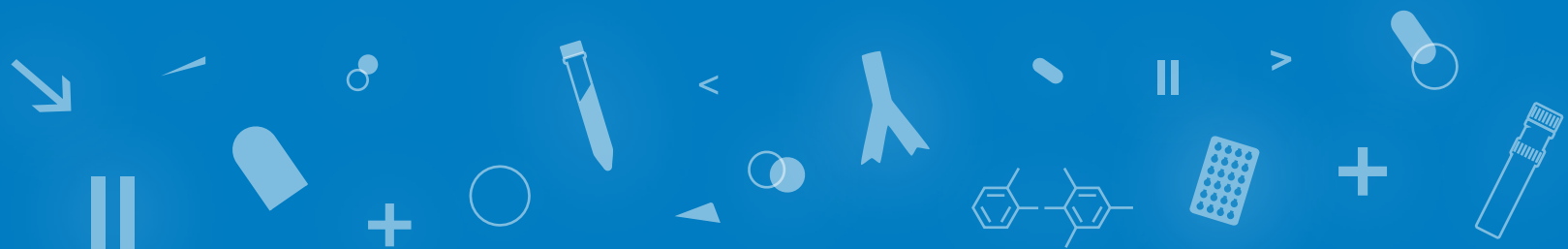
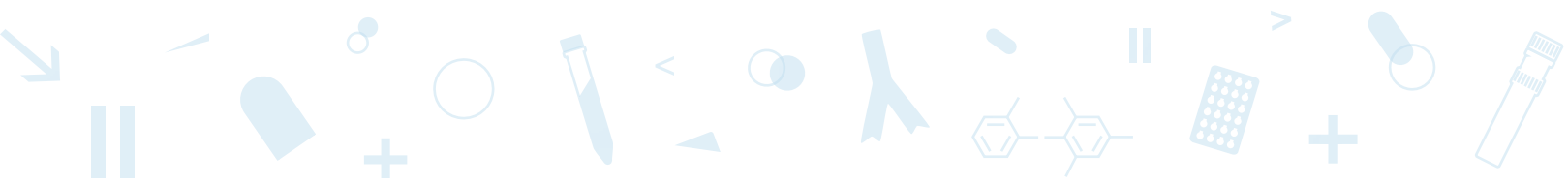




Helping all people
live healthy lives

BD GentestSM Contract Research Services





Partners in the search for new drugs

Introduction

BD GentestSM Contract Research Services

BD Gentest Contract Research Services has over 15 years experience developing *in vitro* services to support pharmaceutical drug discovery and development programs in the early ADME/Tox phase. Our Study Directors are highly skilled scientists with in-depth knowledge of absorption and transport, metabolism, and toxicity. This expertise gives BD Biosciences Study Directors the ability to partner with you to develop and deliver a broad range of *in vitro* ADME/Tox studies to meet your discovery and development project needs. We ensure the highest level of quality standards and adhere to current regulatory requirements and applicable FDA-sponsored guidance documents.

Utilizing state-of-the art techniques and equipment, BD Biosciences is able to assist our clients in screening for viable drug candidates during drug discovery or to prepare regulatory agency submission-quality reports for your drug development compounds. Let our team of experts take you to the next level with studies designed to predict drug-drug interactions and human pharmacokinetics using BD Gentest's innovative *in vitro* products, cell models, and methodologies.

Acronyms

7-BQ: 7-Benzylxyquinoline	BzRes: 7-Benzylxyresorufin	OCT: Organic cation transporter
7-MFC: 7-Methoxy-4-trifluoro-methyl-Coumarin	CEC: 3-Cyano-7-ethoxycoumarin	OMF: 3-O-Methylfluorescein
ABC: ABC-binding cassette	EFC: 7-Ethoxy-4-trifluoro-methyl-Coumarin	PB: Phenobarbital
ACE: Angiotensin converting enzyme	GLP: Good Laboratory Practice	P-gp: P-glycoprotein
AMMC: 3-[2-(N,N-diethyl-N-methylamino)ethyl]-7-methoxy-4-methyl-Coumarin	HLM: Human liver microsome	PEPT: Proton oligopeptide co-transporter
AZA: Azamulin	KTZ: Ketoconazole	RIT: Ritonavir
AZT: Azidothymidine	MAMC: 7-Methoxy-4-amino methyl-Coumarin	RT-PCR: Real-time reverse-transcription polymerase chain reaction
BCRP: Breast cancer resistance protein	MRP: Multidrug resistance-associated protein	SLC: Solute-linked carrier
BCS: Biopharmaceutics Classification System	NCE: new chemical entity	TEA: Tetraethylammonium
BFC: 7-Benzylxy-4-trifluoro-methyl-Coumarin	NTCP: Sodium taurocholate co-transport protein	TDI: Time-dependent inhibition
BSEP: Bile salt export pump	OAT: Organic anion transporter	UGT: UDP-glucuronosyl transferases
	OATP: Organic anion transporting polypeptide	

Ordering Information

United States

BD GentestSM Contract Research Services

To discuss and order BD Gentest Contract Research Services, contact BD Biosciences at:

tel: 888.334.5229 x2246 or
781.935.5115 x2246

Technical Support

Contact a BD Biosciences Technical Support Representative at:

tel: 877.232.8995 or 978.901.7389

Monday through Friday

9:00 a.m. – 6:00 p.m. Eastern Time

fax: 978.901.7491

e-mail: admetox@bd.com

International

Orders for BD GentestSM Contract Research Services, should be placed with your regional BD Biosciences office or contact BDBCcustomerService@bd.com for further details.

