Human Liver Microsomes for *In Vitro* Drug Metabolism Studies

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Agenda

- Overview of BD Gentest™ liver products
- Pooled and single donor Human Liver Microsomes (HLMs)
- Applications for BD Gentest tissue fraction products
- BD UltraPool™ HLM 150

Where Does the Liver Tissue Come From?

- Human Livers
  - Received through Organ Procurement Organizations (OPOs)
    - Organ not suitable for transplant
      - High fat content
      - Anoxia
      - Fibrosis
- Animal Tissue
  - Bred for preclinical studies
  - Untreated control animals or chemically induced

Human Liver Pathogen Tests

- Human liver tissue
  - Tested serologically before arriving at the BD Biosciences facility
  - PCR testing for the following pathogens are done prior to tissue processing (extra step of precaution)
    - HIV I / II
    - Hepatitis B
    - Hepatitis C
    - Human T-cell leukemia virus (HTLV)
    - Cytomegalovirus (CMV)

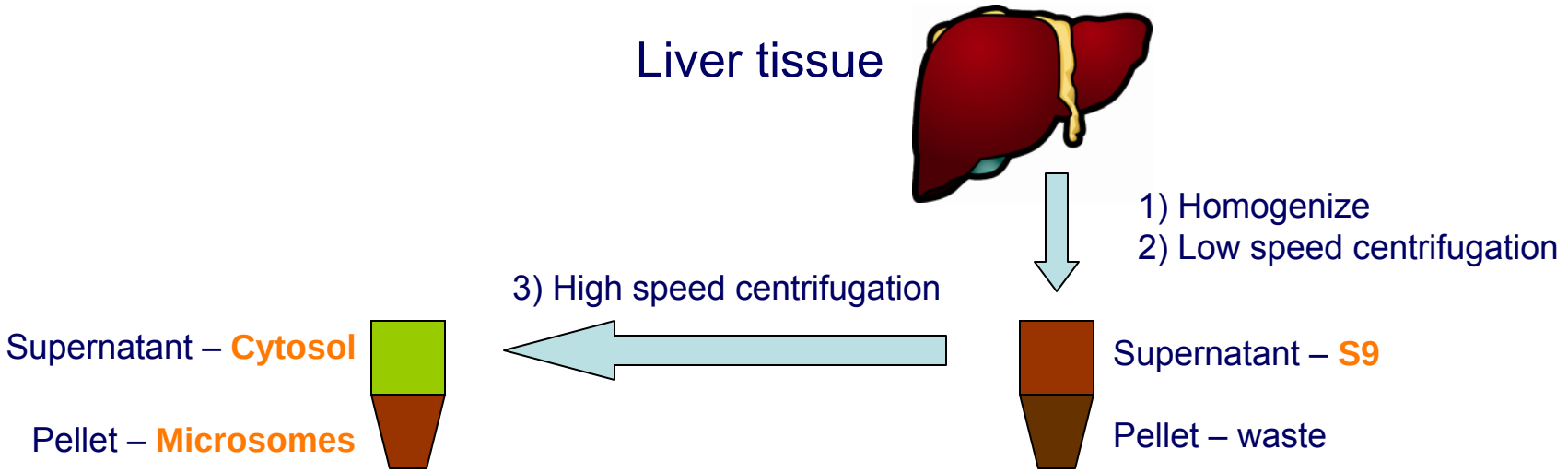
Donor Information Provided on Batch Data Sheet

Specimen	HG45	HG80	HG82	HG83
Gender	Male	Male	Male	Male
Age	32 years	59 years	42 years	31 years
Race	Caucasian	African American	Caucasian	Caucasian
Cause of Death	Closed head trauma	Closed head trauma	Closed head injury	Brain tumor
Social History	Heavy smoker, Former alcoholic, Heroin use	Non-smoker, Occasional alchol use, No drug use	Smoker, Marijuana use, Alcoholic	Non-smoker, No alcohol use, No drug use
Medical History	Amitrypiline	None	MVA, Head injury, Seizure disorder	None
Medication given during Hospitalization	Ancef, DDAVP, Dopamine, KCl, Pavvlon, Zantac	Decadron, Pepcid, Tegretol, Zinacef, Toradol, Phenobarbital	Dopamine, Neosynephrine, Levothyroxin, Lidocaine	Valium, Decadron, Tegretol, Ativan, DDAVP, Dopamine

Tests for Primate Tissue

- Primate (Cyno, Rhesus)
  - Tested serologically before arriving at the BD Biosciences facility
    - Herpes B virus simiae (CHV-1)
    - Simian immunodeficiency virus (SIV)
    - simian T-cell leukemia virus (STLV)
    - simian retrovirus (SRV)
    - Hepatitis A
    - Measles

