renders animal *in vivo* models inappropriate for induction studies. This calls for more reliable and *in vitro* models for humans.

b) Phenobarbital induction of cytochrome P450 gene expression. Induction due to Phenobarbital (PB) and related compounds is generally more pronounced in the liver with significant increase in the total CYP450 concentration, proliferation of smooth endoplasmic reticulum, and subsequent increase in liver weight which is not seen in receptor mediated induction (Murray and Reidy 1990). The major forms of CYP450 induced by PB are CYP2B1-2, CYP2C8-10, CYP3A1-2 (Okey 1990).

Below are some of the mechanisms where PB and related compounds activate transcription of CYP450.

CYP450 dependant induction

A possible site of action of Phenobarbital (PB) and structurally diverse PB-like inducers is the substrate binding site of cytochrome P450 itself. This mechanism would explain the transcriptional activation of CYP2B by large numbers of structurally diverse chemicals (Waxman and Azaroff 1992).

Receptor dependant induction

PB-like inducers and PB are lipophilic in nature hence suggestion of likelihood of intracellular receptor based mechanism analogous to that utilised by the steroid hormones. Their binding to receptor could activate the latent deoxyribonucleic acid (DNA)-binding activity of receptor, and would lead to the binding of the activated receptor to the regulatory DNA sequences within PB-responsive genes. This step could be coupled to the transcriptional activation of target gene expression. The activated PB receptor would act as transcriptional factor, enabling it to transduce directly its signal to the transcription engine (Waxman and Azaroff 1992).

Therefore, based on this literature review highlighting problems in health care delivery and xenobiotic biotransformation, there are deficiencies in the utilization of biochemical pathways for drug metabolism to predict the potential drug-drug interactions that can be useful to doctors and pharmacist during routine practice.

2. AIM AND OBJECTIVES

Aim:

To design a database driven software to assist in predicting pharmacokinetic drug-drug interactions occurring through CYP450 inhibition

Objectives:

1. To generate data describing in vitro pharmacokinetic (CYP450 inhibition) interaction between drugs
2. To develop software for an interactive and dynamic digital tool to be used in drugs prescription to avoid preventable drug-drug interactions associated with drug metabolism, CYP450 inhibition in particular.
3. To validate the software prediction by comparing predicted magnitude of CYP450 inhibition with published *in vivo* data
4. To investigate the utility of the software among doctors and pharmacists

3. METHODOLOGY

3.1 Collating *In vitro* data

Literature sources were assembled including databases, symposia abstracts and original publications on drug-enzyme or drug-drug interaction for both mechanism based and reversible inhibition (Data for all the drugs included in this study is available in appendix 1). The pharmacokinetic data included was based on the model depicted below (Figure 3).

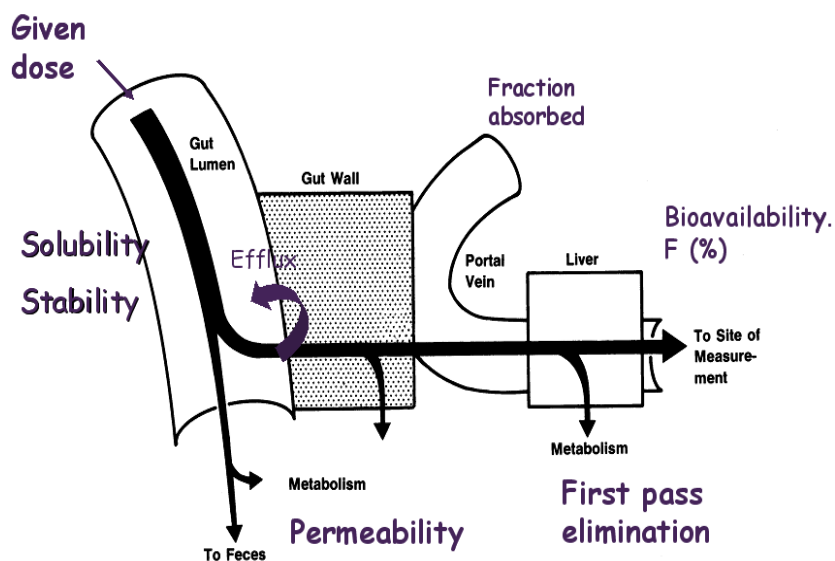


Figure 3: Typical pharmacokinetic mode for drug movement within the body

Sources with validated *in vitro* methods and having the following parameters as well as mechanism of inhibition were considered:

- Inhibition constants (K_i)
- Maximal inactivation rate at saturating inhibitor concentration (K_{inact})
- Inhibitor concentration at which half maximal inactivation rate is achieved (K_I)
- First order rate constant for *in vivo* gut enzyme degradation ($K_{degrad.gut}$)

- First order rate constant for *in vivo* liver enzyme degradation ($K_{degrad.hep}$)

In vivo parameters considered

- Fraction unbound in plasma (f_u)
- Fraction of substrate metabolized in the gut (F_g)
- Fraction of hepatic clearance subject to metabolic inhibition and contribution of hepatic to total clearance (f_m, f_h)
- Fraction absorbed from the gut (f_a)
- First-order absorption rate constant (k_a)
- First-order elimination rate constant (K_{el})
- Time to reach peak plasma concentration (T_{max})

For *in vitro* studies, types of enzymatic models used are also important, for example, hepatocytes, subcellular fractions and recombinant enzymes have different pros and cons in their predictive value of *in vivo* DDIs. There was a bias for drugs used in the treatment of tuberculosis, malaria and HIV/Aids in addition to other well-known drug-drug interactions for non-infectious diseases.

3.2 Collating *In vivo* data

The drugs that we selected had previously been tested in humans with selective probe drugs for five enzymes in brackets: theophylline or clozapine (CYP1A2), tolbutamide or warfarin (CYP2C9), mephenytoin or omeprazole (CYP2C19), desipramine, metoprolol, or dextromethorphan (CYP2D6), or midazolam, alprazolam, triazolam, buspirone, nifedipine, or simvastatin (CYP3A). In cases where perpetrator-probe interaction was performed in different studies, a conservative approach was applied i.e. picking the study

that gave the highest change in exposure of the probe drug. Whenever available, drug interaction data from simultaneous oral administration that reported change in exposure of probe drug or substrate were utilized

3.3 Prediction of *in vivo* potential occurrence of drug-drug interaction using *in vitro* data

Competitive inhibition. The following model which has been previously derived for extrapolation of *in vitro* to *in vivo* prediction of drug-drug interaction was incorporated (Brown, Ito et al. 2005; Galetin, Burt et al. 2006). The model was applicable to all other CYPs except CYP3A4.

$$\frac{CL_{control}}{CL_{inhibitor}} = \frac{AUC_{inhibitor}}{AUC_{control}} = \frac{1}{\frac{f_m \cdot f_h}{\left(1 + \frac{I_{in.vivo}}{K_i}\right)} + 1 - f_m \cdot f_h} \quad (1)$$

$CL_{control}/CL_{inhibitor}$ is the ratio of oral clearance of the drug in the absence and presence of inhibitor respectively, $I_{in.vivo}$ is the *in vivo* concentration of inhibitor and $AUC_{inhibitor}/AUC_{control}$ is the ratio of oral clearance of the drug in the presence and absence of inhibitor respectively.

CYP3A4 inhibition had gut consideration and the following equation was used (Wang , Jones et al. 2004).

$$\frac{CL_{control}}{CL_{inhibitor}} = \frac{AUC_{inhibitor}}{AUC_{control}} = \frac{F_{g.inhibitor}}{F_{g.control}} \cdot \frac{1}{\frac{f_m \cdot f_h}{\left(1 + \frac{I_{in.vivo}}{K_i}\right)} + 1 - f_m \cdot f_h} \quad (2)$$

$F_{g.inhibitor}/F_{g.control}$ was the intestinal wall extraction fractional effect in the presence and absence of inhibitor. Maximal intestinal wall inhibition, with the term assumed to be equal to 1, after multiple doses of inhibitor was considered.

Scaling model for mechanism-based inhibition. The following model was considered for all other CYPs except for CYP3A4 (Mayhew, Jones et al. 2000; Wang, Jones et al. 2004).

$$\frac{CL_{control}}{CL_{inhibitor}} = \frac{AUC_{inhibitor}}{AUC_{control}} = \frac{1}{\frac{f_m \cdot f_h}{\left(1 + \frac{K_{inact} \cdot I_{in.vivo}}{(K_I + I_{in.vivo}) \cdot K_{deg\ rad.\ hep}}\right)} + 1 - f_m \cdot f_h} \quad (3)$$

The gut consideration for CYP3A4 was estimated using the equation below.

$$\frac{CL_{control}}{CL_{inhibitor}} = \frac{AUC_{inhibitor}}{AUC_{control}} = \frac{F_{g.inhibitor}}{F_{g.control}} \cdot \frac{1}{\frac{f_m \cdot f_h}{\left(1 + \frac{K_{inact} \cdot I_{invivo}}{(K_I + I_{invivo}) \cdot K_{deg\ rad.\ hep}}\right)} + 1 - f_m \cdot f_h} \quad (4)$$

3.4 Estimation of input parameters

An estimate of CYP2C9, CYP2C19 or CYP2D6 contribution to substrate metabolism was predicted using the following equation (Venkatakrishnan and Obach 2005).

$$f_m = 1 - \frac{CL_{po.cypPM}}{CL_{po.cypEM}} = 1 - \frac{AUC_{cypEM}}{AUC_{cypPM}} \quad (5)$$

From the above equation, $CL_{pocypPM}$ represents oral clearance in poor metabolizers, and $CL_{pocypEM}$ in extensive metabolizers. This was done where there was no published data. k_a , if not given, was estimated from the equation (6) as previously illustrated by Ito (Ito, Iwatsubo et al. 1998). The result of the calculation must be less than 0.1 min^{-1} which is the maximum absorption rate constant assuming first order kinetics (Oberle, Chen et al. 1990).

$$T_{\max} = \frac{\ln\left(\frac{k_a}{k_{el}}\right)}{k_a - k_{el}} \quad (6)$$

Inhibitor concentration available to enzyme *in vivo* ($I_{in.vivo}$). Various concentrations can be chosen e.g., unbound, maximum concentration of the inhibitor at entrance to the liver with or without consideration of free fraction. However, the maximum concentration of the inhibitor in the portal vein ($I_{in.max}$) was estimated using the following equation as previously described (Kanamitsu, Ito et al. 2000).

$$I_{in.max} = C_{\max} + \frac{D \cdot f_a \cdot k_a}{Q_h} \quad (7)$$

The value of liver blood flow rate used was 1470ml/min assuming a 70kg individual. Multiplication of equation (7) with f_u gives the maximum unbound concentration of the inhibitor at entrance to the liver. CYP3A4 inhibitors affect intestinal wall extraction, and each inhibitor's contributory effect was estimated through the following equation (Venkatakrishan and Obach, 2005).

$$\frac{F_{g.inhibitor}}{F_{g.control}} = \frac{1}{F_g + (1 - F_g) \left(\frac{CL_{int.g.inhibitor}}{CL_{int.g}} \right)} \quad (8)$$

$CL_{int.g.inhibitor} / CL_{int.g.control}$ represented the first pass intrinsic clearance, and the factor was estimated as follows (Equation 9) for competitive inhibition.

$$\frac{CL_{int.g.inhibitor}}{CL_{int.g.inhibitor}} = \frac{1}{1 + \frac{I_{invivo.g}}{K_i}} \quad (9)$$

Mechanism-based inhibition was estimated using equation (10) below.

$$\frac{CL_{int.g.inhibitor}}{CL_{int.g.inhibitor}} = \frac{1}{1 + \frac{I_{invivo.g} K_{inact}}{K_{deg rad.g} (K_i + I_{invivo.g})}} \quad (10)$$

$I_{invivo.g}$ refers to the concentration of inhibitor available to the gut wall absorption site after an oral dose. The dose for estimating the value of the term was estimated through dividing total daily dose by the frequency. $I_{invivo.g}$ was estimated using the intestinal blood flow rate of 248ml/min.

$$I_{invivo.g} = \frac{D \cdot f_a \cdot k_a}{Q_g} \quad (11)$$

Mechanism-based inhibition interaction type more complicated than competitive due to lack of knowledge with regards to the actual time the interaction starts. Table 1 below show some of the in vitro input parameters for mechanism-based inhibition.

Table 1: *In vitro* input parameters for the prediction of DDI due to mechanism-based inhibition

	CYPs	KI(μ M)	kinact (min ⁻¹)	Enzyme system	Kdegrad
Amiodarone	CYP2C8	51	0.029	HLM	0.029
Amiodarone	CYP3A4	10	0.032	HLM	0.032
Amprenavir	CYP3A4	0.34	0.59	cDNA	0.59
Azithromycin	CYP3A4	657	0.021	HLM	0.021
Clarithromycin	CYP3A4	39	0.044	HLM	0.044
Cimetidine	CYP2D6	0.03	77	cDNA	77
Diltiazem	CYP3A4	3.3	0.07	HLM	0.07
Erythromycin	CYP3A4	14	0.025	HLM	0.025
Fluoxetine	CYP3A4	12.8	0.037	HLM	0.037
Isoniazid	CYP1A2	285	0.11	HLM	0.11
Isoniazid	CYP2C19	112	0.09	HLM	0.09
Isoniazid	CYP2C8	170	0.12	HLM	0.12
Isoniazid	CYP3A4	228	0.08	HLM	0.08
Mibefradil	CYP3A4	2.3	0.4	HLM	0.4
Nelfinavir	CYP3A4	1	0.22	HLM	0.22
Paroxetine	CYP2D6	4.9	0.17	HLM	0.17
Ritonavir	CYP3A4	0.17	0.4	HLM	0.4
Saquinavir	CYP3A4	0.65	0.26	HLM	0.26
Saquinavir	CYP2C19	87	0.192	cDNA	0.192
Troleandomycin	CYP3A4	0.08	0.027	HLM	0.027
Verapamil	CYP2C8	18	0.065	cDNA	0.065
Verapamil	CYP3A4	4.2	0.092	HLM	0.092

3.5 Assumptions

The value of K_i was equated to half the IC_{50} . The following assumptions were made in order to simplify extrapolation of *in vitro* to *in vivo* drug-drug interaction:

- for competitive inhibition if K_m equals to substrate concentration
- The fold increase in exposure of the affected drug is related to K_i , $I_{in,vivo}$ and the fraction of clearance of the affected drug that occurs via metabolism of the inhibited CYP (f_m, f_h)
- Equal enzyme activity for either *in vitro* or *in vivo*

- Fraction absorbed (f_a) was assumed to be 1 for rapidly absorbed drugs. In cases where the values were published, factors considered were: dosage form; manufacturer; study population (age groups)
- All the estimation of the fold increase exposure of the affected drug were made assuming a 70kg individual

3.6 System development

The pharmacoinformatic tool was developed in stages.

a) System analysis and design

The design of the system was initially done on paper with all the relevant stages and data processing outlined clearly (Appendix 3). Two windows based databases were evaluated at least for appropriateness in handling data, robustness, and compatibility with user interface. The databases were Microsoft Access (MS-Access) and Standard Query language (SQL) 2000. Predictions of *in vivo* drug-drug interactions were first evaluated in Microsoft excel. A simple and robust pharmaco-informatic tool was proposed. An approximation was made that developing of the software was going to take 3 months.

b) Development

Collected data was added into the corresponding tables developed in SQL server 2000. Each table had a unique identifier, the key. Depending on the need, tables were linked together through creation of fields that contain same data e.g., the table with drugs' common profiles had each drug assigned a numerical value which was then linked to its

available dosage forms under the table with different fields of dosage forms. This process was done through utilization of SQL commands. The databases architecture created allowed addition, retrieval, storage, and database back up among other features anticipated in all commercial software. The user interface was created using *DELPHI 6.0* which was also the programming language. The database server and the user interface were linked through a data link utility.

Drug-drug interactions were predicted using the code shown under appendix 4 through the use of *in vitro* data in the database. The code also links interface for DDI prediction and patient medical record. The published fold increase in exposure of affected drug were stored in the database and retrieved when relevant combinations of drugs were tested for interaction. In the software, linking of clinically significant concentration dependant adverse drug reactions was not performed, and there was no correlation between predicted DDI with pharmacodynamic activity and effects.

3.7 Pilot study to determine the feasibility, usability of using this novel tool among potential users

The medical relevance of the tool was tested on selected 10 pharmacists and 10 doctors. A questionnaire shown below comprised of 22 items to be completed by the user was used to evaluate the medical relevance of the software. Each item had a maximum worst score of 6 points.



UNIVERSITY OF ZIMBABWE – SCHOOL OF PHARMACY

Purpose: Evaluation of AiBST-Pharmacoinformatic software

Profession: Medical doctor ☐ Pharmacist ☐ Sector: Public ☐ Private ☐

Years in Practice..... Gender: Male ☐ Female ☐

Respond to the following questions / items listed in the table below. In the appropriate box, enter a number between 1 and 6 (i.e. 1.2.3.4.5.6) where:

1: Excellent 2: Very Good 3: Good 4: Inadequate 5: Poor 6: Unacceptable

Item	Score
Easy installation	
Compatibility with PCs	
Use of login password	
Presentation of user interface	
Easy selection and addition of drug(s)	
Use of pre-loaded drug pictures (packs or tablets)	
Relevance of details under following pages:	
Product image	
Composition	
Details	
Enzymes	
Parameters	
Drug-drug interaction warning	
Scientific understanding of drug-drug interaction mechanism	
Relevance of (1) "Graph" page & easy navigation	
(2) Abstract(s)	
Integration of Patient medical record	
Patient information captured	
Easy navigation / user friendliness	
Encourage interaction with patient(s)	
Application in:	
Private Practice	
Public practice	
Academia (Scientific understanding of drug-drug interaction mechanism and prediction)	

Before evaluation of the software by either a doctor or a pharmacist, a demonstration of how to use the software was conducted. Each evaluator was allowed to navigate through the software until ready to complete the questionnaire.

3.8 Statistical calculations

Geometric Mean-fold error (GMFE) calculation was used as a measure of bias (Equation 12), and

$$GMFE = 10^{\frac{1}{number} \sum \left| \log \left(\frac{Estimated}{Actual} \right) \right|} \quad (12)$$

The Randomised Mean Square Error (RMSE) was used as a measure of precision (Equation 13).

$$RMSE = \sqrt{\frac{\sum (Estimated - Actual)^2}{Number}} \quad (13)$$

where '*Estimated*' represents the predicted *in vivo* magnitude increase in the exposure of the affected drug, '*Actual*' represents the weighted average of the reported exposure, and '*Number*' for the number of predictions under consideration.