Cytochrome P450 and UGT Reaction Phenotyping Studies

Introduction

The number of cytochrome P450 enzymes responsible for the metabolism of a drug affects population variability in metabolism. Drugs cleared metabolically by few enzymes may exhibit susceptibility to co-medication drug interactions or display excessive population variability in metabolism. Reaction phenotyping experiments can identify the number and type of enzymes responsible for drug clearance.

Enzymes Available	
CYP1A1	CYP19
CYP1A2	FMO1
CYP1B1	FMO3
CYP2A6	FMO5
CYP2B6	UGT1A1
CYP2C8	UGT1A3
CYP2C9	UGT1A4
CYP2C18	UGT1A6
CYP2C19	UGT1A7
CYP2D6	UGT1A8
CYP2E1	UGT1A9
CYP2J2	UGT1A10
CYP3A4	UGT2B4
CYP3A5	UGT2B7
CYP3A7	UGT2B15
CYP4A11	UGT2B17
CYP4F2	Monoamine oxidase A
CYP4F3a	Monoamine oxidase B
CYP4F3b	N-acetyltransferase 1
CYP4F12	N-acetyltransferase 2

In most cases, only a subset of enzymes need be examined to provide a robust reaction phenotyping analysis. However, some investigations may require screening of the entire list of available enzymes. The list above shows the human BD Gentest™ cDNA-expressed enzymes available for phenotyping analysis.

The use of liver microsomes coupled with enzyme selective chemical or antibody inhibitors as well as a panel of cDNA-expressed enzymes provides a robust approach to determine the number and identity of enzymes involved in the metabolism of your test article. The amount of each cDNA-expressed enzyme is selected to be proportional to the activity of the same enzyme in pooled HLMs. Protein concentration is standardized by the addition of control microsomes that lack catalytically active enzyme.

Metabolism can be measured by loss of parent compound and/or formation of metabolites. Multiple protocols are available to meet your needs in both discovery and development. HPLC analysis with absorbance, fluorescence, radiometric, or mass spectrometric detection is available. Alternatively, the incubations can be returned to the Sponsor for analysis. Our protocols are consistent with the experimental approaches in the literature and recent guidance from the FDA.¹⁻⁵

Reaction Phenotyping Services

■ Cytochrome P450 reaction phenotyping – Development

Test a comprehensive panel of P450 isoforms and FMO3. Quantifying the formation of metabolite rather than loss of parent is preferred to provide the most robust analysis.

■ Cytochrome P450 reaction phenotyping – Discovery

Test the five major P450 isoforms, CYP1A2, 2C9, 2C19, 2D6, and 3A4. Quantifying loss of parent is preferred to provide a rapid turnaround of results.

■ Uridine diphosphoglucuronosyl transferase reaction phenotyping

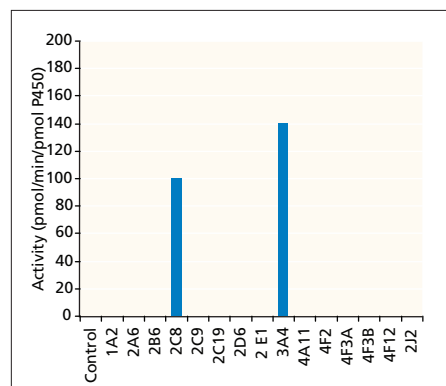
At least 12 UGT enzymes can be examined. Selective chemical inhibition and correlation analysis is available for a subset of these enzymes.⁴

■ Relative role of FMO and cytochrome P450 in metabolism

Heat inactivation of FMO and non-specific chemical inhibition of P450 to determine the relative contributions of these two oxidative enzyme systems in the metabolism of the test article.

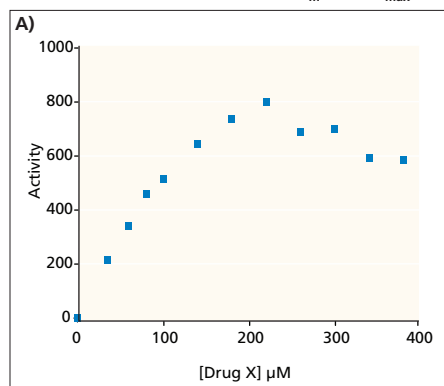
Custom Designed Studies

BD Supersomes™ Enzymes Panel for Drug X

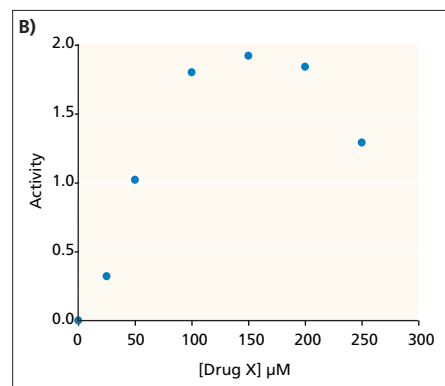


Metabolism of Drug X using BD Supersomes™ Enzymes.

Kinetic Analysis for Drug X (K_m and V_{max})



Comparison of enzyme kinetic parameters in HLM (A) and recombinant CYP3A4 (B).



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