Method of Manufacture

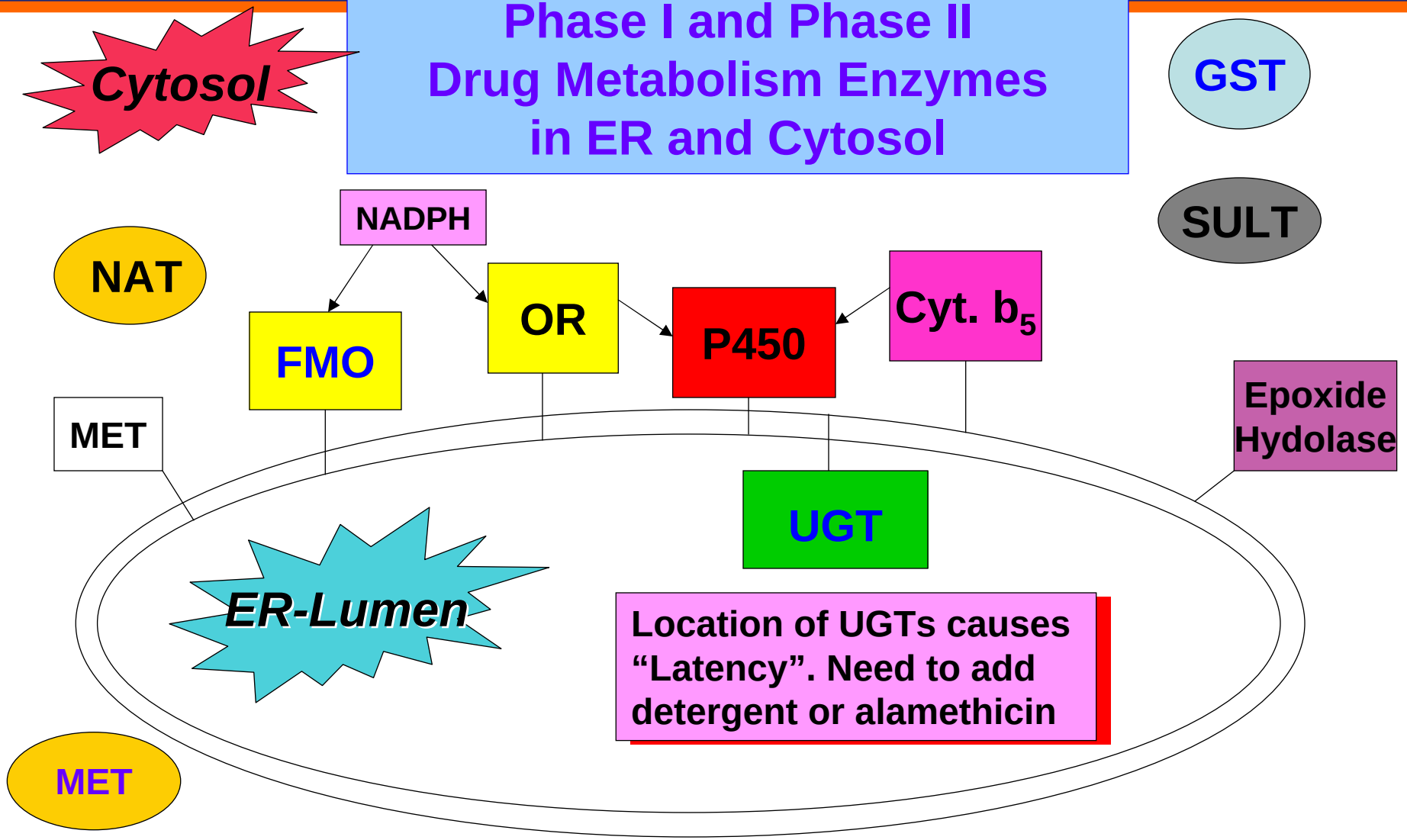


S9 = Both cytosol and microsomes = Phase I and II enzymes

Cytosol = Soluble proteins (phase II enzymes) = NAT, GST, SULT

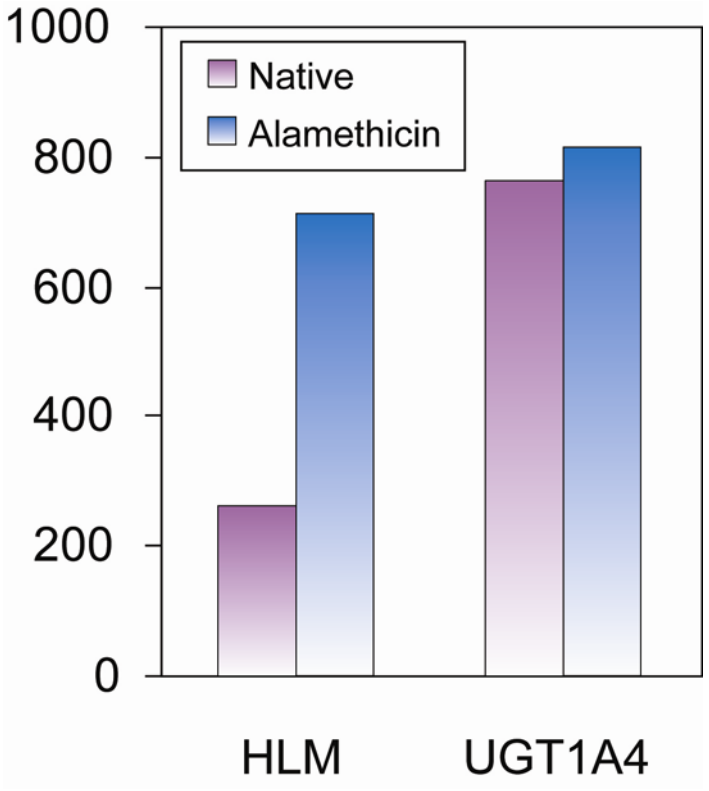
Microsomes = membrane proteins (phase I enzymes) = P450, UGT, FMO

Location of Metabolic Enzymes



UGT Latency in HLM

- UGTs are located on the lumenal face of the microsome
- This limits access of substrates and UDPGA and reduces activity (latency)
- Treatment with detergents or pore forming agents reduces latency
- Treatments can be tricky and kill CYPs



Pooled HLM Product Overview

Human Liver Tissue Fraction Products

- 20-, 50-, and 150-donor pooled HLMs, S9, and cytosol
  - Male, female, and mixed gender
    - Low lot-to-lot variability
    - Represents average patient in population
  - CMV sero negative microsomes
    - Addresses some customer safety concerns
    - Unique product (not available from other vendors)
- Single donor HLMs (allelic variants, mutations)
  - Single donors with high and low CYP activities (represents variability in population)
  - CYP3A5 enriched donors
  - CYP2D6, 2C9, 2C19, 2C8, and UGT1A1 variants