It is also important to realize that all the parameter values were weighted based on the number of observations.

4. RESULTS

A total of 20 tables were used to link *in vitro* and *in vivo* data per drug were developed in SQL 2000. A total of 6 tables were used to develop patient medical record. Two main pages (operation mode and academic mode) each nested with sub-pages were developed as user interfaces. The “operational mode” is where the user can add/delete some oral patient details i.e. capturing patient’s medical data. The “academic mode” is where the user can have a more detailed description of the mechanism behind DDI, and can also add or delete drugs, read abstracts and navigate to other relevant pages.

The software can be run on WINDOWS 1998 and above but is still being optimised for VISTA and Windows 7. It is compatible with most antivirus software. Distribution and Installation of the software is through a CD or USB. The Software had been developed in such a way that it does not interfere with other operating programs. However, to run the software, SQL server 2000 (or above) must first be installed on the machine. SQL server 2000 run well with WINDOWS XP system and has shown not be compatible with WINDOWS 7 and WINDOWS VISTA. It is also anticipated that most of the work is now done through intra-network. Installation can either be a standalone application or networked via the client server. Data back-up is encouraged because the tool has no automated functionality to do so. When the user logs in to the system, a default page appears, the only difference from Figure 4 below is that, the small popped up windows where the physician or pharmacist captures drugs and dosage details will not be displayed, the pop-up can only be prompted by the user when capturing drugs.

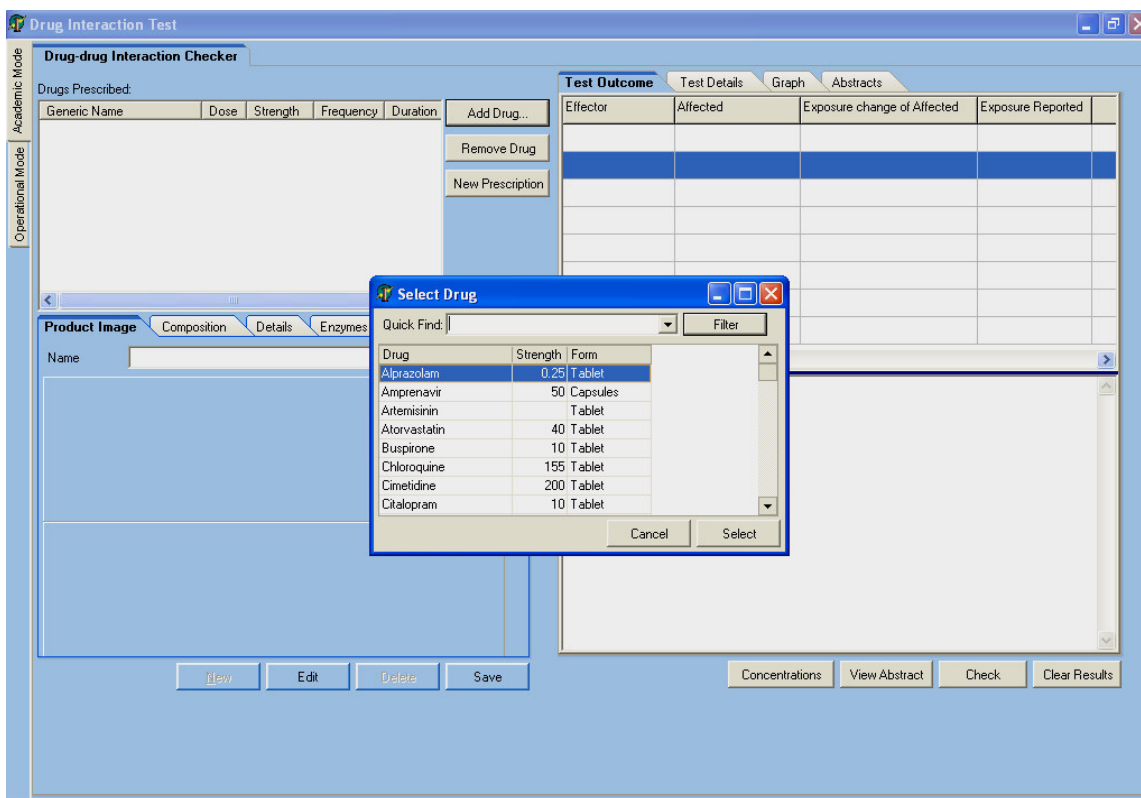


Figure 4: An illustration of the screen from the pharmacoinformatic tool that appears during drug prescription

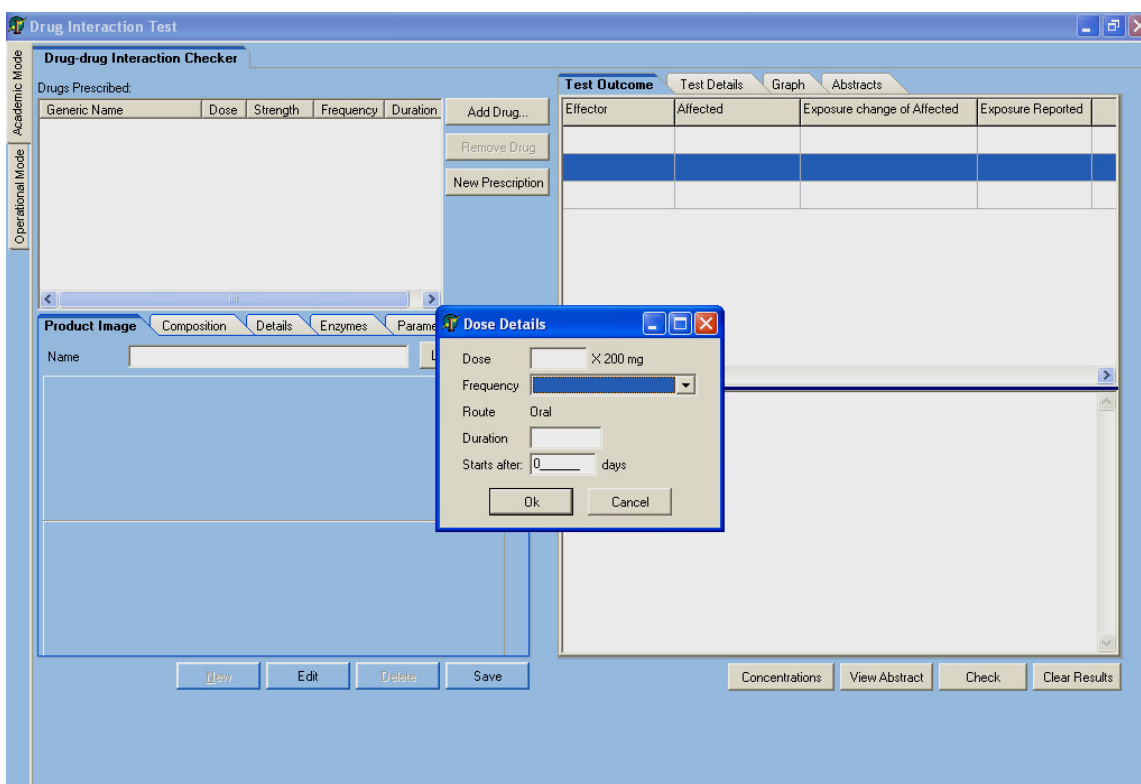


Figure 5: An illustration of the screen from the pharmacoinformatic that appears during capturing of dosage details

During routine drug prescription or dispensing by doctors and pharmacist respectively, when the button “add” drug is clicked, a small pop-up window appears (Figure 4) where a drug of choice is selected. After selecting a drug, a small pop-up window displays (Figure 5) so that the user can capture dosage details. The procedure applies when adding other drugs. When at least two potentially interacting drugs are prescribed, a warning is given (Figure 6) followed by a detailed description of interaction (Figure 7). The interaction is one-to-many. This means, interaction will be tested on all the drugs already prescribed. The pair in which we have major interactions will be shown in test outcome table. Details of interactions of the added drug with the drug already prescribed can be

retrieved through clicking page header, test details, which is next to page header - test outcome. Evaluation of different inhibitor concentration was also done to come up with the one that give better prediction on the fold increase in exposure of affected drug were compared with *in vivo* published data (Figure 8). Figure 9 shows difference fold-increase in exposure of affected drug predicted using different concentrations of inhibitor. Each published *in vivo* data was captured as an abstract and weighted mean of exposure change were used for comparison (Figure 10, abstract page).

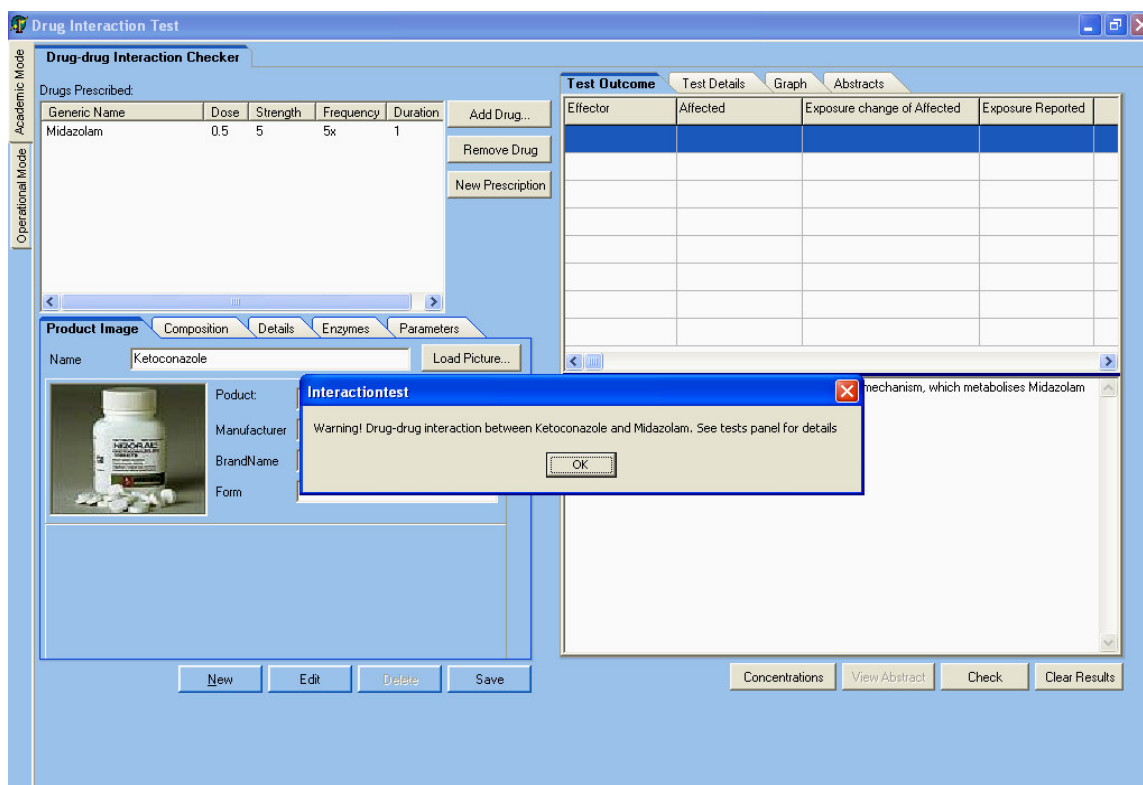


Figure 6: An illustration of a warning given when two potentially interacting drugs are given together

Quantitative predictions of DDIs through *in vitro* to *in vivo* extrapolation for different CYPs are listed in the tables 2-6. Data shown on table 7 summaries different changes in exposure for different substrates and inhibitors through mechanism-based enzyme

inactivation is considered. These predictions had under predicted the AUC fold increase when estimated through competitive *in vitro* to *in vivo* extrapolation method.

Drug Interaction Test

Drugs Prescribed:

Generic Name	Dose	Strength	Frequency	Duration
Midazolam	1	5	5x	1
Ketoconazole	1	200	OD	7

Product Image (Ketoconazole)

Name: Ketoconazole

Product: Nizoral

Manufacturer: Janssen Pharmaceutica

BrandName: Nizoral

Form: 0

Test Outcome

Effector	Affected	Exposure change of Affected	Exposure Reported
Ketoconazole	Midazolam	8.5821	8

Ketoconazole inhibits enzyme 3A4, through Competitive mechanism, which metabolises Midazolam. This results in predicted 8.5821 times increase in exposure of Midazolam and increased severity of side effects. You may possibly use alternative to Ketoconazole, adjust the dose of Midazolam, or change the route of Midazolam. Alternatives for Ketoconazole are: Fluconazole, Itraconazole.

Figure 7: A page that details mechanism of interaction, fold-increase in exposure of affected drug

4.1 CYP1A2 inhibition

Summarised data for this enzyme inhibition is shown in table 2. The interaction with fluvoxamine, which caused interaction of more than two fold, was well predicted from *in vitro* data (Table 2). The only possibility was through the use of maximum concentration at entrance to the liver ignoring protein binding.

Table 2: Summary of predictions of DDI for CYP1A2 under competitive e inhibition

				Predictions of fold increase in exposure of substrate using different concentration values				
Inhibitor	$K_i(\mu m)$	fu	substrate	C_{max}	$fu.C_{max}$	$I_{in,max}$	$fu. I_{in,max}$	Published*
Disulfiram	0.65	0.04	Theophylline	3.90	1.38	4.02	1.44	1.44
Fluoxetine	120	0.05	Clozapine	1.03	1.00	1.03	1.00	1.58
Fluvoxamine	0.018	0.23	Theophylline	4.21	2.93	4.40	3.26	3.33
Ketoconazole	12.5	0.01	Theophylline	1.09	1.00	3.76	1.12	1.11
Nefazodone	26	0.009	Theophylline	1.42	1.00	1.43	1.00	0.97
Paroxetine	4.2	0.05	Clozapine	2.21	1.26	2.23	1.27	1.31
Propranolol	8.5	0.1	Theophylline	4.09	2.00	4.18	2.12	2.08
Sertraline	6.5	0.02	Clozapine	2.39	1.31	2.40	1.33	1.3
Terbinafine	6.0	0.01	Theophylline	1.65	1.01	2.56	1.03	1.16
Ticlopidine	5.5	0.02	Theophylline	4.56	1.56	4.59	1.59	1.58

*Mean fold change in exposure of affected drug that has been published.

4.2 CYP2C9 Inhibition

Very few drugs were evaluated because most of the drugs lack published *in vivo* data to compare against. All the inhibitors tested caused less than two fold predicted increase in the exposure of the affected substrate.

4.3 CYP2C19 Inhibition

Just like CYP2C9 inhibitors, most of the drugs are not shown in table 5 due to the reasons highlighted above. Fluconazole and ticlopidine were predicted to cause more than two fold change in exposure of omeprazole. These two drugs inhibit more than one CYP.

Table 3: Summary of predictions of DDI for CYP2C9 under competitive inhibition

				Predictions of fold increase in exposure of substrate using different concentration values				
Inhibitor	$K_i(\mu\text{M})$	fu	substrate	C_{max}	$fu.C_{\text{max}}$	$I_{\text{in.max}}$	$fu. I_{\text{in.max}}$	Published*
Dicumarol	0.11	0.0025	Tolbutamide	1.82	1.71	1.82	1.71	1.76
Disulfiram	0.48	0.04	Tolbutamide	1.04	1.00	1.05	1.00	0.99
Fluvoxamine	3.05	0.23	Tolbutamide	1.68	1.44	1.72	1.51	1.50
Ketoconazole	2.95	0.01	Tolbutamide	1.69	1.01	2.11	1.02	1.77
Sertraline	40.5	0.02	Tolbutamide	1.01	1.00	1.04	1.00	1.19

Table 4: Summary of predictions of DDI for CYP2C19 under competitive inhibition

				Predictions of fold increase in exposure of substrate using different concentration values				
Inhibitor	$K_i(\mu\text{M})$	fu	substrate	C_{max}	$fu.C_{\text{max}}$	$I_{\text{in.max}}$	$fu. I_{\text{in.max}}$	Published*
Fluconazole	2.8	0.89	Omeprazole	6.33	6.25	6.47	6.33	6.29
Ketoconazole	4.7	0.01	Omeprazole	6.53	1.30	6.78	1.40	1.36
Moclobemide	80	0.5	Omeprazole	2.63	1.93	2.71	1.98	1.96
Ticlopidine ^a	0.39	0.02	Omeprazole	7.43	3.21	7.45	3.32	3.39

*Mean fold change in exposure of affected drug that has been published.

^a Can also show mechanism based inactivation of CYP2C19

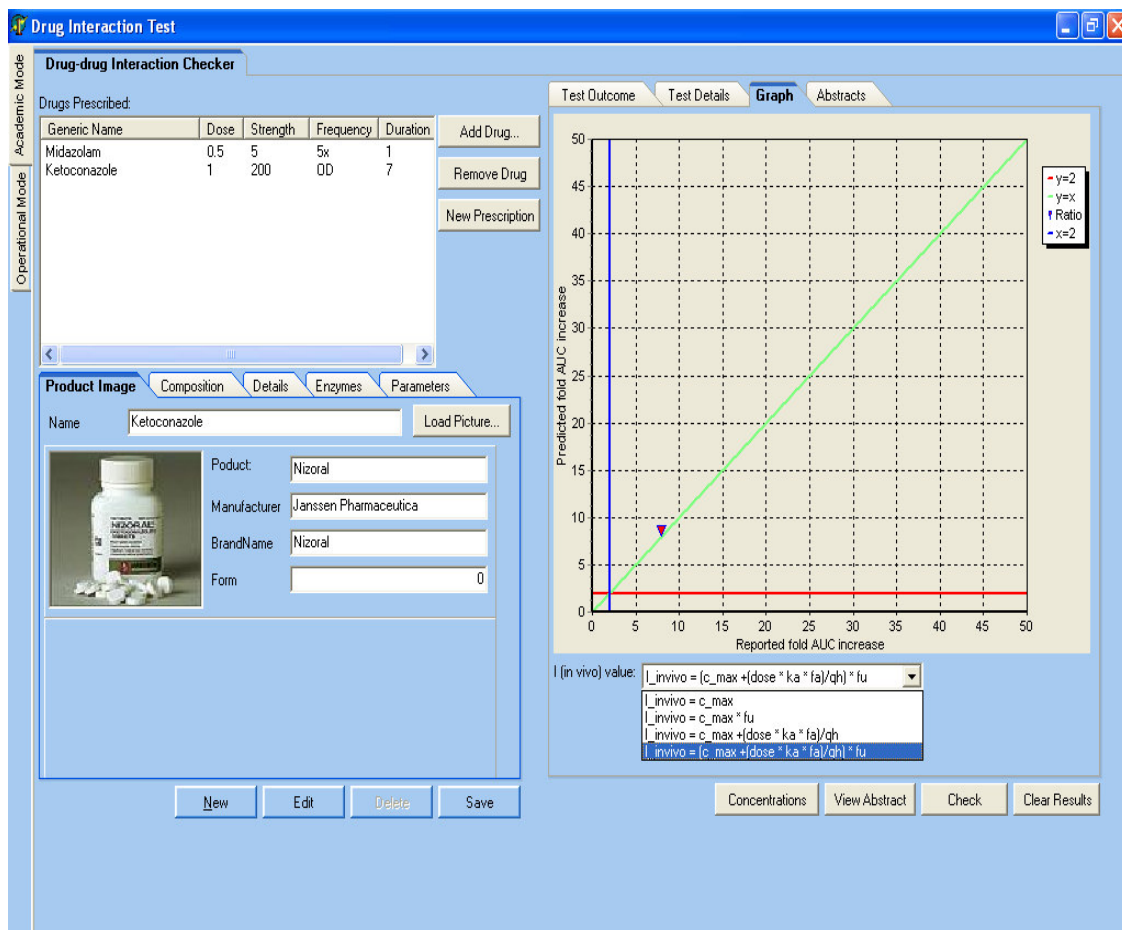


Figure 8: Illustration of how different inhibitor concentrations can be analyzed and their corresponding effect on the accuracy of prediction

4.4 CYP2D6 inhibition

Out of the 12 drugs shown (Table 6), 4 are antimalarials. This again points out the importance of this enzyme with regards to the African population where antiparasitic drugs are commonly administered together with other drugs cleared via hepatic pathway with CYP2D6 playing a major role. Terbinafine was predicted to cause highest effect on substrates ahead of quinidine. Even though this was not expected, the reason could be related to the determination of *in vitro* K_i , which were calculated estimates from different studies.

Table 5: Summary of predictions of DDI for CYP2D6 under competitive inhibition

				Predictions of fold increase in exposure of substrate using different concentration values				
Inhibitor	$K_i(\mu\text{M})$	f_u	substrate	C_{max}	$f_u \cdot C_{\text{max}}$	$I_{\text{in.max}}$	$f_u \cdot I_{\text{in.max}}$	Published*
Cimetidine ^a	65	0.79	Desipramine	1.43	1.34	1.69	1.56	1.56
Citalopram	15	0.2	Desipramine	2.58	1.37	2.75	1.44	1.50
Diphenhydramine	6	0.22	Metoprolol	2.76	1.59	2.83	1.63	1.61
Diltiazem	150	0.22	Metoprolol	2.13	1.32	2.15	1.33	1.33
Disulfiram	6	0.04	Desipramine	4.98	1.28	5.32	1.32	1.32
Fluoxetine	0.135	0.05	Desipramine	9.95	9.22	9.96	9.22	10.1
Fluvoxamine	2.6	0.23	Desipramine	1.47	1.11	1.64	1.16	1.14
Ketoconazole	14	0.01	Desipramine	2.38	1.02	2.74	1.02	1.02
Paroxetine ^a	0.16	0.05	Desipramine	9.09	3.78	9.13	3.85	5.21
Quinidine	0.029	0.13	Desipramine	8.87	5.27	9.40	6.81	6.70
Sertraline	0.9	0.02	Desipramine	7.88	1.55	8.03	1.60	1.54
Terbinafine	0.021	0.01	Desipramine	9.86	4.45	9.88	5.00	4.90

*Mean fold change in exposure of affected drug that has been published.

^a Can also show mechanism based inactivation of CYP2D6

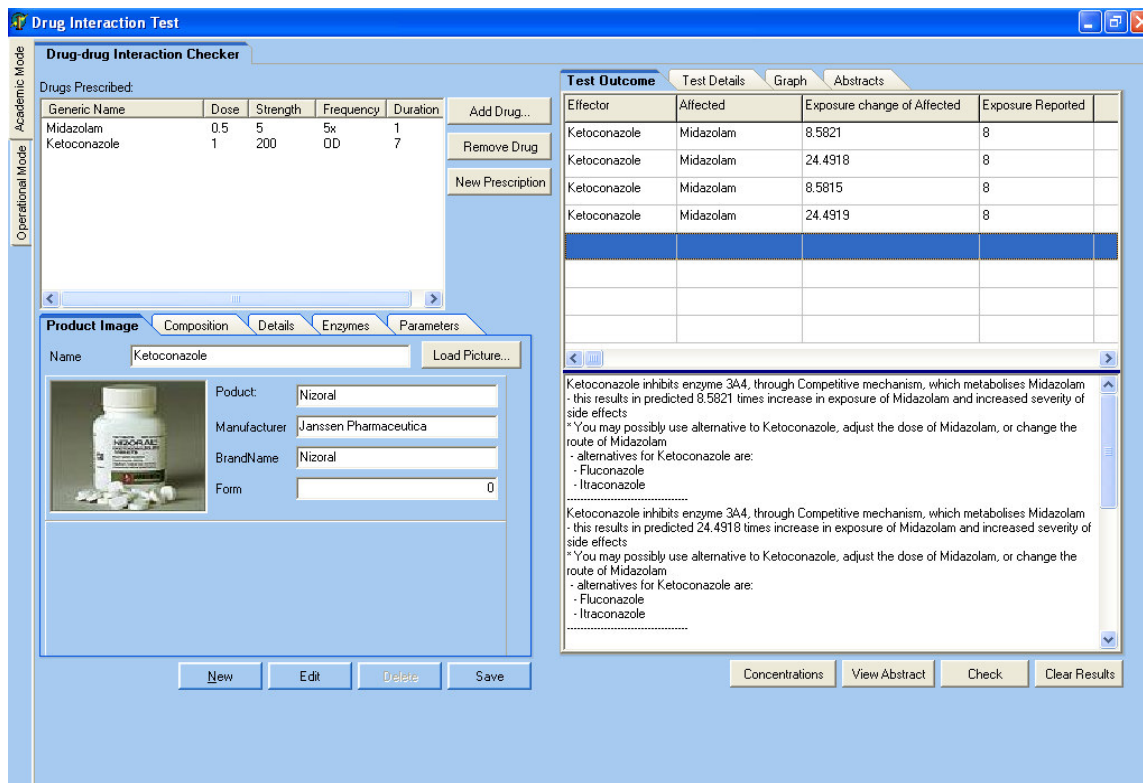


Figure 9: Different fold increase in exposure of affected drug due to different inhibitor concentrations

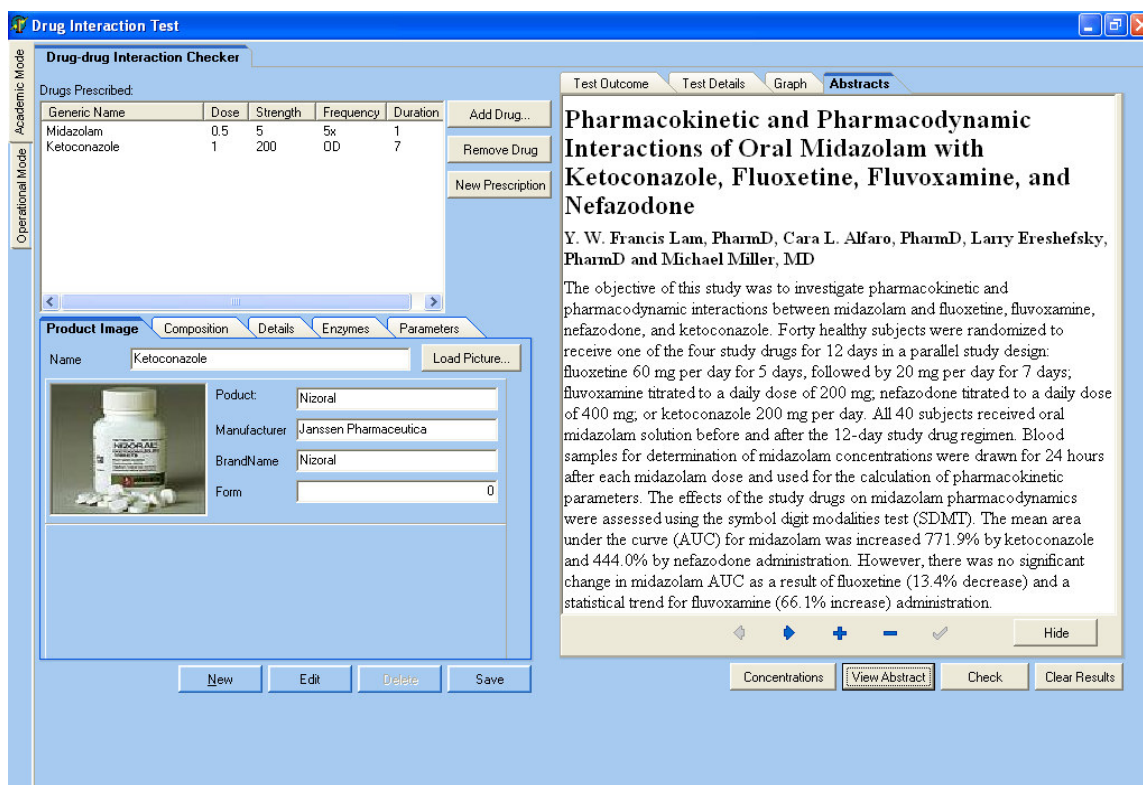


Figure 10: A page that shows a retrieved referenced abstract of *in vivo* drug-drug interaction and fold changes in exposure of affected drug

4.5 CYP3A4 inhibition

This was estimated to be the most abundant enzyme. It is a high capacity and low affinity enzyme. Expectations are that, most the known DDIs emanate from CYP3A4 involvement. Table 6 summarises the predicted fold increase in AUC of affected drugs. Almost all the drugs used were estimated to cause more than two-fold increase in exposure of corresponding substrates. This makes CYP3A4 and other isoenzymes under CYP3A highly prioritized for characterization in the field of clinical biochemistry. The most potent inhibitor of CYP3A4 was ritonavir which was predicted to cause more than 20 fold under competitive inhibition.

Table 6: Summary of predictions of DDI for CYP3A4 under competitive inhibition

				Predictions of fold increase in exposure of substrate using different concentration values				
Inhibitor	$K_i(\mu\text{M})$	f_u	substrate	C_{max}	$f_u \cdot C_{\text{max}}$	$I_{\text{in.max}}$	$f_u \cdot I_{\text{in.max}}$	Published*
Azithromycin ^a	30	0.12	Midazolam	1.12	1.11	1.12	1.11	1.27
Diltiazem ^a	30	0.22	Buspirone	5.55	4.73	5.57	4.73	5.33
Disulfiram	1.8	0.04	Midazolam	2.48	1.78	2.60	1.79	5.44
Erythromycin ^a	8	0.16	Buspirone	8.55	5.36	9.29	5.48	5.91
Fluconazole	3.4	0.89	Midazolam	3.76	3.53	3.89	3.65	3.30
Fluoxetine ^a	8	0.05	Alprazolam	2.89	1.31	2.89	1.31	1.32
Fluvoxamine	14	0.23	Buspirone	2.44	2.44	2.44	2.44	2.40
Itraconazole	0.01	0.002	Buspirone	272	6.00	425	12.38	19.2
Ketoconazole	0.06	0.01	Midazolam	28.24	7.50	28.48	8.90	8.77
Paroxetine	0.085	0.05	Alprazolam	1.11	1.02	1.11	1.02	0.99
Ritonavir ^a	0.037	0.015	Triazolam	19.41	12.33	19.42	12.5	20.3
Saquinavir ^a	0.255	0.02	Midazolam	22.58	4.11	23.2	4.39	5.17
Verapamil ^a	11.5	0.1	Midazolam	2.29	1.74	2.29	1.74	2.91

*Mean fold change in exposure of affected drug that has been published.

^a Can also show mechanism based inactivation of CY3A4

Table 7: Fold increase in the exposure of the substrate in the presence of inhibitor for Mechanism-based inhibitor

			Predictions of fold increase in exposure of substrate using steady state concentrations	
Inhibitor	CYP	substrate	C_{max}	<i>fu</i>.C_{max,u}
Azithromycin	CYP3A4	Midazolam	1.86	1.28
Cimetidine	CYP2D6	Metoprolol	2.3	1.54
Diltiazem	CYP3A4	Buspirone	18.0	8.0
Erythromycin	CYP3A4	Buspirone	11	5.3
Fluoxetine	CYP3A4	Alprazolam	3.2	1.98
Paroxetine	CYP2D6	Desipramine	6.4	4.1
Ritonavir	CYP3A4	Triazolam	20	20
Saquinavir	CYP3A4	Midazolam	5.8	9.3
Ticlopidine	CYP2C19	Omeprazole	7.4	3.6
Verapamil	CYP3A4	Midazolam	19	6.6

Table 8: Summarized comparison of accuracy and bias of drug-drug interaction prediction methods using different inhibitor concentrations

Enzyme	Different concentrations	GMFE ^a	RMSE ^b
CYP1A2	C_{\max}	1.86	1.81
	$fu.C_{\max}$	0.95	0.46
	$I_{in.\max}$	1.55	1.50
	$fu. I_{in.\max}$	0.76	0.19
CYP2C9	C_{\max}	1.05	1.06
	$fu.C_{\max}$	0.83	1.08
	$I_{in.\max}$	0.98	1.04
	$fu. I_{in.\max}$	0.82	0.44
CYP2C19	C_{\max}	1.99	3.41
	$fu.C_{\max}$	1.01	0.10
	$I_{in.\max}$	1.94	3.30
	$fu. I_{in.\max}$	0.60	0.05
CYP2D6	C_{\max}	1.90	7.057
	$fu.C_{\max}$	0.97	1.585
	$I_{in.\max}$	1.80	6.67
	$fu. I_{in.\max}$	0.60	1.16
CYP3A4	C_{\max}	1.16	112.8
	$fu.C_{\max}$	0.80	4.447
	$I_{in.\max}$	1.53	70.50
	$fu. I_{in.\max}$	0.71	2.14

Table 9: The overall comparison of accuracy and bias of drug-drug interaction prediction methods using different inhibitor concentrations

Enzyme	Different concentrations	GMFE ^a	RMSE ^b
Without MBI consideration	C_{\max}	0.89	2.28
	$fu.C_{\max}$	1.52	7.77
	$I_{in.\max}$	0.93	5.85
	$fu. I_{in.\max}$	0.68	3.13
MBI considered	C_{\max}	0.73	2.01
	$fu.C_{\max}$	0.49	1.71

^a Geometric mean fold error for measuring bias

^b Randomised mean square error for measuring precision

4.6 Evaluation of the software by medical doctors and pharmacists

The software had acceptable scores in most critical and relevant items shown in the questionnaire under methodology. As shown in figure 11 below which indicates a combined responses from doctors and pharmacists, if a threshold 10 is applied on responses, the tool had high numbers in very good/good scores for application in academia and private practice, easy navigation / user friendliness, and relevance in scientific understanding of drug-drug interaction mechanism. Encouragingly, only “good” to “excellent” scores were noted on integration of presentation of user interface, integration of patient medical record, and easy selection and addition of drugs. Excellent scores had high frequency on the use of abstracts, relevance of drug-drug interaction warning. However, unacceptable scores had high frequency in details captured under composition page and product image. Other items were evaluated with mixed responses.