Standard QC Assays for 50- and 150-Donor Pooled HLMs (CYP, UGTs, FMO and CYP3A Western Blot)

Enzyme Measured	Assay
Total P450	Omura and Sato
OR	Cytochrome c Reductase
Cytochrome b_5	Spectrophotometric
CYP1A2	Phenacetin O-deethylase
CYP2A6	Coumarin 7-hydroxylase
CYP2B6	(S)-Mephenytoin N-demethylase
CYP2C8	Paclitaxel 6 -hydroxylase
CYP2C9	Diclofenas 4'-hydroxylase
CYP2C19	(S)-Mephenytoin 4'-hydroxylase
CYP2D6	Fufuralol 1'-hydroxylase (The amount of activity inhibited by 1 µm quinidine.)
CYP2E1	Chlorzoxazone 6-hydroxylase
CYP3A4	Testosterone 6 -hydroxylase
CYP4A11	Lauric acid 12-hydroxylase
FMO	Methyl p-Tolyl Sulfide Oxidase
UGT1A1	Estradiol 3-Glucuronidation
UGT1A4	Trifluoperazine N-Glucuronidation
UGT1A6	Serotonin Glucuronidation
UGT1A9	Propofol Glucuronidation
UGT2B7	AZT Glucuronidation
CYP3A Abundance Measurements	
CYP3A4	Western Blot
CYP3A5	Western Blot

- 10 CYP assays
- 5 UGT assays
- FMO assay
- WB for 3A4 and 3A5

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20-, 50-, and 150-Donor Pooled HLMs

- BD Gentest 20-Donor Pool (cat. no. 452161)
  - ~ 20 donors (18 to 30)
  - Gender is seldom 50:50
  - Not equal mix
  - Mixed at ratios to give pre-specified CYP activities for Big 5 P450s (CYP1A2, 2C9, 2C19, 2D6, and 3A4)
  - Target CYP activities were established using BD Gentest database consisting of > 300 livers
  - Target activities represent the average patient
- BD UltraPool HLM 150 (cat. no. 456117) and 50-Donor Pool (cat. no. 452156)
  - Gender is 50:50 (equal male:female ratio)
    - 50-donor pool is equal +/- 5%
    - 150-donor pool is exactly equal gender mix
  - Large lots sizes; ~ 3 year supply
  - Matched donor sets for HLMs, S9, and Cytosol
  - Activities are not “targeted” in the same way as the 20-donor pool
  - Equal mix of donors on a per mg microsomal protein basis, i.e. the activities are what they are, but they end up being very similar to cat. no. 456161 targeted values based on law of averages

Big 5 CYP Activities for 50-Donor Pool: Comparison to 20-Donor Pool

Activity	Cat. No. 452161 Mean from 5 lots	50-donor pool (lot 1)
CYP1A2	522	540
CYP2C9	2517	2900
CYP2C19	55	55
CYP2D6	76	81
CYP3A4	5266	5700

- ***Conclusion:*** Non targeted 50-donor pool and targeted 20-donor pools have very similar CYP activities

Single Donor HLM Product Overview

Allelic Variant Single Donor Panel
High/Low CYP Activity Panel

Allelic Variant HLM Panel

- Panel designed to help address Pharma's growing concerns over personalized medicine
- FDA wants drugs to be safe for all patients…including outlier patients with polymorphic genes (CYPs, UGTs, etc.)
- Genetic polymorphisms exist for many drugs (most P450s have been shown to possess mutant alleles-no two humans are alike with respect to P450 profile)
- ~ 40% of human P450 drug metabolism is carried out by polymorphic enzymes
- Polymorphisms may explain some idiosyncratic reactions
- Genetic polymorphism: > 1% of population have defect
- < 1% = "rare mutation"

When is Polymorphism Important?

- Drugs with restricted routes of elimination
  - The polymorphic pathway is the principle route of elimination
- Drugs with narrow therapeutic indices
  - Small window before toxicity
- Prodrugs
  - The active metabolite is not formed

Types of Polymorphism

- Null – Enzyme is absent
  - CYP2D6, 2C19, 2A6, 3A5
- Amino Acid Substitution – Kinetic properties of the enzyme are altered
  - CYP2C9, 2C8, 2D6
  - Can have substrate-dependent effect
- Amplification (UM phenotype) – multiple copies of the gene
  - CYP2D6 (up to 14 copies)
- Regulation – Mutation in non-coding “promoter” region of gene
  - UGT1A1

BD Gentest Allelic Variant Donor HLMs

Cat. No.	Description	Min/Max Donor #
452141	HLM 2D6 Allelic Variant	3 to 5
452142	HLM 2C9 Allelic Variant	3 to 5
452143	HLM 2C19 Allelic Variant	2 to 3
452144	HLM 2C8 *3*3 Allelic Variant	2 to 3
452132	HLM UGT1A1 *28*28 Allelic Variant	2 to 3
452133	HLM UGT1A1 *1*28 Allelic Variant	2 to 3
452134	HLM UGT1A1 *1*1 Wild Type	2 to 3
452135	HLM 3A5 *1*1 Allelic Variant	2 to 3
452136	HLM 3A5 *1*3 Allelic Variant	2 to 3
452137	HLM 3A5 *3*3 Wild Type	2 to 3

CYP2D6 Allelic Variants

- CYP2D6 metabolizes ~20 to 30% of drugs on market
- Predominant Mutations: *3 thru *8, *10 and *27
- Prevalence in Ethnic groups
  - Caucasians/African Americans: 5-10% CYP2D6 PM and 1% UM
  - Asians: 1% PM and 1% UM
- CYP2D6 is highly polymorphic P450 (~20 mutants identified)
  - Pharma will discontinue drugs with CYP2D6 as primary route of metabolism
  - Patients with alleles *3 through *8 are considered poor metabolizers (PM) of 2D6; inactive or absent enzyme
  - CYP2D6*10 is predominant in Asians; show reduced enzyme activity
  - CYP2D6*17 is predominant in AA populations; also with reduced activity
  - UM (Ultra-extensive metabolizors) occurs with 2 or more copies of CYP2D6*2/*2

CYP2D6*10

- Two Substitutions P34S and S486T
- Allele frequency:
  - 26 to 70% in Asians
  - 0.05% in Caucasians
- Associated with decreased rates of metabolism

1. J. Biol. Chem. **265**:17209 (1990)
2. Clin. Pharm. Ther. **53**:410 (1993)
3. Pharmacogenetics **3**:256 (1993)
4. Molec. Pharmacol. **46**:452 (1994)

CYP2C9 Allelic Variants

- CYP2C9 is involved in metabolism of ~15 to 25% of drugs on market
- Most prevalent CYP2C9 mutants: 2C9*2 and 2C9*3 (R144C and I359L, respectively)
- Prevalence in Ethnic groups
  - Caucasians/Hispanics: 1 to 3% prevalence for *2 or *3 allele
  - Asians/African Americans: < 1% prevalence for either *2 or *3 alleles (East Asian completely lack the *2 allele)
- CYP2C9 *2 and *3 alleles exhibit reduced rates of turnover for selected substrates such as Warfarin relative to 2C9*1*1 (WT)
- Heterozygote genotypes have intermediate turnover rates relative to 2C9 *1*1
- CYP2C9*2 and CYP2C8*3 allelic variants are linked (96% of 2C9*2/*2 are 2C8*3/*3, 85% of 2C8*3/*3 are 2C9*2/*2)

S-Warfarin Gene-Dose Response Curve (CYP2C9 Allelic Variants)

- Warfarin (Coumadin) is a racemic drug (R + S enantiomers); S-Warfarin is more active than R-Warfarin
- CYP2C9 catalyzes 7- and 6-hydroxylation of S-Warfarin (2C19, 1A2 and 3A4 metabolize R-Warfarin)
- ~40% of population express one or both of the variant CYP2C9 alleles
- *2 has 70% of wild-type efficiency for 7-OH S-Warfarin metabolism; *3 has ~5% efficiency compared to wild-type

Genotype	Warfarin Daily Maintenance Dose
CYP2C9*1/*1	5.63
CYP2C9*1/*2	4.88
CYP2C9*1/*3	3.32
CYP2C9*2/*2	4.07
CYP2C9*2/*3	2.34
CYP2C9*3/*3	1.60

- Study consisted of 185 patients
- Compared to patients with wild-type genotypes, patients with 1 or more alleles experienced greater incidence of bleeding events (i.e. patients more susceptible to over-dose)
- From Higashi, *JAMA* (2002)

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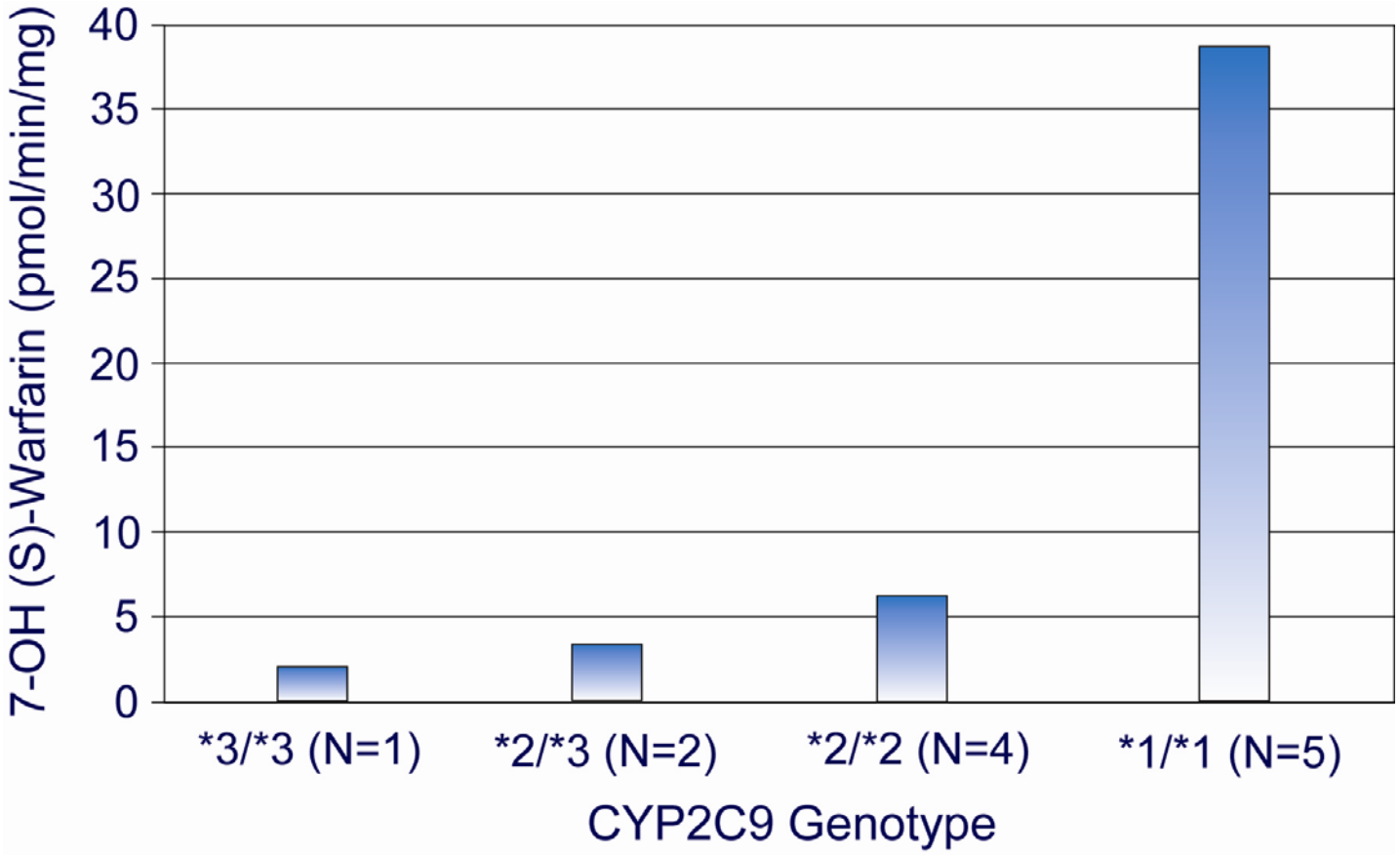
(S)-Warfarin 7-Hydroxylase by Single Donor HLM