The responses evaluators were also categorised. Figure 12 show responses from pharmacist and figure 13 show responses from medical doctors. Using a cut-off in response of 5, most items had almost similar scores. However, pharmacist had higher frequencies than medical doctors in recommending the application of the tool in academia and private practice, details captured under “Enzymes” and “Details” page within the software. Differences in opinions were also reflected in the use of abstracts, use of login password, presentation user interface and use of drug pictures

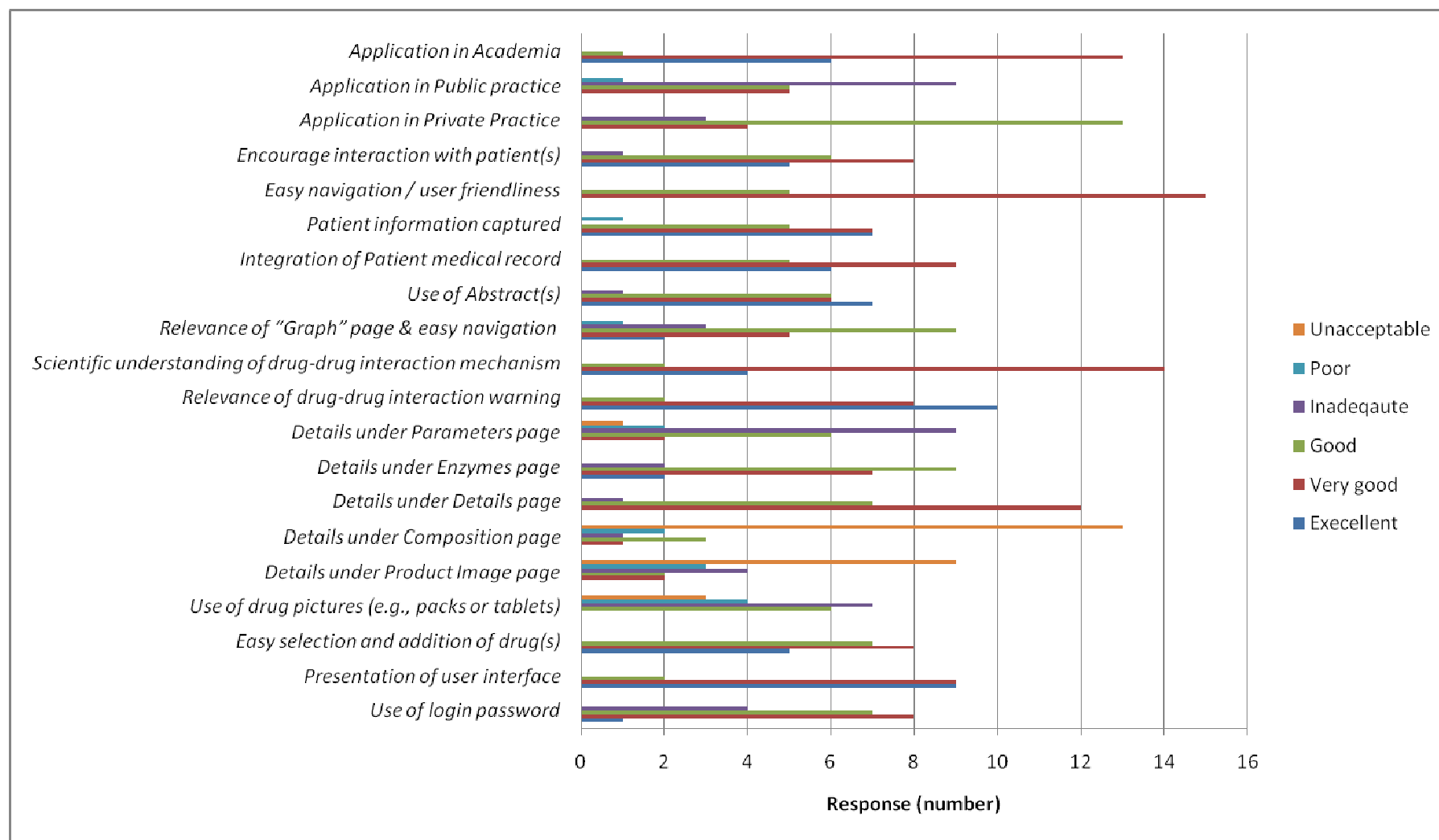


Figure 11: Overall response of software evaluation by 10 medical doctors and 10 pharmacists

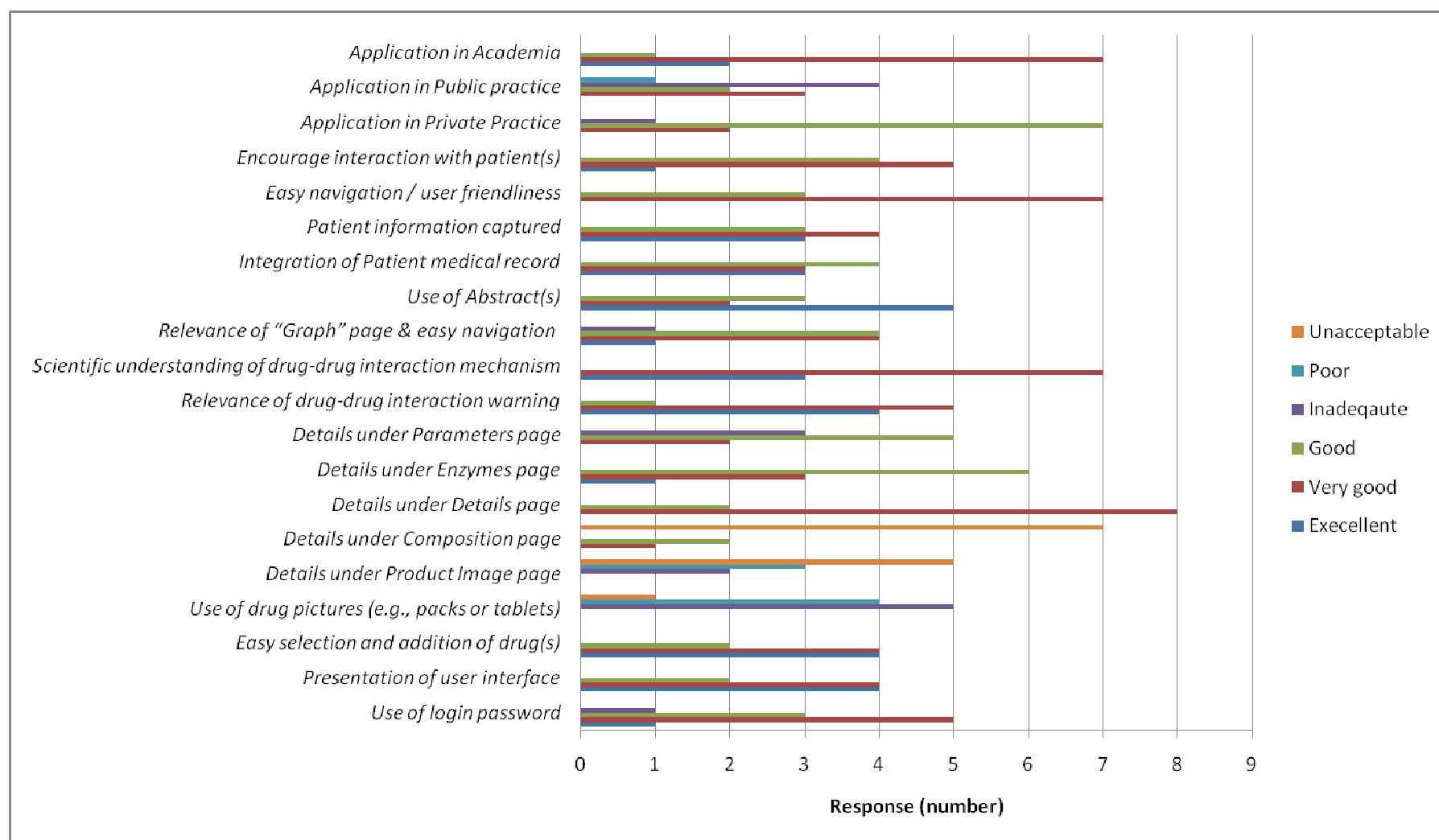


Figure 12: Response of software evaluation by 10 pharmacists from either public or private sector

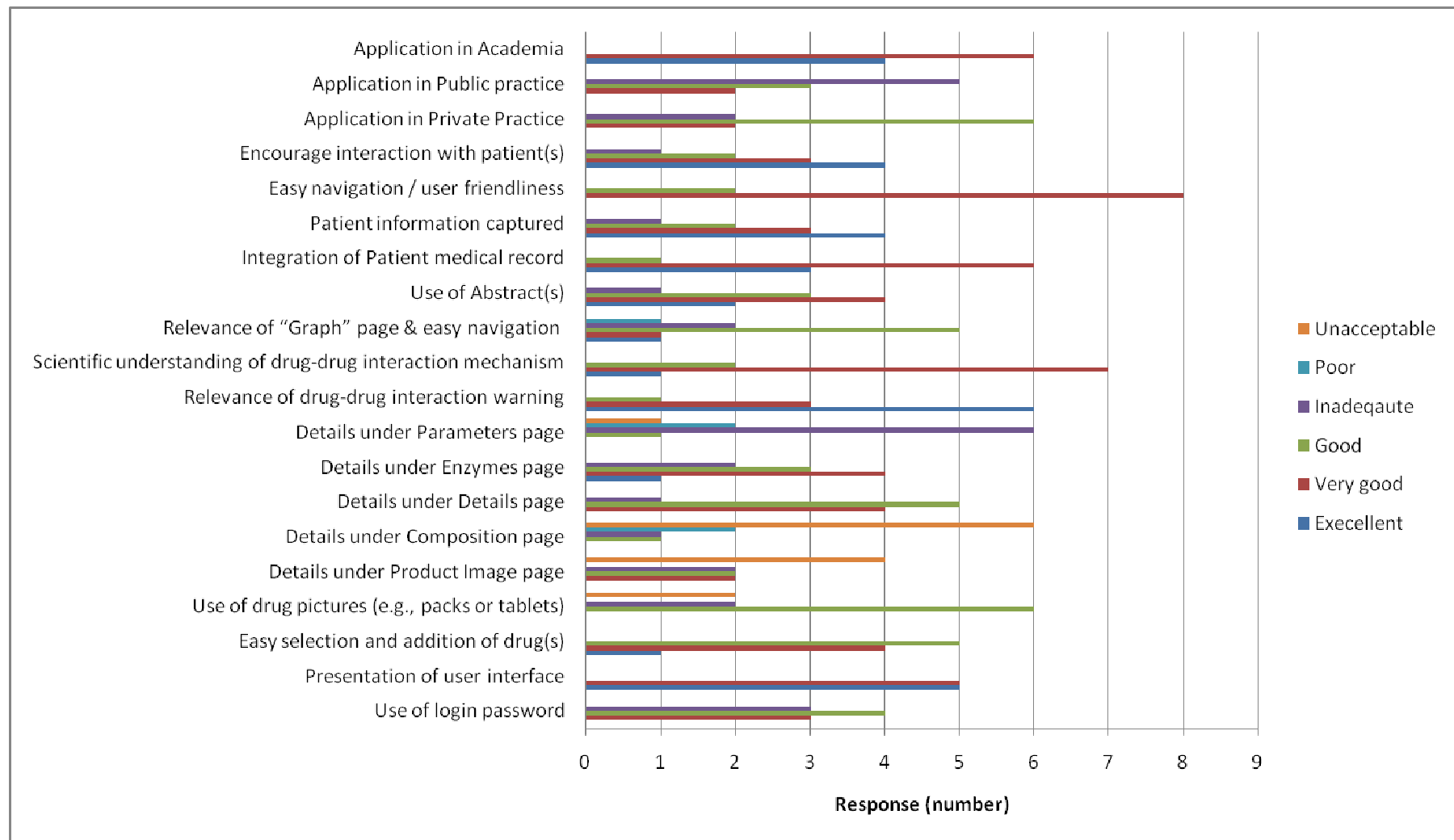


Figure 13: Response of software evaluation by 10 medical medical from either public or private sector or both

5. DISCUSSION

The In vitro In vivo extrapolation (IVIVE) field has received great attention and various modeling software have emerged over the past few years due to its potential to predict, detect and minimize potential DDIs in the drug discovery, development and clinical use value chain even though a considerable number of DDIs are detected when the drug is already on market. Existence of various approaches to IVIVE marked the success of this predictive industry.

Software which focuses on population pharmacokinetics has been gaining popularity due to its success, SimCyp® (SimCyp Limited). The software utilizes *in vitro* data then extrapolates to the intrinsic enzyme activity through *in vivo* through various scaling factors : microsomal protein per gram of human liver (MPPGL) or (Hepatocellularity per gram of liver (HPGL) then to human liver weight (Proctor, Tucker et al. 2004). However, SimCyp® is mainly suitable for drug discovery and early phases of clinical trials. With this ability, it has gained wider application in various pharmaceutical industries.

Pharsight, like SimCyp Limited, developed its clinical trials simulator which predicts the outcome of clinical trials on the basis of data obtained from early *in vivo* studies and on disease progression. However, although this proved to be a powerful vehicle for linking pharmacokinetic outcomes to pharmacodynamic outcomes in virtual populations, it lacked the ability to incorporate fundamental *in vitro* information on drug metabolism and enzymology in building such populations.

All the above two software however do not process the drug discovery data into something sensible to physicians who are closer to the beneficiary, the patient.

5.1 How the tool operates

In this work, the main focus was on the clinical application rather than early phases of drug discovery. Even though a bigger study is yet to be done to test the user friendliness and acceptability of our tool, savings in time to access DDI data, relevance of warnings and adoption of recommendations are already self-evident. Evaluation by doctors and pharmacists showed a positive result. Operation of the software doesn't require wide knowledge and expertise in computers, though basic literacy is important. Information retrieval can simply be done through clicking page headers. When the physician or pharmacist logs on in the software, during addition of prescription drugs, dosage details are captured through a small activated window as shown in figure 4 and figure 5. Because the user can make mistakes, which is common in the medical field (Marschner, Thurmann et al. 1994; Gurwitz, Field et al. 2005), the captured details are shown on the left corner of the page output allowing for quick and easy editing.

If more than one drug is captured and there is a potential for interaction, an intercepting warning message displayed (Figure 6). This is an important function because it alerts the physician who would otherwise fail to recognize the message if it is shelved or highlighted on other parts of the interface. The message is followed by a description of mechanism of interaction, alternative drugs and approaches, and the interacting drugs coupled with the fold increase in the exposure of the affected drug (Figure 7). Displaying of alternative drugs is based on the magnitude of increase in exposure of affected drug

(substrate) due to the effector drug (inhibitor). Detection and minimization of potential DDIs is extremely important in patient care since it reduces chances of adverse drug reactions and events which have been demonstrated to cause ADR, death and in increased health care costs (Gurwitz, Field et al. 2000; Vincent 2001). The use of this tool is hoped to lead to improved interaction between doctors and pharmacists when potential DDIs have been detected in order to give correct drug doses and/or drug combinations to patients.

Following the recommendations reached after evaluation of our software, the user can also learn how the interaction varies with change in inhibitor concentration as illustrated in figure 9 through the use of drop down menus. This also educates users on the possibility of underprediction or overprediction when protein binding is taken or not taken into account for the various models. The tool will therefore be responsive to the ongoing advances in research where the role of drug transporters could be important for making better and successful DDI predictions.

5.2 Estimation of fold increase in exposure of substrates

The predictive capability of previously described mathematical models and algorithms for IVIVE of DDIs resulting from competitive enzyme inhibition has been demonstrated in this investigation for different CYPs as shown in various tables (Table 2-6). Table 7 shows predictions when considering mechanism-based inhibition type. It is important to note that the accuracy of prediction of an IVIVE drug–drug interaction is critically hinged upon the value of the *in vivo* inhibitor concentration, K_i , the fraction of substrate

metabolized *in vivo* as previously shown from various equations under methodology. Determination of concentration at the enzyme active site is impossible.

Many attempts are being made to estimate the drug concentration within the liver, with varying degrees of success (Brown, Ito et al. 2005; Galetin, Burt et al. 2006). Recent studies and as indicated in our prediction tool, show that better predictive accuracy and precision was achieved when the unbound concentration of the inhibitor entering the liver from the portal vein was used. This was confirmed in this study where low geometric mean-fold error and randomized mean-square error was observed with maximum concentration at entrance to the liver (Table 8 and 9). We have therefore used the unbound plasma concentration as a default concentration for calculations for competitive inhibition. However, this was different from the recommended steady-state plasma concentration (Tucker 2000) when evaluating mechanism-based inactivation. The selection or use of K_i values derived from *in vitro* experiments poses some problems as well. The mechanism of enzyme inhibition, non-competitive or competitive does not matter in cases where the substrate concentration is much lower than the K_m value. The predictions are fairly comparable regardless of concentration used. However, the experimental K_i may vary depending upon the nature of the *in vitro* system used, e.g. human liver microsomes versus heterologous expression systems (Rodrigues, Winchell et al. 2001). Microsomal protein concentration, which affects microsomal protein binding, is a determinant of the apparent inhibitory potency of CYP inhibitors, at least CYP3A inhibitors (Tran, Von Moltke et al. 2002). Disparities due to the use of heterologous expression systems can be corrected through the use of relative activity factors as recommended in other studies.

Estimation of DDI for CYP3A4 was associated with low accuracy compared to results of other enzymes. Inclusion of intestinal wall metabolism is hoped to improve the predictive accuracy. Another possible explanation could be the accurate and precise determination of K_i values. CYP3A4 has multiple binding arrangements for different inhibitors and K_i values for a single inhibitor may vary by more than 10-fold, depending upon the substrate used (Kenworthy, Bloomer et al. 1999). Carefully structured *in vitro* studies with more than one substrate found no mutual inhibition of CYP3A4 when combinations of nifedipine, midazolam, felodipine, and testosterone were used simultaneously (Galetin, Clarke et al. 2003). Clearly, the failure to account for atypical kinetics in *in vitro* experiments could give rise to wrong K_i values. In addition, the *in vitro* systems mostly used were the human liver microsomes (HLMs). These systems contain all the enzymes. Low inhibitory activity for azithromycin could be due to its metabolism by CYP3A4 even though it inhibits the same enzyme in a time-dependant manner. It is also important to note that CYP3A activities measured in human liver microsomes comprise of CYP3A4 and CYP3A5, and a clear understanding of the contribution of each in pooled human liver microsomes is not yet available. The presence of CYP3A4 in the intestine and this tissue has been demonstrated to contribute a substantial portion to first-pass extraction of some CYP3A-cleared drugs. The previous methods employed for predicting drug interactions from *in vitro* data for the other P450 enzymes only considered the liver. However, the *in vivo* probe substrates midazolam, triazolam, alprazolam, and buspirone all have different relative contributions of gut and liver to exposure after oral administration. The effect of inhibitors on CYP3A in the intestine has been included for substrates which undergo considerable intestinal metabolism after oral administration.

Likewise, failure to acknowledge the occurrence of mechanism-based inhibition could lead to errors in the prediction of the AUC ratio and risk of DDIs. For this type of interaction, the unbound maximum plasma concentration is favoured and has been thoroughly discussed elsewhere (Obach, Walsky et al. 2007). The results of MBI (Table 7) were estimated using steady-state plasma concentration following previous recommendations (Tucker 2000).

The harnessing of the growing field of information technology into various disciplines has gained recognition and popularity over the past decades. Large amounts of data generated in the medical fraternity from drug discovery to clinical practice often leaves physicians with a tough task to handle. It is documented that only a small percentage of clinically relevant data that is churned is utilized during routine practice (Grol and Grimshaw 2003). A number of decision support systems have been developed to match the increase in the amount of data although it calls for a well articulated plan and distinct leadership to achieve success. Most medical informatic tools available are mainly to capture and analyse patient medical data. The few that capture drug-drug interactions act as electronic version of the hard copies and have been shown to be medically useful in minimising medication errors (Bates, Cohen et al. 2001).

Under normal circumstances, patients can either send a relative or a child to purchase medications on their behalf, it becomes difficult for a pharmacist to know the drugs the patient might also be taking in addition to the one being dispensed. With this in mind, pharmacist may not be able to detect potential drug-drug interaction. So the best targets

were doctors who came face to face with the patient during disease diagnosis and subsequent drug prescription.

5.3 Acceptability of the tool

The results from the pilot study were quite encouraging. The tool scored high points in most relevance sections which includes relevance of warnings and references, scientific understanding mechanisms behind drug interaction, user friendliness and presentation of user interface. The tool had highest recommendation for application in academia. Its application in both private and public practice was fair. The lower scores for application in public practice could be due to inadequate number of drugs uploaded so far, which may not be suitable during routine practice. The tool had unacceptable scores in the use of drug pictures, details captured under “Composition” page which calls for improvement in the next version of the software.

Of interest was categorizing responses based on profession. Pharmacist had higher frequencies than medical doctors in recommending the application of the tool in academia and private practice, details captured under “Enzymes” and “Details” page within the software which highlights differences in preferences in practice. In addition, high number of pharmacists gave “excellent” scores on the use of abstracts than doctors highlighting their academic desire, and is in agreement with their recommendation for the application of the tool. On the other hand doctors favour the use of login passwords which reflects the need to protect patient data and privacy.

6. CONCLUSION

In conclusion, the tool has the potential to quantitatively predict potential DDIs and could be used by pharmacists and doctors in minimization of potential DDIs based adverse drug reactions, and as a teaching tool. The tool has been accepted in all critical areas, but needs modifications in few items such as details captured under product composition. More drugs used routinely need to be added and a high sample size evaluation of relevance and acceptability conducted. The predictive capacity had low levels of bias when the concentration of inhibitor was set at the unbound maximum concentration at entrance to the liver enzymes. The overall GMFE was 0.684. Supporting the same observation was the measure of predictive precision, RMSE, with overall rating of 3.125. However, efforts to correct for microsomal binding were not attempted in this study but could have a bearing on the accuracy of predictions of DDI for some compound classes. More work needs to be done to include DDIs due to induction and irreversible enzyme inhibition or through inhibition of other enzymes not considered in this study.

Summary list

What was known before our work

- The qualitative and quantitative nature of drug-drug interaction.
- The contribution of drug prescription error to adverse drug events.
- Need for simple, reliable and easily accessible drug interaction databases.

Contribution of our work

- The continued need for simple computer-based decision support systems with ability to predict potential interaction among given combinations of drugs at clinical level.
- Clinical decision support systems with functions on how the decision is reached help in teaching physicians and pharmacist on how to detect potential drug-drug interaction and this improves their knowledge.
- Assistance in picking alternative drugs during drug prescription minimises the trial-and-error approach, and saves time.
- Electronic systems which enable clinicians to easily access published scientific data improve interaction between researchers and medical personnel.

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APPENDIX 1: Different drugs (as inhibitors) that were used in the evaluation of the mathematical algorithm

Drug	Inhibited enzyme	K_i (μM)	K_a(per min)	C_{max}(μM)
Amiodarone	CYP2D6	52.7	0.1	0.037
	CYP3A4	47	0.1	0.037
Amprenavir	CYP3A4		0.07	0.2
Amitriptylline	CYP2D6	4	0.018	0.036
Azithromycin	CYP3A4	30	0.06	0.12
Buspirone	CYP2B6		0.024	0.05
	CYP2C19	13	0.024	0.05
	CYP2D6	28	0.024	0.05
	CYP3A4	29.5	0.024	0.05
Chloroquine	CYP2D6	12.68	0.1	0.39
Chlorpheniramine	CYP2D6	25.6	0.014	0.28
Chlorpromazine	CYP2D6	4.8	0.039	0.02
Cimetidine	CYP2D6	40	0.011	0.79
	CYP3A4	115	0.011	0.79
Ciprofloxacin	CYP1A2	150	0.003	0.8
Citalopram	CYP2D6	15	0.1	0.2
Clarithromycin	CYP3A4	29.5	0.1	0.3
Codeine	CYP3A4	276	0.1	0.93
Cyclosporine	CYP3A4	7	0.1	0.07
Dapsone	CYP2E1	4	0.018	0.3
Dicumarol	CYP2C9	0.105	0.1	0.0025
Diltiazem	CYP3A4	58	0.1	0.22
Diphenhydramine	CYP2D6	6	0.1	0.22
Disulfiram	CYP1A2	0.65	0.1	0.04
	CYP2C9	0.48	0.1	0.04
	CYP2C19	2.75	0.1	0.04
	CYP2D6	6	0.1	0.04
	CYP3A4	1.8	0.1	0.04
Erythromycin	CYP3A4	77	0.054	0.16
Fluconazole	CYP2C9	5.5	0.056	0.89
	CYP2C19	2.9	0.056	0.89
	CYP3A4	8	0.056	0.89
Fluoxetine	CYP2D6	0.405	0.088	0.05
	CYP3A4	8	0.088	0.05
Fluvoxamine	CYP2C9	3.05	0.1	0.23
	CYP2C19	0.175	0.1	0.23
	CYP3A4	14	0.1	0.23
Indinavir	CYP3A4	0.17		0.39
Isoniazid	CYP2C19	25.4	0.1	0.9
	CYP2D6	126	0.1	0.9
	CYP2E1	110	0.1	0.9
	CYP3A4	51.8	0.1	0.9

Drug	Inhibited enzyme	K_i (μM)	K_a (per min)	C_{max}(μM)
Itraconazole	CYP3A4	0.01	0.014	0.002
Ketoconazole	CYP2C9	2.95	0.011	0.01
	CYP2C19	4.7	0.011	0.01
	CYP3A4	0.006	0.011	0.01
Mefloquine	CYP2C8	4	0.1	0.02
Moclobemide	CYP2C19	80	0.015	0.5
Nefazodone	CYP2C9	8.5	0.015	0.009
	CYP3A4	0.45	0.015	0.009
Nelfinavir	CYP3A4	0.085	0.1	0.015
Omeprazole	CYP3A4	34.2	0.1	0.05
Paroxetine	CYP2C9	65	0.01	0.05
	CYP2C19	11	0.01	0.05
	CYP2D6	0.505	0.01	0.05
	CYP3A4	8.5	0.01	0.05
Primaquine	CYP1A2	0.22	0.024	0.45
Proguanil	CYP2D6	6.67	0.014	0.25
Propoxyphene	CYP3A4	36	0.026	0.24
Propranolol	CYP3A4	70	0.03	0.1
Quinidine	CYP2D6	0.009	0.016	0.13
	CYP3A4	29	0.016	0.13
Quinine	CYP2D6	15.51	0.042	0.19
Ranitidine	CYP3A4	170	0.022	0.85
Repaglinide	CYP3A4	60	0.1	0.026
Risperidone	CYP2C19	145	0.05	0.11
	CYP2D6	6	0.05	0.11
Ritonavir	CYP3A4	0.0037	0.095	0.015
Roxithromycin	CYP3A4	34	0.03	0.14
Saquinavir	CYP3A4	0.26	0.043	0.02
Sertraline	CYP2C9	40.5	0.0077	0.02
	CYP2D6	0.9	0.0077	0.02
	CYP3A4	4.3	0.0077	0.02
Simvastatin	CYP3A4	0.385	0.1	0.05
Terbinafine	CYP2D6	0.021	0.03	0.01
Thiabendazole	CYP1A2	1.54	0.012	24
Ticlopidine	CYP2C9	55	0.1	0.02
	CYP2C19	0.39	0.1	0.02
Verapamil	CYP2D6	16	0.1	0.1
	CYP3A4	11.5	0.1	0.1

APPENDIX 2: Substrate Drugs with determined metabolic pathways and predicted CYP isoenzyme contribution

Drug name	CYPs	fm	fh	Fgut
Alprazolam	CYP3A4	0.8	0.9	0.99
Amodiaquine	CYP2C8	1	0.99	
Amprenavir	CYP3A4	1	0.9	ND
Azithromycin	CYP3A4	1	0.35	ND
Artemisinin	CYP2B6	0.24	0.5	
	CYP2D6	0.16	0.5	
	CYP3A4	0.6	0.5	ND
Busipirone	CYP3A4	1	0.99	0.21
Chloroquine	CYP2C8	0.45	0.5	
	CYP2D6	0.44	0.5	
	CYP3A4	0.11	0.5	ND
Cisapride	CYP3A4	1	0.95	ND
Clarithromycin	CYP3A4	1	0.7	ND
Clozapine	CYP1A2	1	0.6	
Cyclosporine	CYP3A4	1	0.71	0.39
Codeine	CYP2D6	0.1	0.9	
Dapsone	CYP2C8	0.095	0.85	
	CYP2C9	0.46	0.85	
	CYP2C19	0.11	0.85	
	CYP2D6	0.04	0.85	
	CYP3A4	0.295	0.85	ND
Desipramine	CYP2D6	1	0.9	
Indinavir	CYP3A4	1	0.8	ND
Itraconazole	CYP3A4	0.8	0.8	ND
Ketoconazole	CYP3A4	0.8	0.9	ND
Metoprolol	CYP2D6	1	0.8	
Midazolam	CYP3A4	1	0.94	0.57
Omeprazole	CYP2C19	1	0.87	
Nelfinavir	CYP3A4	1	0.2	ND
Nifedipine	CYP3A4	1	0.71	0.74
Praziquantel	CYP1A2	0.45	0.9	
	CYP2C19	0.17	0.9	
	CYP3A4	0.36	0.9	ND
Quinidine	CYP3A4	1	0.76	0.9
Quinine	CYP2C19	0.05	0.8	
	CYP3A4	0.95	0.8	ND
Saquinavir	CYP3A4	1	0.9	ND
Theophylline	CYP1A2	1	0.8	
Thiabendazole	CYP1A2	1	0.5	
Tolbutamide	CYP2C9	1	0.45	
Triazolam	CYP3A4	1	0.92	0.64

Key: ND – not determined

APPENDIX 3: Working instructions

Working instruction: pilot software in excel

Overview

The overall goal of the project is to develop software which predicts potential drug-drug interactions. There are quite a number of mechanisms of drug-drug interactions but the focus in this work is on interaction due to inhibition of enzyme activity i.e if you give a drug (substrate) that is cleared from the human body by CYP3A4 together with a drug (inhibitor) that stops activity of CYP3A4, it means the duration of effect and the amount of substrate builds up. The way to achieve this is through the use pharmacokinetic algorithms i.e pharmacokinetic equations to predict the relative increase in exposure of affected. So the outputs are digits or general numbers

Questions:

1. What is the fold increase in exposure of affected drug much is the exposure of substrate increases?
2. How close are the estimates from published data?

Overall aim

To develop a software and test its acceptability by clinicians for the prediction of potential drug-drug interaction (bear in mind that we are only accounting for one mechanism, it is the starting point)

Logical flow (User)

1. The user **log in** to the software
2. Get to the default user interface with brief instructions of how to get started
3. Add **one drug** from the list of **inhibitors**
 - Dose of inhibitor is required
 - The frequency is required i.e How many mg per day e.g. 500 mg per day

4. Combine it with **one drug** from the list of **substrates** making a total of **two drugs** in the panel
 - Note that some drugs can appear as both substrates and inhibitors
5. After clicking the interaction button, the user gets a drug-drug interaction prediction results based on the equations below (to be described in detail in the following sections)
 - There will be **four** results from the prediction, these will be due to different values for concentrations of inhibitor (to be highlighted in detail later)
 - All the predictions for the increase in exposure should be in **tabular form** e.g

Inhibitor drug	Concentration used (these should be four and ranked according to the one close to change published	Affected drug	Change published	Reference (on click should lead to stored abstracts)

6. The user should also get a message which details the mechanism of interaction
 - There are two possibilities for the inhibition of enzymes.
 - There is **mechanism based inhibition and competitive inhibition**. Other drugs may show both mechanisms while others its only one which is dominant.

- The user needs prediction from all the mechanisms, all **two** only applies to drugs which have two mechanisms otherwise **one mechanism and four corresponding concentrations (four rows)**
 - For drugs with more than one mechanism, its **two mechanisms and four corresponding concentrations for each mechanism (8 rows) will be displayed**
7. The user will have a section which **details the possible mechanisms** of enzyme inhibition based on the prediction **very close to the published data**. E.g. Drug A is a competitive inhibitor of CYP3A4 therefore combining it with drug B results in *(figure wanted from predicted exposure close to published data / reference I,e rank predictions based on which one will be close to published data)* fold in exposure on substrate (*name?*) drug
8. Finally the user needs to do a little tricks here
- To be able **to plot** predicted versus published changes in exposure
 - Can be in a position to chose either of the concentration four different ones
 - One concentration and one matching mechanism
 - Plot all mechanisms for drugs with two mechanisms or one mechanism for drug with one mechanism **refer 7 above**

How the calculation comes about

The model was applicable to all other CYPs **except CYP3A4**, which means under CYP on SUBS sheet and CYP_CIH / CYP_MBI from PK sheet, do not use the equations if you see CYP3A4 on the rows. From the equation below, the two left parts are a representation of exposure change. **The following only applies for inhibited enzymes under CYP_CIH (from sheetPK)**

$$\frac{CL_{control}}{CL_{inhibitor}} = \frac{AUC_{inhibitor}}{AUC_{control}} = \frac{1}{\frac{f_{m(sheetSUBS)} \times f_{h(sheetSUBS)}}{\left(1 + \frac{Conc_{inhibitor}}{K_{i(sheetPK)}}\right)} + 1 - f_m \times f_h}$$

It is important to note that the same enzyme which is inhibited is the same enzyme which metabolize the substrate e.g. if you open sheet SUBS you find a column CYP which contains the cyp isoenzyme that metabolises the drug under sheet SUBS. The corresponding **fm** and **fh** are from the same sheet (**sheetSUBS**) for the same drug. Take this one.... **Clozapine vs Amiodarone**

1. Sheet SUBS contains Clozapine under field drug
2. Its corresponding fm and fm are also there for corresponding CYP1A2
3. Sheet PK contains Amiodarone which inhibits CYP1A2 and the mechanism is under CYP_CIH (**therefore the above equation holds**)
4. and there are field for the **four CONC** for Amiodarone under PK. replace Conc with

- cmax
- fu_cmax
- in_cmax
- fu_in_cmax

To demonstrate how the interaction is tested for mechanism based inhibition (MBI) **except for CYP3A4 is done**

Take this one.... **Clozapine vs isoniazid**

5. Sheet SUBS contains Clozapine under field drug

6. Its corresponding f_m and f_h are also there for corresponding CYP1A2
7. Sheet PK contains isoniazid which inhibits CYP1A2 and the mechanism is under CYP_MBI (**therefore the following equation holds**)
8. and there are field for the **four CONC.** replace Conc with

- c_{max}
- fu_{cmax}
- in_{cmax}
- $fu_{in_{cmax}}$

$$\frac{CL_{control}}{CL_{inhibitor}} = \frac{AUC_{inhibitor}}{AUC_{control}} = \frac{1}{\frac{f_{m(sheetSUBS)} \times f_{h(sheetSUBS)}}{\left(1 + \frac{K_{inact(sheetPK)} \times Conc_{inhibitor}}{(KI_{(sheetPK)} + Conc_{inhibitor}) \times K_{deg\ rad.\ hep(sheetPK)}}\right)} + 1 - f_m \times f_h}$$

Interactions involving CYP3A4

The first thing is to look at competitive mechanism CYP_CIH under PK and if the same enzyme appears under SUBS and PK

Take this**Alprazolam and ketoconazole**

9. Sheet SUBS contains alprazolam under field drug
10. Its corresponding **f_m** and **f_h** are also there for corresponding **CYP3A4** and **Fgut**
11. Sheet PK contains ketoconazole which inhibits CYP3A4 via competitive mechanism which is under CYP_CIH

First calculate Fg_ratio using the following equation:

$$\frac{F_{g.inhibitor}}{F_{g.control}} = \frac{1}{F_{gut (sheetSUBS)} + (1 - F_{gut (sheetSUBS)}) \times gratio_{SheetPK}}$$

Then use the following equation for AUC or % exposure increase

$$\frac{CL_{control}}{CL_{inhibitor}} = \frac{AUC_{inhibitor}}{AUC_{control}} = \frac{F_{g.inhibitor}}{F_{g.control}} \times \frac{1}{\frac{f_m \times f_h}{\left(1 + \frac{Conc_{inhibitor}}{K_i}\right)} + 1 - f_m \cdot f_h}$$

12. and there are field for the **four CONC** for ketoconazole under PK. replace Conc with

- cmax
- fu_cmax
- in_cmax
- fu_in_cmax

if the mechanism is mechanism based inhibition (MBI)

The first thing is to look at MBI, CYP_MBI under PK and if the same enzyme appears under SUBS and PK

Take this**midazolam and verapamil**

13. Sheet SUBS contains midazolam under field drug

14. Its corresponding **fm** and **fm** are also there for corresponding **CYP3A4** and **Fgut**

15. Sheet PK contains verapamil which inhibits CYP3A4 via mechanism based inhibition which is under CYP_MBI

First calculate Fg_ratio using the following equation:

$$\frac{F_{g.inhibitor}}{F_{g.control}} = \frac{1}{F_{gut(sheetSUBS)} + (1 - F_{gut(sheetSUBS)}) \times mratio_{SheetPK}}$$

Then use the following equation for AUC or % exposure increase

$$\frac{CL_{control}}{CL_{inhibitor}} = \frac{AUC_{inhibitor}}{AUC_{control}} = \frac{F_{g.inhibitor}}{F_{g.control}} \times \frac{1}{\frac{f_m \cdot f_h}{\left(1 + \frac{Conc_{inhibitor}}{K_i}\right)} + 1 - f_m \cdot f_h}$$

16. and there are field for the **four CONC** for ketoconazole under PK. replace Conc with

- cmax
- fu_cmax
- in_cmax
- fu_In_max

APPENDIX 4: Code for the final software

```
unit PharmObjects;
```

```
interface
```

```
uses FDataStructures, ADODB, dialogs, SysUtils, Controls, StdCtrls, math;
```

```
type
```

```
PRealArray = array of Currency;
```

```
P2DRealMatrix = array of PRealArray;
```

```
PExposure = class(TObject)
```

```
private
```

```
value: single;
```

```
mechanism,
```

```
enzyme: shortString;
```

```
protected
```

```
public
```

```
procedure setValue(v: single);
```

```
procedure setMechanism(m: shortString);
```

```
procedure setEnzyme(e: shortString);
```

```
function getValue(): single;
```

```
function getValueAsString(): shortString;
```

```
function getMechanism(): shortString;
```

```
function getEnzyme(): shortString;
```

```
published
```

```
end;
```

```
PDrug = class(FComparable)
```

```
private
```

```
concentrations_done: boolean;
```

```
cp_cb,
```

```
C_ss,
```

```
C_max,
```

```
QG,
```

```
FU,
```

```
KA,
```

```
FA,
```

```
QH,
```

```
dose,
```

```
RMM,
```

```
DefaultStrength,
```

```
F,
```

```
V,
```

```

CL,
ExposureDecrease,
startHour,
RegimenStartHour: single;
duration,
frequency,
compoundID: integer;
T_half,
T_max,
StrengthUnit,
DosageForm,
Bioavailability,
Precautions,
Name,
SideEffects: string;

function I_inVivo(which: smallint): single;
function concentration(time_hr: single; ed: boolean): single;

protected

public
matrix :P2DRealMatrix;
concentrations: FOrderedList;
Strength,
divideBy: single;
inhibitingEnzymes, metabolisingEnzymes, inducedEnzymes: FOrderedList;
procedure doConcMatrix();
constructor create(proc, inhibited, induced, metabo: TADOStoredProc);
function getStrength(): single;
function getT_half(): string;
function getT_max(): string;
function getCp_cb(): single;
function getC_ss(): single;
function getC_max(): single;
function getQg(): single;
function getFu(): single;
function getKa(): single;
function getFa(): single;
function getQh(): single;
function getCl(): single;
function getV(): single;
function getF(): single;
function getExposureDecrease(): single;
function getStrengthunit(): string;
function getDosageform(): string;
function getBioavailability(): string;
function getPrecautions(): string;