CYP2C8 Allelic Variants

- Alleles: *2 and *3
- Cat. no. 452144 is for *3*3 homozygote donor only
- CYP2C8 is involved of metabolism of ~1 to 2% of drugs on market
- Prevalence in Ethnic groups
  - **Caucasians:** 1 to 3% prevalence for *3*3
  - **African Americans:** 1 to 3% prevalence for *2*2
  - **Asians:** < 1% for either allele
- CYP2C8*3 is the major variant allele in Caucasian populations
- The mutation results in significantly lower activity for certain CYP2C8 substrates relative to the wild-type enzyme. Paclitaxel and arachadonic acid metabolism are both reduced in *3*3 subjects

CYP2C19 Allelic Variants

- CYP2C19 is involved of metabolism of ~ 4 to 8% of drugs on market
- Alleles *2 thru *5 result in Null (PM) phenotype. Very low S-Mephenytoin 4′-hydroxylase activity
  - Most prevalent CYP2C19 mutants: CYP2C19*2 and 2C19*3
- Prevalence in Ethnic groups
  - Caucasians: 3 to 5% CYP2C19 PM – ~ 80% of PM phenotype is due to *2 allele
  - Asians: 15 to 20% CYP2C19 PM – 100% of PM phenotype is due to *2 and *3 allele

CYP3A5 Allelic Variants

- CYP3A5 Mutant Panel
  - *1*1: cat. no. 452135 (high expresser of CYP3A5)
  - *1*3: cat. no. 452136 (high expresser of CYP3A5)
  - *3*3 (WT): cat. no. 452137 (low expresser)
- *3 is most prevalent allele (wt); *1 allele is the major variant
- *1*1, *1*3 alleles = high CYP3A5 protein levels; *3*3 = low CYP3A5 protein levels
- Prevalence of CYP3A5 High Single Donor Phenotype (*1*1 and *1*3) in Ethnic groups
  - **African Americans:** 50 to 60%
  - **Caucasians/Asians:** 20 to 30%
  - **Hispanics:** 30 to 40%
- CYP3A5 catalyzes the oxidation of testosterone and other substrates common to the CYP3A family
- CYP3A5 is the predominant 3A isoform in the kidney
- **Mutation:** The CYP3A5*3 defective allele is caused by a single nucleotide polymorphism in intron 3. This mutation activates a cryptic acceptor splice site, which leads to the insertion of an intronic sequence containing premature termination codons in the mature mRNA, and hence the very low CYP3A5 protein expression in subjects with the *3*3 genotype.

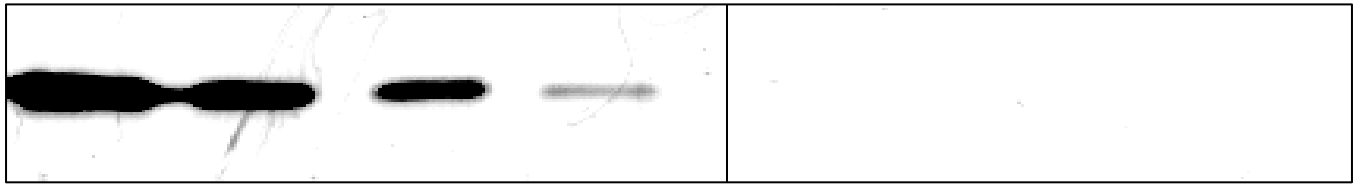
CYP3A Western Blot Data for CYP3A5 Mutant HLM Donors

CYP3A5 standard curve | HH860 samples (3A5*1*1)

CYP3A5 Blot
Donor: HH860
3A5*1/*1

CYP3A5 standard curve | HH189 samples (3A5*3*3)

CYP3A5 Blot
Donor: HH189
3A5*3/*3



CYP3A4 standard curve | HH189 samples (3A5*3*3)

CYP3A4 Blot
Donor: HH189
3A5*3/*3

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UGT1A1 Allelic Variants

- UGT1A1 Mutant Panel
  - *28*28: cat. no. 452132 (low UGT1A1 expresser)
  - *1*28: cat. no. 452133 (moderate UGT1A1 expresser)
  - *1*1 (WT): cat. no. 452134 (high expresser)
- UGT1A1*28*28 is a functional UGT promoter polymorphism associated with Gilbert's disease (hyperbilrubinemia/jaundice)
  - [$(TA)_7TAA$] TATA box mutation
  - [$(TA)_6TAA$] TATA box, wild-type
- Prevalence of mutation in Ethnic groups
  - **Caucasians:** ~15% prevalence for *28*28
  - **African Americans:** ~50% prevalence for *28*28
- UGT1A1 detoxifies bilirubin and several therapeutic drugs (a process influenced by mutations in the UGT1A1 gene)
- The mutation results in lowered UGT1A1 expression
  - Relative UGT1A1 protein expression levels resulting from the allele combinations are: *1*1>*1*28>*28*28