```



```

function getName(): string;
function getSideEffects(): string;
function getDuration(): integer;
function getFrequency(): integer;
function getStartHour(): single;
function getCompoundID(): integer;
procedure setCompoundID(id: integer);
function getRegStartHour(): single;
procedure setRegStartHour(i: single);
procedure setStartHour(i: single);
procedure setExposureDecrease(ed: single);
procedure setDuration(i: integer);
procedure setFrequency(i: integer);
procedure setDose(d: single);
function getDose(): single;
function exposure(d2: PDrug; control: TWinControl; InVivo, mechanism: integer):
PExposure;
function induction_ratio(): single;
function clearance_ratio(d2: PDrug): single;
function gut_inhibition_ratio(d2: PDrug): single;
procedure extractFromProc(proc, inhibited, induced, metabo: TADOStoredProc);
function concentrationAt(time_hr: single): single;
function getConcentrations(): FOrderedList;
published

end;

PEnzymeInduced = class(FComparable)
private
protected

public
    AutoID,
    DrugID: integer;
    EnzymeName,
    Notes: string;
    Fraction: single;
    E_max,
    EC_50: single;
    constructor create(proc: TADOStoredProc);
    procedure extractFrom(proc: TADOStoredProc);
published

end;

PEnzymeInhibited = class(FComparable)
private
protected

```

```

public
  AutoID,
  DrugID: integer;
  EnzymeName,
  Notes: string;
  InhibitionMechanism: integer;
  InhibitionMechanismName: string;
  Fraction,
  K_I,
  K_e,
  K_inact,
  K_i: single;
  constructor create(proc: TADOStoredProc);
  procedure extractFrom(proc: TADOStoredProc);
published

```

```

end;

```

```

PEnzymeMetabolised = class(FComparable)

```

```

private
protected
public
  AutoID,
  DrugID: integer;
  FG,
  FH,
  FM: single;
  InhibitionMechanism: integer;
  EnzymeName,
  InhibitionMechanismName: string;
  constructor create(proc: TADOStoredProc);
  procedure extractFrom(proc: TADOStoredProc);
published

```

```

end;

```

```

PDrugCompound = class(FComparable)

```

```

private
  drugs: FOrderedList;
  dose: single;
  route: smallint;
  routeName: shortString;
  duration,
  frequency,
  start_hr: integer;
protected

```

```

public
  dispensableID: integer;
  compoundID: integer;
  constructor create(ado: TADOStoredProc);
  function extractFrom(ado: TADOStoredProc): boolean;
  function getDrugs(): FOrderedList;
  function getDrug(ix: integer): PDrug;
  procedure setDose(d: single);
  function getDose(): single;
  function getRoute(): smallint;
  function getRouteName(): shortString;
  procedure setRoute(r: smallint; rn: shortString);
  procedure setDuration(d: integer);
  procedure setStart(d: integer);
  procedure setFrequency(d: integer);
  function getDuration(): integer;
  function getStart(): integer;
  function getFrequency(): integer;
  function exposure(cmp: PDrugCompound; inVivoWhich: smallint): single;
published

```

```

end;

```

```

PRegimen = class(FComparable)

```

```

private

```

```

  start_hr: single;

```

```

  concentrations_done: boolean;

```

```

protected

```

```

public

```

```

  drugs,

```

```

  concentrations: FOrderedList;

```

```

  constructor create();

```

```

  function concentrationAt(hour: single): single;

```

```

  function getStartHour(): single;

```

```

  procedure doConc();

```

```

  procedure add(drug: PDrug);

```

```

published

```

```

end;

```

```

PPrescription = class(FComparable)

```

```

private

```

```

  compounds,

```

```

  regimens: FOrderedList;

```

```

  patientID: integer;

```

```

  matrix: P2DRealMatrix;

```

```

  timeDivision: single;

```

```

PrescriptionID: integer;
procedure conc(left, right, top: integer; drug: PDrug; ed: boolean);
protected

public
  constructor create();
  procedure configRegs();
  function getCompounds(): FOrderedList;
  function getCompound(i: integer): PDrugCompound;
  function getRegimens(): FOrderedList;
  function getRegimen(i: integer): PRegimen;
  function getRegimenByID(i: integer): PRegimen;
  function getPatientID(): integer;
  procedure setPatientID(i: integer);
  function exposure(drg1, drg2: PDrug): single; overload;
  function exposure(cmp1, cmp2: PDrugCompound; inVivoWhich: smallint): single;
overload;
  function interacts(d: PDrugCompound): integer; //returns number of drugs in
    //prescription which interact with d
  function concentrations(): P2DRealMatrix;
  function getPrescriptionID(): integer;
  procedure setPrescriptionID(i: integer);
  procedure add(comp: PDrugCompound);
published

end;

implementation
{* class PEnzymeInduced *
  constructor PEnzymeInduced.create(proc: TADOStoredProc);
  begin
    extractFrom(proc);
  end;

  procedure PEnzymeInduced.extractFrom(proc: TADOStoredProc);
  begin
    AutoID := proc.FieldByName('AutoID').AsInteger;
    DrugID := proc.FieldByName('DrugID').AsInteger;
    Fraction := proc.FieldByName('Fraction').value;
    EnzymeName := proc.FieldByName('ScienceName').AsString;
    Notes := proc.FieldByName('Notes').AsString;
    E_max := proc.FieldByName('E_max').value;
    EC_50 := proc.FieldByName('EC_50').value;
  end;
{* end of class PEnzymeInduced *

{* class PInhibitedEnzyme *
  constructor PEnzymeInhibited.create(proc: TADOStoredProc);

```

```

begin
    extractFrom(proc);
end;

procedure PEnzymeInhibited.extractFrom(proc: TADOStoredProc);
begin
    //EnzymeInhibited := proc.FieldByName('EnzymeInhibited').value;
    DrugID := proc.FieldByName('DrugID').AsInteger;
    Fraction := proc.FieldByName('Fraction').AsCurrency;
    InhibitionMechanism := proc.FieldByName('InhibitionMechanism').AsInteger;
    InhibitionMechanismName
:=
proc.FieldByName('InhibitionMechanismName').value;
    EnzymeName := proc.FieldByName('ScienceName').value;
    Notes := proc.FieldByName('Notes').AsString;
    K_I := proc.FieldByName('K_I').value;
    //showMessage('K_I='+currtostr(K_I));
    K_e := proc.FieldByName('K_e').value;
    K_inact := proc.FieldByName('K_inact').value;
    K_i := proc.FieldByName('K_i').value;
end;

{* end of class PInhibitedEnzyme *}

{* class PMetabolisedEnzyme *}
constructor PEnzymeMetabolised.create(proc: TADOStoredProc);
begin
    extractFrom(proc);
end;

procedure PEnzymeMetabolised.extractFrom(proc: TADOStoredProc);
begin
    //EnzymeInhibited := proc.FieldByName('EnzymeInhibited').value;
    AutoID := proc.FieldByName('AutoID').AsInteger;
    DrugID := proc.FieldByName('DrugID').AsInteger;
    {InhibitionMechanism := proc.FieldByName('InhibitionMechanism').AsInteger;
    InhibitionMechanismName
:=
proc.FieldByName('InhibitionMechanismName').value; }
    EnzymeName := proc.FieldByName('ScienceName').value;
    //Notes := proc.FieldByName('Notes').AsString;
    FG := proc.FieldByName('FG').value;
    FH := proc.FieldByName('FH').value;
    FM := proc.FieldByName('FM').value;
end;
{* end of class PMetabolisedEnzyme *}

{* class PRegimen *}
    constructor PRegimen.create();
    begin

```

```

        drugs := FOrderedList.create(false);
        concentrations := FOrderedList.create(false);
        concentrations_done := false;
        start_hr := -1;
    end;

function PRegimen.getStartHour(): single;
begin
    result := start_hr;
end;

function PRegimen.concentrationAt(hour: single): single;
begin
    if not concentrations_done then
        doConc();
    //showMessage('regimen # of concentrations: '+inttostr(concentrations.count()));
    if concentrations.find(hour) = nil then
        Result := 0
    else
        Result := strtocurr(concentrations.find(hour).getCaption());
    end;
end;

procedure PRegimen.doConc();
var
    ix0: integer;
    hour, tempTotal, tempConc, total_hrs: single;
    more_time: boolean;
drug: PDrug;
begin
    //gets all drugs to do their concentrations, then integrates them
    if concentrations <> nil then
        concentrations.Free();
        concentrations := FOrderedList.create(false);
        hour := start_hr;
        more_time := true;
        // showMessage('doin regimen's concentrations; # start hour
        '+currtostr(hour));

        drug := PDrug(drugs.get(0));
        tempTotal := drug.concentrationAt(10);
        // showMessage('done matrix');
        total_hrs := 0; //PDrug(drugs.get(0)).concentrations.get(drug.concentrations.count()-
        1).getKey();
        for ix0 := 0 to drugs.count() -1 do begin
            //add up each drug's duration
            drug := PDrug(drugs.get(ix0));
            tempTotal := drug.concentrationAt(10);

```

```

{
    //showMessage(drug.getName()+' # of conc entries=' +
currtostr(drug.concentrations.count()));
    if total_hrs < drug.concentrations.get(drug.concentrations.count() - 1).getKey()
then}
    total_hrs := total_hrs + drug.concentrations.count();
end;

//showMessage('last hour='+currtostr(total_hrs));

{
    for ix0 := 0 to drugs.count() -1 do begin
        //add up each drug's concentration at this hour
        drug := PDrug(drugs.get(ix0));
        showMessage('drug start hour='+currtostr(drug.getStartHour()));
    end;}

    while more_time do begin
        more_time := false;
        tempTotal := 0;
        for ix0 := 0 to drugs.count() -1 do begin
            //add up each drug's concentration at this hour
            drug := PDrug(drugs.get(ix0));
            {showMessage(' drug='+ drug.getName());
            showMessage('# of concentrations in drug:
'+inttostr(drug.getConcentrations.count()));
            showMessage('hour='+currtostr(hour) +
conc='+currtostr(drug.concentrationAt(hour)));
            }tempConc := drug.concentrationAt(hour);
            tempTotal := tempTotal + tempConc;
            //if {(tempConc > 0) or }(concentrations.count() <
total_hrs) then begin
                //if hour < drug.concentrations.get(drug.concentrations.count()-1).getKey() then
begin
                    if hour < total_hrs then begin
                        more_time := true;
                    end;
                end;
                //all at this point now added up:
                concentrations.append(FComparable.create(hour,
currtostr(tempTotal)));
                //showMessage('appended conc');
                //go to next time mark:
                hour := hour + 1;
            end;
            //showMessage('done doin concentrations');

            //showMessage('# of concentrations in regimen: '+inttostr(concentrations.count()));

            concentrations_done := true;
        end;
    end;

```

```

    procedure PRegimen.add(drug: PDrug);
var
  ix0: integer;
  begin
    if (drugs.count()>0) and (drug.getKey() <> key) then
      showMessage('this drug does not belong in this regimen')
    else begin
      key := drug.getKey();
      caption := drug.getCaption();
      drugs.append(drug);
      if (start_hr<0 )or (start_hr > drug.getStartHour() * 24) then
        start_hr := drug.getStartHour() * 24;
      //announce start hour to all:
      for ix0 := 0 to drugs.count() - 1 do begin
        PDrug(drugs.get(ix0)).setRegStartHour(start_hr);
      end;
    end;
  end;
end;
{* end of class PRegimen *}

{* class PDrug *}

function PDrug.getConcentrations(): FOrderedList;
begin
  if not concentrations_done then
    doConcMatrix();
  Result := concentrations;
end;

procedure PDrug.doConcMatrix();
var
  y, x, start, steadyStateHour, compound, aDrug, start_top, start_left,
  copy_start, right: integer;
  row: PRealArray;
  tempTotal, A, k, expo, calc_KA, t, calc_CL : extended;
  ExposureDecrease, phase, t1, t2, timeDivision, v1, v2, v3: single;
  drug: PDrug;
begin
  timeDivision := 1;
  start_top := 0;
  start_left := 1;
  setLength(matrix, 0);
  right := 1;
  v1 := 0;
  v2 := 0;
  v3 := 0;

```



```

    drug := self;
    //showMessage(drug.getName + ' starts after: ' + inttostr(drug.getStartHour()) + '
hours');
    start_left := right + 1;
    start_top := 0;{ceil(drug.getStartHour() * 24 / timeDivision);}
    phase := drug.getFrequency()/timeDivision;
    steadyStateHour := ceil(4 * strtocurr(drug.getT_half()) - startHour*24)-24;
    //Initialize matrix:
    setLength(matrix, 2*ceil(drug.getDuration() * 24/timeDivision));
    for y:= 0 to length(matrix) - 1 do begin
        setLength(matrix[y], 2 + {length(matrix[y])+ } ceil(drug.getDuration()*24 *24/
drug.getFrequency()/drug.getFrequency()));
        matrix[y][0] := y;
        matrix[y][1] := 0;
        for x := 2 to length(matrix[y]) - 1 do begin
            matrix[y][x] := 0;
        end;
    end;
    //showMessage('done with matrix dimensions');

    // if t + startHour < RegimenStartHour + steadyStateHour then
    { showMessage('steadyStateHour='+currtostr(steadyStateHour)+ ' startHour='
+currtostr(startHour) + ' drug.getDuration()='currtostr(drug.getDuration()));}
    if (startHour < steadyStateHour) then begin
        right := 2 + right + floor((steadyStateHour / 24 ) * 24 / drug.getFrequency());
        if drug.getDuration() * 24 < steadyStateHour then
            right := 1 + floor(drug.getDuration() * 24 / drug.getFrequency());
        //showMessage('start_left='+inttostr(start_left)+'
start_top='+inttostr(start_top));

        //Put calculated data:
        for y:= start_top to Length(matrix) - 1 do begin
            //apply the formula:
            t := matrix[y][0]-start_top;
            matrix[y][start_left] := drug.concentration(t, false);
        end;
        //showMessage('done calcs (1)');

        //copy elementary sequence of values
        for x := start_left + 1 to right do begin
            start := start_top + ceil((x-start_left) * phase);
            copy_start := start_top;
            //showMessage('start := '+ currtostr(start));
            for y:= start to length(matrix) - 1 do begin
                matrix[y][x] := matrix[copy_start][start_left];
                copy_start := copy_start + 1;
            end;
        end;
    end;

```

```

        //showMessage('done copying (1)');
    end;

    start_left := right + 1; //start_left + round(steadyStateHour/24);
    right := length(matrix[0])-1; //start_left + ceil(drug.getDuration()*24 *24/
drug.getFrequency()/drug.getFrequency());
    if steadyStateHour<0 then
        start_top := 0
    else
        start_top := start_top + ceil(phase+ ceil((floor(steadyStateHour/phase) + 1) *
phase)/timeDivision);
    // showMessage('start_left='+inttostr(start_left)+' start_top='+inttostr(start_top));

    if( startHour + drug.getDuration() * 24 > steadyStateHour ) then begin
        //Put calculated data:
        for y:= start_top to Length(matrix) - 1 do begin
            //apply the formula:
            t := matrix[y][0]-start_top;
            matrix[y][start_left] := drug.concentration(t, true);
        end;
        //showMessage('done calcs (2)');

        //copy elementary sequence of values
        right := length(matrix[0]);
        for x := start_left + 1 to right - 1 do begin
            start := start_top + ceil((x - start_left) * phase);
            copy_start := start_top;
            //showMessage('start := '+ currtostr(start));
            for y:= start to length(matrix) - 1 do begin
                matrix[y][x] := matrix[copy_start][start_left];
                copy_start := copy_start + 1;
            end;
        end;
        //showMessage('done copying (2)');
    end;

    if concentrations <> nil then
        concentrations.Free();

        concentrations := FOrderedList.create(false);
        //showMessage('done creating concentrations');
        //add up rows
        for y:= 0 to Length(matrix) - 1 do begin
            tempTotal := 0;
            //showMessage('length(matrix[y]) = '+inttostr(length(matrix[y])));
            for x := 2 to length(matrix[y]) - 1 do begin
                // add up all in this row:
                tempTotal := tempTotal + matrix[y][x];
            end;
        end;
    end;

```

```

end;
matrix[y][1] := tempTotal;

{if matrix[y][0] < 2 then
  showMessage('conc level='+currtostr(matrix[y][1]));
}
concentrations.append(FComparable.create(matrix[y][0], currtostr(matrix[y][1]));
end;
//showMessage('done APPENDING concentrations');
//showMessage('drug start hour='+currtostr(getStartHour()));
//delete all null entries:
{showMessage('last='+concentrations.getLast().getCaption());
while strtocurr(concentrations.getLast().getCaption()) < 0.13 do
  concentrations.deleteLast();}

concentrations_done := true;
end;

function PDrug.concentrationAt(time_hr: single): single;
var
  value: FValue;
  conc_out: single;
begin
  if not concentrations_done then
    doConcMatrix();
  {if time_hr < startHour then
    Result := 0
  else begin}
    value := concentrations.find(time_hr - startHour * 24);
    if value = nil then begin
      conc_out := 0;
    end else begin
      //showMessage('conc='+value.getCaption());
      conc_out := strtocurr(value.getCaption());
    end;
  // end;
  //showMessage('[PDrug]    hour    =    '+currtostr(time_hr)+'    conc    =
'+currtostr(conc_out));
  Result := conc_out;
end;

function PDrug.concentration(time_hr: single; ed: boolean): single;
var
  y, x, start, steadyStateHour: integer;
  row: PRealArray;
  tempTotal, A, k, expo, calc_KA, calc_CL: extended;
  timeDivision : single;
begin