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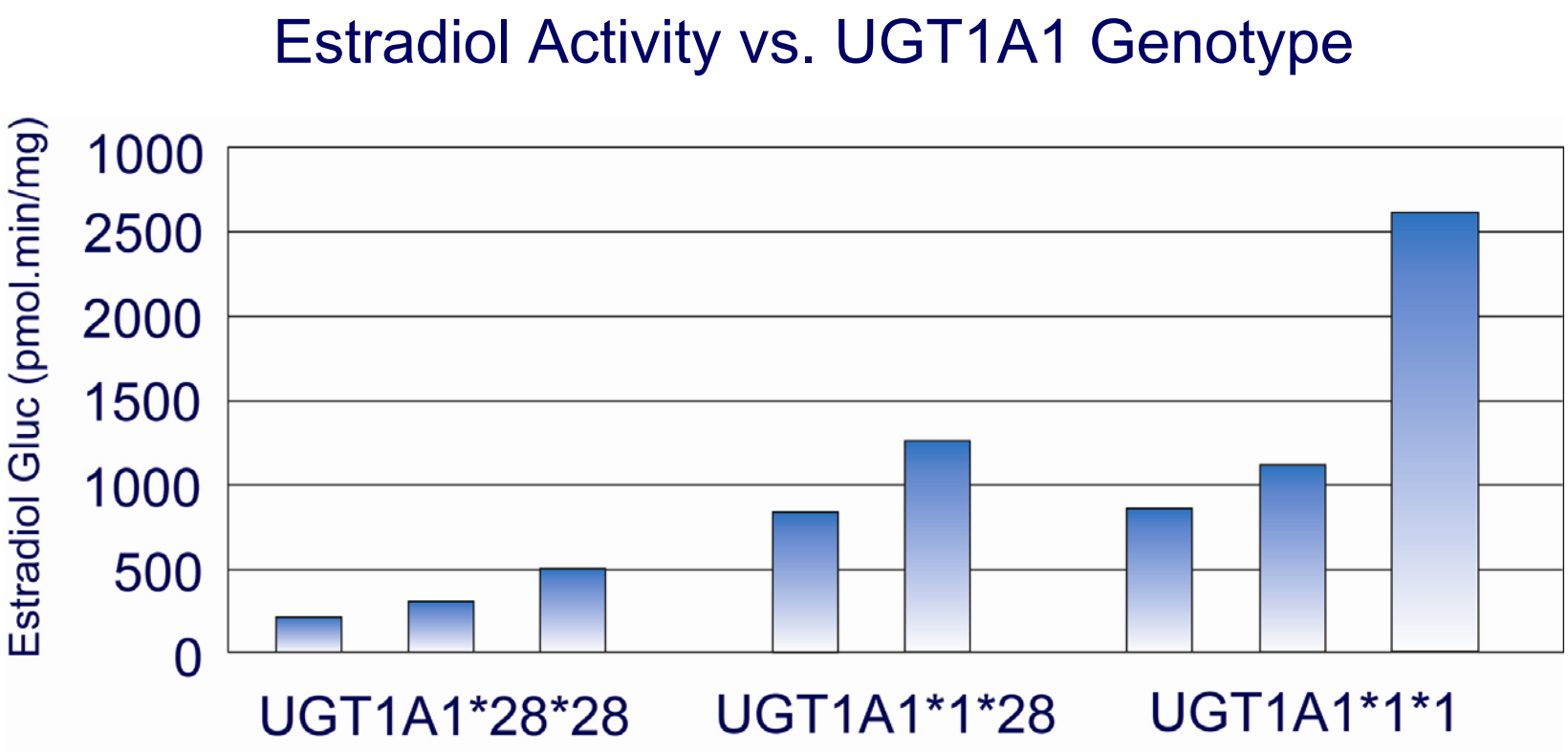
UGT1A1 Genotype/Activity Relationship



Single Donor HLM Panel

- High/Low CYP activity panel with low correlation between CYP/UGT probe substrate activities
- Suitable for correlation analysis and mechanistic studies

Number of High and Low Activity Donors for each CYP Activity

CYP	CYP1A2	CYP2C9	CYP2C19	CYP2B6	CYP2D6	CYP3A4
High Donors	1	4	2	1	3	2
Low Donors	3	3	5	4	3	3

*Total number of donors in panel = 14

Correlation analysis between major CYPs in single donor HLM panel (r-values)

	CYP1A2	CYP2C9	CYP2C19	CYP2B6	CYP2D6	CYP3A4
CYP1A2		0.2446	0.0685	0.0025	-0.3785	0.2627
CYP2C9	0.2446		-0.3924	0.3876	0.1798	0.4786
CYP2C19	0.0685	-0.3924		-0.1748	-0.4706	0.0769
CYP2B6	0.0025	0.3876	-0.1748		0.1844	0.4683
CYP2D6	-0.3785	0.1798	-0.4706	0.1844		-0.3600
CYP3A4	0.2627	0.4786	0.0769	0.4683	-0.3600	3

Correlation analysis between major UGTs in single donor HLM panel (r-values)