```

```

    expo := 1;
    calc_KA := 60 * KA; //convert to hours
    if ed then begin
        calc_CL := CL * ExposureDecrease;
    end else begin
        calc_CL := CL;
    end;

    k := (ln(2) * calc_CL/V)/expo;
    A := calc_KA * F * dose / (V * (calc_KA - k));

    {if time_hr < 3 then
        showMessage('conc level='+currtostr(A*(exp(-k * time_hr) - exp(-calc_KA *
time_hr))));
    }result := A*(exp(-k * time_hr) - exp(-calc_KA * time_hr));
end;

function PDrug.getRegStartHour(): single;
begin
    Result := RegimenStartHour;
end;

procedure PDrug.setRegStartHour(i: single);
begin
    RegimenStartHour := i;
end;

function PDrug.getDuration(): integer;
begin
    Result := duration;
end;

function PDrug.getFrequency(): integer;
begin
    Result := frequency;
end;

procedure PDrug.setDuration(i: integer);
begin
    duration := i;
end;

procedure PDrug.setFrequency(i: integer);
begin
    frequency := i;
end;

procedure PDrug.setDose(d: single);

```

```

begin
  dose := d;
end;

function PDrug.getDose(): single;
begin
  result := dose;
end;

function PDrug.getCompoundID(): integer;
begin
  result := compoundID;
end;

procedure PDrug.setCompoundID(id: integer);
begin
  compoundID := id;
end;

function PDrug.I_inVivo(which: smallint): single;
begin
  //showMessage('function InVivo: using '+inttostr(which));
  case(which) of
    0:begin
      result := dose/DefaultStrength * c_max;
    end;
    1:begin
      result := dose/DefaultStrength * c_max * fu;
    end;
    2:begin
      result := dose/DefaultStrength * c_max +(dose * ka * fa)/qh;
    end;
    3:begin
      result := ((dose/DefaultStrength * c_max) +(dose * ka * fa)/qh) * fu;
    end;
  end;
end;

function PDrug.exposure(d2: PDrug; control: TWinControl; InVivo, mechanism:
integer): PExposure;
var
  ix1, ix2, enzInhibited1, enzInhibited2, enzInduced1, enzInduced2,
  enzMetab1, enzMetab2, enzInhibited, enzInduced, enzMetab: integer;
  expo, I_in, I_g, d2_fm, d2_fh, K_I, K_inact, k_I, k_e, fg_inh, clint, fg: double;
  interaction: boolean;
  mech, enzyme, msg1, msg2: string;
  cdose: Single;
  output: PExposure;

```

```

begin
  cdose := dose*1000000/RMM;
  enzInhibited1 := -1;
  enzInhibited2 := -1;
  enzInduced1 := -1;
  enzInduced2 := -1;
  enzMetab1 := -1;
  enzMetab2 := -1;
  interaction := false;
  expo := -1; //assume no interaction
  enzyme := '';
  //Exposure(AUC'/AUC) = 1/((fh"*fm"/(1 + I_in * K_inact/(k_I * k_e))) + 1 - fm" *
fh''))
  //result := 1/((d2.fh"*fm"/(1 + I_in * K_inact/(k_I * k_e))) + 1 - fm" * fh''))
  //method: iterate through other drug's enzymes, stop at match & calculate
exposure
  //first check if those metabolised by this are inhibited by d2
  //showMessage('1. Checking for interaction... d1.metEnz =
');//+inttostr(metabolisingEnzymes.count())+'
d2.enhEnz.count='+inttostr(d2.inhibitingEnzymes.count());
  if (metabolisingEnzymes.count()>0) and (d2.inhibitingEnzymes.count()>0) then
begin
  //BOTH have something to do with enzymes:
  for ix1:= 0 to metabolisingEnzymes.count() -1 do begin
    //iterate through first's enzymes
    for ix2:= 0 to d2.inhibitingEnzymes.count() -1 do begin
      //iterate through second's enzymes. Only interested in given mechanism:
      //      showMessage('1. Checking for interaction... ix1='+inttostr(ix1)+'
ix2='+inttostr(ix2));

{showMessage(PEnzymeMetabolised(metabolisingEnzymes.get(ix1)).EnzymeName);
  showMessage(PEnzymeInhibited(d2.inhibitingEnzymes.get(ix2)).EnzymeName);
  }if (PEnzymeInhibited(d2.inhibitingEnzymes.get(ix2)).InhibitionMechanism =
mechanism)
    and(
      PEnzymeMetabolised(metabolisingEnzymes.get(ix1)).EnzymeName =
PEnzymeInhibited(d2.inhibitingEnzymes.get(ix2)).EnzymeName) then begin
      //interaction likely to occur:
      interaction := true;
      enzMetab1 := ix1;
      enzInhibited2 := ix2;
      mech :=
PEnzymeInhibited(d2.inhibitingEnzymes.get(ix2)).InhibitionMechanismName;
      enzyme := PEnzymeMetabolised(metabolisingEnzymes.get(ix1)).EnzymeName;
      msg1 := Enzyme + ' metabolises ' + Name + ', and is inhibited by ' +
d2.getName());

```

```

        //showMessage('1. interaction may occur on ');//+
PEnzymeInhibited(inhibitingEnzymes.get(ix2)).EnzymeName + ' and ' +
PEnzymeMetabolised(metabolisingEnzymes.get(ix2)).EnzymeName );
    end;
    end;
    end;
    end;

    //showMessage('done with first');
    //then check if those inhibited by this are metabolised by d2
    if (inhibitingEnzymes.count()>0 )and (d2.metabolisingEnzymes.count()>0) then
begin
    for ix1:= 0 to inhibitingEnzymes.count() -1 do begin
        for ix2:= 0 to d2.metabolisingEnzymes.count() -1 do begin
            //showMessage('2. Checking for interaction... ix1='+inttostr(ix1)+'
ix2='+inttostr(ix2));
            if (PEnzymeInhibited(inhibitingEnzymes.get(ix1)).InhibitionMechanism =
mechanism)
                and(
                    PEnzymeInhibited(inhibitingEnzymes.get(ix1)).EnzymeName =
                    PEnzymeMetabolised(d2.metabolisingEnzymes.get(ix2)).EnzymeName)
then begin
                    //interaction likely to occur:
                    interaction := true;
                    mech
                    :=
PEnzymeInhibited(inhibitingEnzymes.get(ix1)).InhibitionMechanismName;
                    enzMetab2 := ix2;
                    enzInhibited1 := ix1;
                    enzyme := PEnzymeInhibited(inhibitingEnzymes.get(ix1)).EnzymeName;
                    msg2 := Name + ' inhibits enzyme ' + Enzyme + ', through ' + mech +
                    ' mechanism, which metabolises ' + d2.getName();
                    //showMessage('2. interaction may occur on ');// +
PEnzymeInhibited(inhibitingEnzymes.get(ix1)).EnzymeName + ' and ' +
PEnzymeMetabolised(d2.metabolisingEnzymes.get(ix2)).EnzymeName );
                    end;
                    end;
                    end;
                end;
            end;
        end;
    end;
    //end;

    //showMessage('done with second');
    if( interaction = true ) and (inhibitingEnzymes.count > 0)then begin
    // showMessage('interaction = true');
    if enzInhibited1 > -1 then begin
        //enzInhibited := enzInhibited1
        K__I := PEnzymeInhibited(inhibitingEnzymes.get(enzInhibited1)).K__I;
        K_inact
        :=
PEnzymeInhibited(inhibitingEnzymes.get(enzInhibited1)).K_inact;

```

```

        k_I := PEnzymeInhibited(inhibitingEnzymes.get(enzInhibited1)).K_I;
        k_e := PEnzymeInhibited(inhibitingEnzymes.get(enzInhibited1)).k_e;
    end else begin
        enzInhibited := enzInhibited2;
        K_I := PEnzymeInhibited(d2.inhibitingEnzymes.get(enzInhibited2)).K_I;
        K_inact :=
PEnzymeInhibited(d2.inhibitingEnzymes.get(enzInhibited2)).K_inact;
        k_I := PEnzymeInhibited(d2.inhibitingEnzymes.get(enzInhibited2)).K_I;
        k_e := PEnzymeInhibited(d2.inhibitingEnzymes.get(enzInhibited2)).k_e;
    end;

    if enzInduced1 > -1 then begin
        enzInduced := enzInduced1
    end else begin
        enzInduced := enzInduced2;
    end;

    if enzMetab1 > -1 then begin
        //enzMetab := enzMetab1
        d2_fm := PEnzymeMetabolised(metabolisingEnzymes.get(enzMetab1)).FM;
        d2_fh := PEnzymeMetabolised(metabolisingEnzymes.get(enzMetab1)).Fh;
    end else begin
        enzMetab := enzMetab2;
        d2_fm :=
PEnzymeMetabolised(d2.metabolisingEnzymes.get(enzMetab2)).FM;
        d2_fh :=
PEnzymeMetabolised(d2.metabolisingEnzymes.get(enzMetab2)).Fh;
    end;

    // showMessage('calcuations...' + enzyme);
    { showMessage('assigning values');
        showMessage('d2='+d2.Name+' '+ inttostr(d2.metabolisingEnzymes.count())+'
enzMetab= '+inttostr(enzMetab));
        d2_fm := PEnzymeMetabolised(d2.metabolisingEnzymes.get(enzMetab)).FM;
        showMessage('got fm');
        d2_fh := PEnzymeMetabolised(d2.metabolisingEnzymes.get(enzMetab)).Fh;
        showMessage('got fh');
        K_I := PEnzymeInhibited(inhibitingEnzymes.get(enzInhibited)).K_I;
        showMessage('got k_I');
        K_inact := PEnzymeInhibited(inhibitingEnzymes.get(enzInhibited)).K_inact;
        showMessage('got K_inact');
        k_I := PEnzymeInhibited(inhibitingEnzymes.get(enzInhibited)).K_I;
        showMessage('got K_I');
        k_e := PEnzymeInhibited(inhibitingEnzymes.get(enzInhibited)).k_e;
        showMessage('got k_e'); }
        I_in := I_in Vivo(InVivo);
    // showMessage('I_in = '+currtostr(I_in));
    //showMessage('done assigning values');

```



```

case mechanism of
1,2,3: begin //Competitive
    //showMessage('Competitive mechanism ('+ inttostr(mechanism)+'));
    if (lowerCase(enzyme) = '3a4' )or(lowerCase(enzyme) = 'cyp3a4')then
begin
    //gir
    1/(PEnzymeMetabolised(d2.metabolisingEnzymes.get(enzMetab)).FG      :=
    PEnzymeMetabolised(d2.metabolisingEnzymes.get(enzMetab)).FG      +(1
    )*clearance_ratio(self));
    //showMessage('3a4 involved');
    I_g := (cdose * ka * fa)/QG;
    clint := 1/(1 + I_g/k_i);
    fg := PEnzymeMetabolised(d2.metabolisingEnzymes.get(enzMetab)).FG;
    fg_inh := 1 / (fg + (1 - fg)*clint);
    //if ((lowerCase(mech) = 'competitive') or (lowerCase(mech) = 'non-
competitive') or (lowerCase(mech) = 'uncompetitive' )) then begin
        expo := fg_inh * (1/((d2_fh * d2_fm/(1 + I_in/k_i)) + 1 - d2_fm *
d2_fh));
    //end;
    end else begin
        //no 3a4
        //if (lowerCase(mech) = 'competitive') or (lowerCase(mech) = 'non-
competitive') or (lowerCase(mech) = 'uncompetitive' )then begin
            //competitive
            expo := 1/((d2_fh * d2_fm/(1 + I_in/k_i)) + 1 - d2_fm * d2_fh);
        //end;
    end;
end;
{2: begin //Non-competitive
    showMessage('Non-competitive mechanism');
end;
3: begin //Uncompetitive
    showMessage('Uncompetitive mechanism');
end; }
4: begin //MechanismBased
    //showMessage('Time Based mechanism');
    if (lowerCase(enzyme) = '3a4' )or(lowerCase(enzyme) = 'cyp3a4')then
begin
    //gir
    1/(PEnzymeMetabolised(d2.metabolisingEnzymes.get(enzMetab)).FG      :=
    PEnzymeMetabolised(d2.metabolisingEnzymes.get(enzMetab)).FG      +(1
    )*clearance_ratio(self));
    //showMessage('3a4 involved');
    I_g := (cdose * ka * fa)/QG;
    clint := 1/(1 + I_g * K_inact/(k_e*(k__I + I_g)));
    fg := PEnzymeMetabolised(d2.metabolisingEnzymes.get(enzMetab)).FG;
    fg_inh := 1 / (fg + (1 - fg)*clint);

```

```

        if not(((lowerCase(mech) = 'competitive') or (lowerCase(mech) = 'non-
competitive') or (lowerCase(mech) = 'uncompetitive' )) )then begin
            expo := fg_inh/(d2_fh * d2_fm/(1 + C_ss * FU * K_inact/(k_e*(k__I +
C_ss * FU))) + 1 - d2_fm * d2_fh);
            end;
        end else begin
            //no 3a4
            //if not((lowerCase(mech) = 'competitive') or (lowerCase(mech) = 'non-
competitive') or (lowerCase(mech) = 'uncompetitive' ))then begin
                expo := 1/(d2_fh * d2_fm/(1 + C_ss * FU * K_inact/(k_e*(k__I + C_ss *
FU))) + 1 - d2_fm * d2_fh);
                //1/((fm/((1+(kinact*Iu)/(kdeg*(Ki+Iu)))))+(1-fm))
                //end;
            end;
        end;
    end;
end;
end;
if expo > 0 then begin
    output := PExposure.Create();
    output.setValue(expo);
    output.setMechanism(mech);
    output.setEnzyme(enzyme);
    if (control<>nil )then begin
        if (msg1 <> '')then
            TMemo(control).lines.add(msg1);
        if (msg2 <> '')then
            TMemo(control).lines.add(msg2);
    end;
end;
//showMessage('done calculation');
{showMessage(' d2_fh = '+currtostr(d2_fh) +chr(13)+
' d2_fm = '+currtostr(d2_fm) +      chr(13)+
' I_in = '+currtostr(I_in) +      chr(13)+
' K_inact = '+currtostr(K_inact) +      chr(13)+
' k__I = '+currtostr(k__I) +      chr(13)+
' k_e = '+currtostr(k_e) +chr(13)+
' clint = '+currtostr(clint) +  chr(13)+
' k_i = '+currtostr(k_i) +      chr(13)+
' d2_fh = '+currtostr(d2_fh) + chr(13)+
' fg = '+currtostr(fg) + chr(13)+
' fg_inh = '+currtostr(fg_inh) + chr(13)+
' QG = '+currtostr(QG) + chr(13)+
' QH = '+currtostr(QH) + chr(13)+
' C_max = '+currtostr(C_max) + chr(13)+
' FU = '+currtostr(FU) + chr(13)+
' dose = '+currtostr(dose) + chr(13)+
' expo = '+currtostr(expo));
}

```

```

    //showMessage('done calculation');
    result := output;
end;

function PDrug.induction_ratio(): single;
begin
    // result := 1 + (E_max * C_ss * FU)/(EC_50 + C_ss * FU);
end;

function PDrug.clearance_ratio(d2: PDrug): single;
var
    I_g: single;
begin
    // showMessage('d2.QG =' + currtostr(d2.QG));
    I_g := d2.dose * d2.KA * d2.FA/d2.QG;
    // result := 1/(1 + I_g/d2.k_i)
end;

function PDrug.gut_inhibition_ratio(d2: PDrug): single;
begin
    // result := 1/ (d2.FG +(1 - d2.FG)*(clearance_ratio(d2)));
end;

constructor PDrug.create(proc, inhibited, induced, metabo: TADOStoredProc);
begin
    extractFromProc(proc, inhibited, induced, metabo);
    concentrations_done := false;
end;

function PDrug.getStrength(): single; begin result := Strength; end;
function PDrug.getT_half(): string; begin result := T_half; end;
function PDrug.getT_max(): string; begin result := T_max; end;
function PDrug.getCp_cb(): single; begin result := cp_cb; end;
function PDrug.getC_ss(): single; begin result := C_ss; end;
function PDrug.getC_max(): single; begin result := C_max; end;
function PDrug.getQg(): single; begin result := QG; end;
function PDrug.getFu(): single; begin result := FU; end;
function PDrug.getKa(): single; begin result := KA; end;
function PDrug.getFa(): single; begin result := FA; end;
function PDrug.getCl(): single; begin result := CL; end;
function PDrug.getV(): single; begin result := V; end;
function PDrug.getF(): single; begin result := F; end;
function PDrug.getExposureDecrease(): single; begin result :=
ExposureDecrease; end;

function PDrug.getStartHour(): single;
begin
    //showMessage('start_hr=' + currtostr(startHour));

```

```

    result := startHour;
end;

procedure PDrug.setStartHour(i: single);
begin
    startHour := i;
end;

procedure PDrug.setExposureDecrease(ed: single);
begin
    ExposureDecrease := ed;
end;

function PDrug.getQh(): single; begin result := QH; end;
function PDrug.getStrengthunit(): string; begin result := StrengthUnit; end;
function PDrug.getDosageform(): string; begin result := DosageForm; end;
function PDrug.getBioavailability(): string; begin result := Bioavailability; end;
function PDrug.getPrecautions(): string; begin result := Precautions; end;
function PDrug.getName(): string; begin result := Name; end;
function PDrug.getSideeffects(): string; begin result := SideEffects; end;

procedure PDrug.extractFromProc(proc, inhibited, induced, metabo:
TADOStoredProc);
begin
    if proc.RecordCount > 0 then begin
        if not proc.FieldByName('ExposureDecrease').IsNull then
            ExposureDecrease := proc.FieldByName('ExposureDecrease').value;

        if not proc.FieldByName('T_half').IsNull then
            T_half := proc.FieldByName('T_half').value;

        if not proc.FieldByName('RMM').IsNull then
            RMM := proc.FieldByName('RMM').value;

        if not proc.FieldByName('DrugID').IsNull then
            key := proc.FieldByName('DrugID').value;

        if not proc.FieldByName('T_max').IsNull then
            T_max := proc.FieldByName('T_max').value;

        if not proc.FieldByName('cp_cb').IsNull then
            cp_cb := proc.FieldByName('cp_cb').value;

        if not proc.FieldByName('C_ss').IsNull then
            C_ss := proc.FieldByName('C_ss').value;

        if not proc.FieldByName('C_max').IsNull then
            C_max := proc.FieldByName('C_max').value;
    end;
end;