UGT	UGT1A1	UGT1A4	UGT1A9
UGT1A1		-0.252	0.317
UGT1A4			0.135
UGT1A9			

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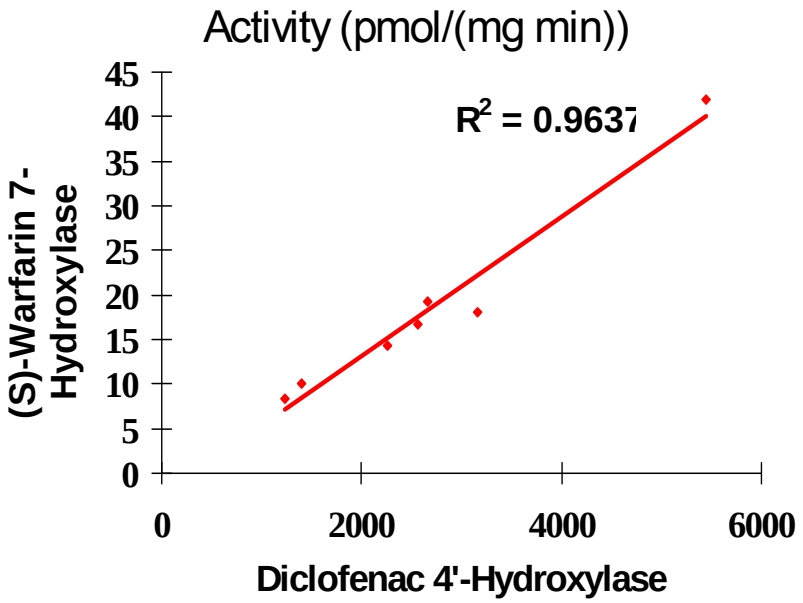
Correlation Analysis for Reaction Phenotyping

- Panel of characterized HLM samples
- Correlate rates of metabolism - unknown and reference activity
- Labor intensive
- Works best when one enzyme is involved per metabolite
- Beware of outliers

Two CYP2C9 Substrates



Tissue Fraction Applications for *In Vitro* ADME Studies

Questions Answered by *In Vitro* Drug Metabolism Studies

- Reaction Phenotyping (enzyme mapping): Which drug metabolizing enzymes (DMEs) are involved in metabolism of new chemical entities (NCEs) and what is the relative importance of each pathway (RAF and ISEF calculations)?
- Metabolic stability for predictive PK parameters
  - Microsomal scaling factors to predict drug clearance *in vivo*
    - Scaling factor: 40 to 50 mg microsomes per gram liver
    - $Cl_{int} = \frac{0.693}{in\ vitro\ T_{1/2}} \frac{mL\ incubation}{mg\ microsomes} \frac{45\ mg\ microsomes}{gm\ liver} \frac{20\ gm\ liver}{kg\ b.w.}$
- Metabolite ID
- Drug-Drug Interactions (DDIs)
  - DME inhibition (CYPs)
  - DME induction (CYPs)

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In Vitro Systems—*Hepatocytes*

- Prepared from fresh human livers (organ donors)
- Available as fresh plated or cryopreserved cells
- Gold-Standard for DM Studies
  - Contain all the enzymes, transporters, and co-factors for drug metabolism
    - Metabolic stability (screening for long half-life drugs)
    - Metabolite profiling (structures of metabolites)
    - Liver toxicity studies
    - Enzyme induction studies (P450 induction)
    - *In vitro* / *In vivo* scaling

<u>Not used for:</u>

- Enzyme Mapping/Reaction Phenotyping
- DDI

Liver Tissue Fraction Uses (Microsomes, S9, and Cytosol)

- Liver fractions contain multiple ADME enzymes
- Compared to hepatocytes:
  - More abundant and less expensive
  - Easier to use
- Applications
  - Metabolic Stability
    - HTS protocols using Mass Spectrometry
    - *In vitro* / *in vivo* clearance scaling
  - Reaction phenotyping
  - CYP Inhibition
    - HTS using LC-MS
  - Species-specific metabolic profiling
  - Toxicology

Recombinant Enzymes

- **Recombinant Enzymes (e.g., BD Supersomes™ Enzymes)**
  - Provided as single enzymes (vs. multi-enzyme systems; HLMs or hepatocytes)
  - CYPs embedded in membrane (consistent with native membrane structure)
  - Kinetics and substrate specificity consistent with HLMs
  - Primary uses:
    - Reaction phenotyping (RAF, ISEF scaling to HLM and percent contribution)
    - DDI (HTS-Fluor substrates)
    - Mechanistic studies