```

```

if not proc.FieldByName('QG').IsNull then
    QG := proc.FieldByName('QG').value;

if not proc.FieldByName('FU').IsNull then
    FU := proc.FieldByName('FU').value;

if not proc.FieldByName('KA').IsNull then
    KA := proc.FieldByName('KA').value;

if not proc.FieldByName('FA').IsNull then
    FA := proc.FieldByName('FA').value;

if not proc.FieldByName('QH').IsNull then
    QH := proc.FieldByName('QH').value;

if not proc.FieldByName('Strength').IsNull then
    Strength := proc.FieldByName('Strength').value;

if not proc.FieldByName('divideBy').IsNull then
    divideBy := proc.FieldByName('divideBy').value;

if not proc.FieldByName('DosageForm').IsNull then
    DosageForm := proc.FieldByName('DosageForm').value;

if not proc.FieldByName('Bioavailability').IsNull then
    Bioavailability := proc.FieldByName('Bioavailability').value;

if not proc.FieldByName('Cautions').IsNull then
    Precautions := proc.FieldByName('Cautions').value;

if not proc.FieldByName('DrugName').IsNull then begin
    Name := proc.FieldByName('DrugName').value;
    caption := proc.FieldByName('DrugName').value;
end;

if not proc.FieldByName('SideEffects').IsNull then
    SideEffects := proc.FieldByName('SideEffects').value;

if not proc.FieldByName('DefaultStrength').IsNull then
    dose := proc.FieldByName('DefaultStrength').value;

if not proc.FieldByName('F').IsNull then
    F := proc.FieldByName('F').value;

if not proc.FieldByName('V').IsNull then
    V := proc.FieldByName('V').value;

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```

    if not proc.FieldByName('CL').IsNull then
        CL := proc.FieldByName('CL').value;

    if not proc.FieldByName('DefaultStrength').IsNull then
        DefaultStrength := proc.FieldByName('DefaultStrength').value;
    end else begin
        showMessage('no drug data');
    end;
    //load enzymes
    inhibitingEnzymes := FOrderedList.create(false);
    metabolisingEnzymes := FOrderedList.create(false);
    inducedEnzymes := FOrderedList.create(false);

    inhibited.First();
    while not inhibited.Eof do begin
        inhibitingEnzymes.append(PEnzymeInhibited.create(inhibited));
        inhibited.Next();
    end;

    induced.First();
    while not induced.Eof do begin
        inducedEnzymes.append(PEnzymeInduced.create(induced));
        induced.Next();
    end;

    metabo.First();
    while not metabo.Eof do begin
        metabolisingEnzymes.append(PEnzymeMetabolised.create(metabo));
        metabo.Next();
    end;
    // showMessage('extracted');
end;

{* end of class PDrug *}

{* class PDrugCompound *}
constructor PDrugCompound.create(ado: TADOStoredProc);
begin
    //extracts drugs from compounds
    // showMessage(ado.fieldByName('CompoundID').AsString);    //muroyi!
    key := ado.fieldByName('CompoundID').Value;
    compoundID := ado.fieldByName('compoundID').Value;
    dispensableID := ado.fieldByName('dispensableID').Value;
    caption := ado.fieldByName('CompoundName').Value;
    dose:= 0;
    route := -1;
    drugs := FOrderedList.create(false);
    frequency := 0;

```

```

    start_hr := 0;
    duration := 0;
end;

function PDrugCompound.extractFrom(ado: TADOStoredProc): boolean;
begin
    showMessage('PDrugCompound can''t extract drugs by itself');
    result := false; //success
end;

function PDrugCompound.getDrugs(): FOrderedList;
begin
    result := drugs;
end;

function PDrugCompound.getDrug(ix: integer): PDrug;
begin
    result := PDrug(drugs.get(ix));
end;

function PDrugCompound.getDose(): single;
begin
    result := dose;
end;

procedure PDrugCompound.setDuration(d: integer);
var
    ix0: integer;
begin
    duration := d;
    for ix0 := 0 to drugs.count() - 1 do
        PDrug(drugs.get(ix0)).setDuration(d);
    end;
end;

procedure PDrugCompound.setFrequency(d: integer);
var
    ix0: integer;
begin
    frequency := d;
    for ix0 := 0 to drugs.count() - 1 do
        PDrug(drugs.get(ix0)).setFrequency(d);
    end;
end;

procedure PDrugCompound.setStart(d: integer);
var
    ix0: integer;
begin
    start_hr := d;

```

```

    for ix0 := 0 to drugs.count() - 1 do
        PDrug(drugs.get(ix0)).setStartHour(d);
    end;

    procedure PDrugCompound.setDose(d: single);
    var
        ix0, ix1: integer;
    begin
        for ix0 := 0 to drugs.count() - 1 do begin
            getDrug(ix0).setDose(d);
        end;
    end;

    function PDrugCompound.getDuration(): integer;
    begin
        result := duration;
    end;

    function PDrugCompound.getStart():integer;
    begin
        result := start_hr;
    end;

    function PDrugCompound.getFrequency(): integer;
    begin
        result := frequency;
    end;

    function PDrugCompound.getRouteName(): shortString;
    begin
        result := routeName;
    end;

    function PDrugCompound.getRoute(): smallint;
    begin
        result := route;
    end;

    procedure PDrugCompound.setRoute(r: smallint; rn: shortString);
    begin
        route := r;
        routeName := rn;
    end;

    function PDrugCompound.exposure(cmp: PDrugCompound; inVivoWhich:
smallint): single;
    var
        x1, x2, x3: integer;

```



```

    drug1, drug2: PDrug;
begin
    x3:=0;
    for x1 := 0 to drugs.count - 1 do begin
        drug1 := PDrug(drugs.get(x1));
        for x2 := 0 to cmp.drugs.count - 1 do begin
            drug2 := PDrug(cmp.drugs.get(x2));
            if (drug1.getKey()<>drug2.getKey()) and
                ((drug1.exposure(drug2, nil, inVivoWhich,0)<>nil) or
                 (drug2.exposure(drug1, nil, inVivoWhich,0)<>nil)) then
                x3:=1;
            end;
        end;
    end;
    Result := x3;
end;
{* end of class PDrugCompound *}

```

```

{* class PPrescription *}
function PPrescription.getRegimens(): FOrderedList;
begin
    Result := regimens;
end;

function PPrescription.getRegimen(i: integer): PRegimen;
begin
    Result := PRegimen(regimens.get(i));
end;

function PPrescription.getRegimenByID(i: integer): PRegimen;
begin
    Result := PRegimen(regimens.find(i));
end;

```

```

procedure PPrescription.configRegs();
var
    ix0, ix1: integer;
    regimen: PRegimen;
    drug: PDrug;
    comp: PDrugCompound;
    obj: TObject;
begin
    {then add individual drugs to regimens:
    0. Sort regimens
    1. find regimen where this belongs
    2. if found add to that regimen
    3. else create a new regimen
    }
    //showMessage('Redoing regimens');

```

```

regimens.Free();
regimens := FOrderedList.create(false);
for ix0 := 0 to compounds.count() - 1 do begin
  comp := getCompound(ix0);
  regimens.qSortByKey();
  //showMessage('created regimens');
  for ix1 := 0 to comp.drugs.count() - 1 do begin
    //for this drug:
    drug := PDrug(comp.drugs.get(ix1));
    //showMessage('drug = '+drug.getName());
    regimen := PRegimen(nil); //empty
    //showMessage('done emptying regimen');
    //showMessage('count='+inttostr(regimens.count()));
    regimen := PRegimen(regimens.find(drug.getKey()));
    //showMessage('done converting object to PRegimen');
    if regimen <> nil then begin
      regimen.add(drug);
      // showMessage('done adding drug in regimen');
    end else begin
      regimen := PRegimen.create();
      regimen.setKey(drug.getKey());
      regimen.setCaption(drug.getCaption());
      regimen.add(drug);
      regimens.append(regimen);
      //showMessage('done appending regimen '+drug.getCaption());
    end;
  end;
end;
end;

procedure PPrescription.add(comp: PDrugCompound);
var
  ix0: integer;
  regimen: PRegimen;
  drug: PDrug;
  obj: TObject;
begin
  //first add to compounds:
  compounds.append(comp);

  {then add individual drugs to regimens:
  0. Sort regimens
  1. find regimen where this belongs
  2. if found add to that regimen
  3. else create a new regimen
  }
  regimens.qSortByKey();
  //showMessage('created regimens');

```

```

for ix0 := 0 to comp.drugs.count() - 1 do begin
  //for this drug:
  drug := PDrug(comp.drugs.get(ix0));
  //showMessage('drug = '+drug.getName());
  regimen := PRegimen(nil); //empty
  //showMessage('done emptying regimen');
  //showMessage('count='+inttostr(regimens.count()));
  regimen := PRegimen(regimens.find(drug.getKey()));
  //showMessage('done converting object to PRegimen');
  if regimen <> nil then begin
    regimen.add(drug);
    // showMessage('done adding drug in regimen');
  end else begin
    regimen := PRegimen.create();
    regimen.setKey(drug.getKey());
    regimen.setCaption(drug.getCaption());
    regimen.add(drug);
    regimens.append(regimen);
    //showMessage('done appending regimen '+drug.getCaption());
  end;
end;
// showMessage('after count='+inttostr(regimens.count()));
end;

procedure PPrescription.conc(left, right, top: integer; drug: PDrug; ed: boolean);
var
  y, x, start, copy_start: integer;
  t, phase: single;
begin

  showMessage('left='+inttostr(left)+' right='+inttostr(right)+' top='+inttostr(top));
  phase := drug.getFrequency()/timeDivision;
  //Put calculated data:
  for y:= top to Length(matrix) - 1 do begin
    //apply the formula:
    t := matrix[y][0]-top;
    matrix[y][left] := drug.concentration(t, ed);
  end;
  //showMessage('done calcs (2)');

  //copy elementary sequence of values
  for x := left + 1 to right do begin
    start := top + ceil((x-left) * phase);
    copy_start := top;
    //showMessage('start := '+ currtostr(start));
    for y:= start to length(matrix) - 1 do begin
      matrix[y][x] := matrix[copy_start][left];
      copy_start := copy_start + 1;
    end;
  end;
end;

```

```

    end;
end;
showMessage('left='+inttostr(left)+' right='+inttostr(right)+' top='+inttostr(top));
//showMessage('done copying (2)');
end;

function PPrescription.concentrations(): P2DRealMatrix;
var
    y, x, start, steadyStateHour, compound, aDrug, start_top, start_left,
    copy_start, right: integer;
    row: PRealArray;
    tempTotal, A, k, expo, calc_KA, t, calc_CL : extended;
    ExposureDecrease, phase, t1, t2: single;
    drug: PDrug;
begin
    timeDivision := 1;
    start_top := 0;
    start_left := 1;
    setLength(matrix, 0);
    right := 1;
    //go thru the compounds:

    for compound := 0 to compounds.count() - 1 do begin
        //go thru the drugs
        for aDrug := 0 to getCompound(compound).drugs.count() - 1 do begin
            drug := getCompound(compound).getDrug(aDrug);
            showMessage(inttostr(aDrug) + ' ' + drug.getName+ ' starts after: ' +
currtostr(drug.getStartHour())+ ' hours');
            start_left := right + 1;
            start_top := ceil(drug.getStartHour() / timeDivision);
            //Initialize matrix:
            setLength(matrix, length(matrix) + ceil(drug.getDuration() * 24/timeDivision));
            for y:=0 to length(matrix) - 1 do begin
                setLength(matrix[y], 2 + length(matrix[y]) + ceil(drug.getDuration()*24 *24/
drug.getFrequency()/drug.getFrequency()));
                matrix[y][0] := y * timeDivision;
                matrix[y][1] := 0;
                for x := 2 to length(matrix[y]) - 1 do begin
                    matrix[y][x] := 0;
                end;
            end;
            //showMessage('done with matrix dimensions');

            steadyStateHour := ceil(4 * strtocurr(drug.getT_half()));
            right := 2 + right + floor((steadyStateHour / 24 ) * 24 / drug.getFrequency());
            //showMessage('start_left='+inttostr(start_left)+' start_top='+inttostr(start_top));
            conc(start_left, right, start_top, drug, false);
        end;
    end;
end;

```

```

    phase := drug.getFrequency()/timeDivision;
    start_left := right + 1; //start_left + round(steadyStateHour/24);
    right      :=      start_left      +      ceil(drug.getDuration()*24      *24/
drug.getFrequency()/drug.getFrequency());
    start_top := start_top + ceil(ceil(floor(steadyStateHour/phase) + 1) *
phase)/timeDivision); //(right-2) * drug.getFrequency()/timeDivision + phase);
    //showMessage('start_left='+inttostr(start_left)+' start_top='+inttostr(start_top));
    conc(start_left, right, start_top, drug, true);

//add up rows
for y:= 0 to Length(matrix) -1 do begin
    tempTotal := 0;
    for x := 2 to length(matrix[y])-1 do begin
        // add up all in this row:
        tempTotal := tempTotal + matrix[y][x];
    end;
    matrix[y][1] := tempTotal;
end;
end;{for}
end;{for}

result := matrix;
end;

function PPrescription.exposure(cmp1, cmp2: PDrugCompound; inVivoWhich:
smallint): single;
begin
    Result := cmp1.exposure(cmp2, inVivoWhich)
end;

constructor PPrescription.create();
begin
    compounds := FOrderedList.create(false);
    regimens := FOrderedList.create(false);
end;

function PPrescription.getCompound(i: integer): PDrugCompound;
begin
    result := PDrugCompound(compounds.get(i));
end;

function PPrescription.getCompounds(): FOrderedList;
begin
    result := compounds;
end;

function PPrescription.getPatientID(): integer;
begin

```

```

    result := patientID;
end;

function PPrescription.getPrescriptionID(): integer;
begin
    Result := PrescriptionID;
end;

procedure PPrescription.setPrescriptionID(i: integer);
begin
    PrescriptionID := i;
end;

procedure PPrescription.setPatientID(i: integer);
begin
    patientID := i;
end;

function PPrescription.interacts(d: PDrugCompound): integer; //returns number of
drugs in
    //prescription which interact with d
var
    ix0, ix1, count: integer;
begin
    count := 0;
    if self.compounds = nil then
        showMessage('No compounds');

    //showMessage(inttostr(self.compounds.count()));
    for ix0 := 0 to self.compounds.count() - 1 do begin
        if getCompound(ix0).exposure(d, 3) > 0 then
            count := count + 1;
        {for ix1 := 0 to getCompound(ix0).drugs.count() - 1 do begin
            if getCompound(ix0).getDrug(ix1) = nil then showMessage('drug 1 null');
            showMessage(getCompound(ix0).getDrug(ix1).caption + ' vs ' + d.caption);
            if getCompound(ix0).getDrug(ix1).exposure(d, nil, 0) > 0 then
                count := count + 1;
            end; }
        end;
    end;
    result := count;
end;

function PPrescription.exposure(drg1, drg2: PDrug): single;
var
    exp1, exp2, indn: single;
begin
    {fraction cleared by enzyme: fm
    I_in - calculated per prescription = c_max +(dose * ka * fa)/qh

```

interaction only occurs if two or more of the drugs affect enzymes and enzyme metabolising drug 1 is inhibited by drug 2 or vice versa. Equation to use depends on mechanism of inhibition.

where drug inhibits enzymes (mechanism-based inhibition):

-'' means reading from second drug

$$\text{Exposure(AUC'/AUC)} = 1 / ((f_{h''} * f_{m''} / (1 + I_{in} * K_{inact} / (k_I * k_e))) + 1 - f_{m''} * f_{h''})$$

if exposure exceeds a certain threshold (1.2 min) then interaction occurs; dose adjustment becomes 1/exposure

Competitive, Non-competitive, Uncompetitive:

$$\text{Exposure(AUC'/AUC)} = 1 / ((f_{h''} * f_{m''} / (1 + I_{in} / k_I)) + 1 - f_{m''} * f_{h''})$$

if exposure exceeds a certain threshold (1.2 min) then interaction occurs; dose adjustment becomes 1/exposure

If enzyme 3a4 is one the enzymes inhibited, use the these equations:

$$\text{calculate } I_g = \text{dose} * k_a * f_a / q_g$$

$$\text{Clearance ratio} = 1 / (1 + I_g / k_i)$$

$$\text{gut inhibition ratio} = 1 / (f_{g''} + (1 - f_{g''}) * (\text{clearance ratio}))$$

Exposure ratio:

for Competitive, Non-competitive, Uncompetitive mechanisms multiply the exposure ratio by the gut inhibition ratio.

$$\text{For mechanism-based: clearance ratio} = 1 / (1 + I_g * k_{inact} / (k_I * k_e))$$

$$\text{gut inhibition ratio} = 1 / (f_{g''} + (1 - f_{g''}) * (\text{clearance ratio}))$$

then multiply the exposure ratio by the gut inhibition ratio.

$$\text{Induction ratio, } R = 1 + (E_{max} * C_{ss} * f_u) / (EC_{50} + C_{ss} * f_u)$$

always calculated. If $R > 1.2$ then multiply dose by R

}

end;

{* end of class PPrescription *}

{* class PExposure *}

procedure PExposure.setValue(v: single);

begin

value := v;

end;

procedure PExposure.setMechanism(m: shortString);

begin

mechanism := m;

end;

procedure PExposure.setEnzyme(e: shortString);

begin

```

    enzyme := e;
end;

function PExposure.getValue(): single;
begin
    Result := value;
end;

function PExposure.getMechanism(): shortString;
begin
    Result := mechanism;
end;

function PExposure.getEnzyme(): shortString;
begin
    Result := enzyme;
end;

function PExposure.getValueAsString(): shortString;
begin
    Result := currtostr(value);
end;
{* class PExposure *}
end.

```


APPENDIX 5: Publication resulting from the work