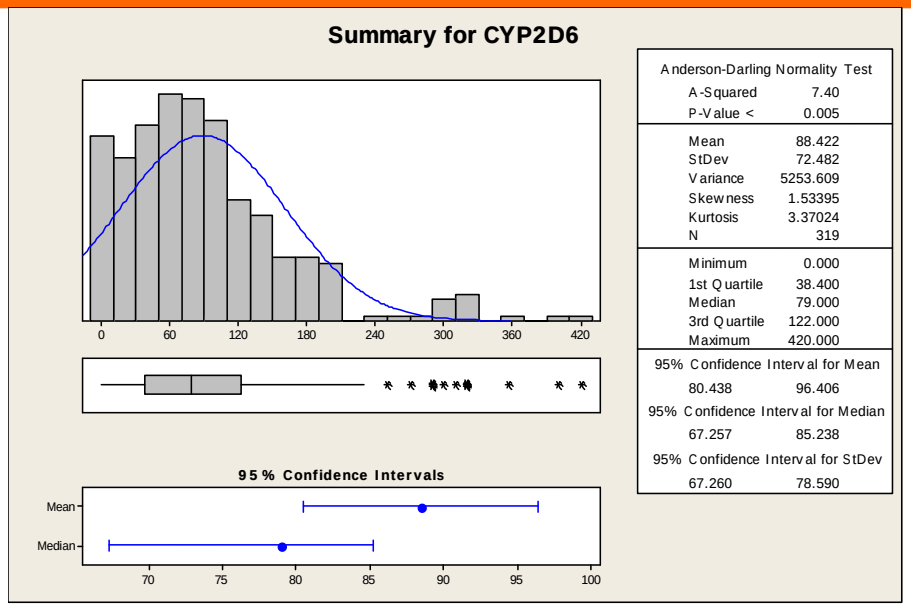
BD UltraPool™ HLM 150

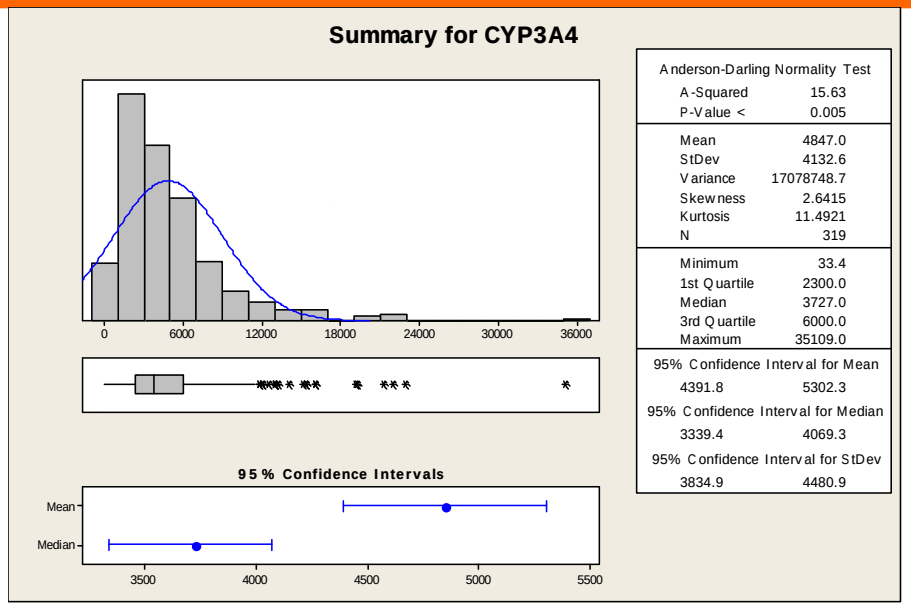
Redesigning Pooled HLM for Improved Performance

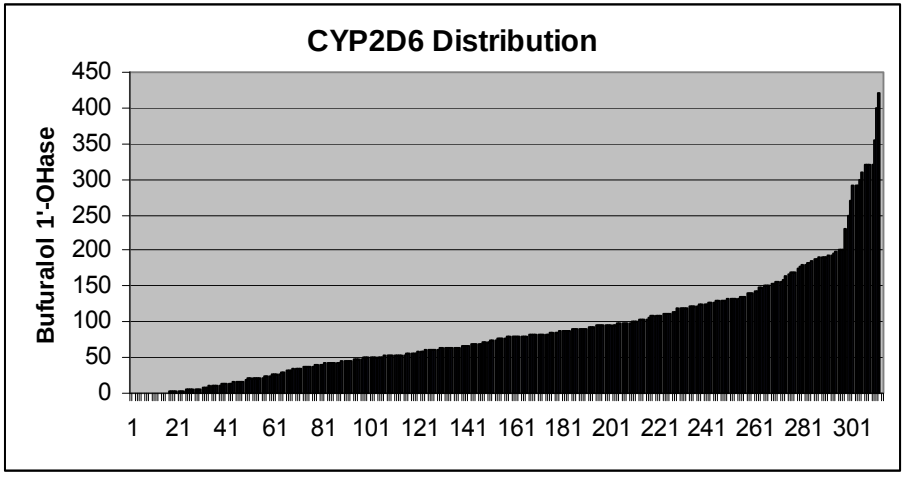
HLM Activity Distributions

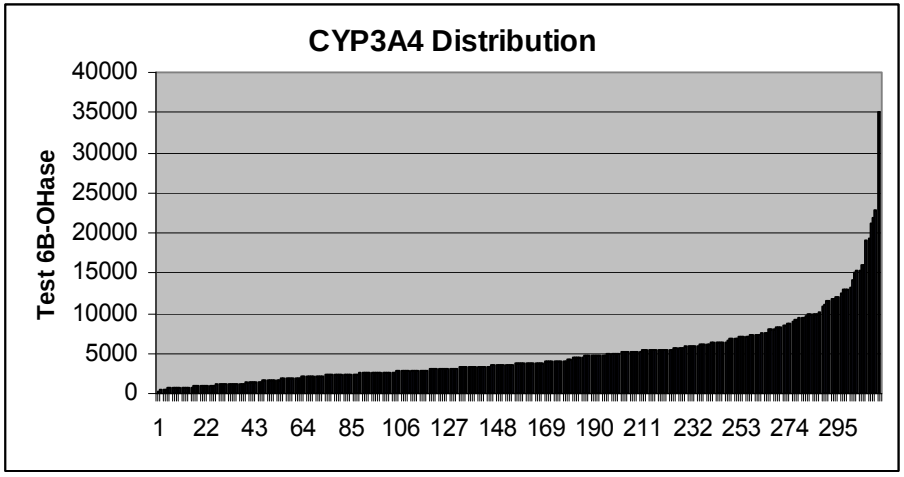
- Over many years, we have characterized HLMs from **over 300** US donors for the major P450s (1A2, 2C8, 2C9, 2C19, 2D6, and 3A4 [2B6])
- The activity distributions for the 5 CYPs were used to establish the number for the required lot-to-lot variability and the product spec (Monte Carlo Analysis)

CYP Activity Distributions









CYP Activity Distributions—Conclusions

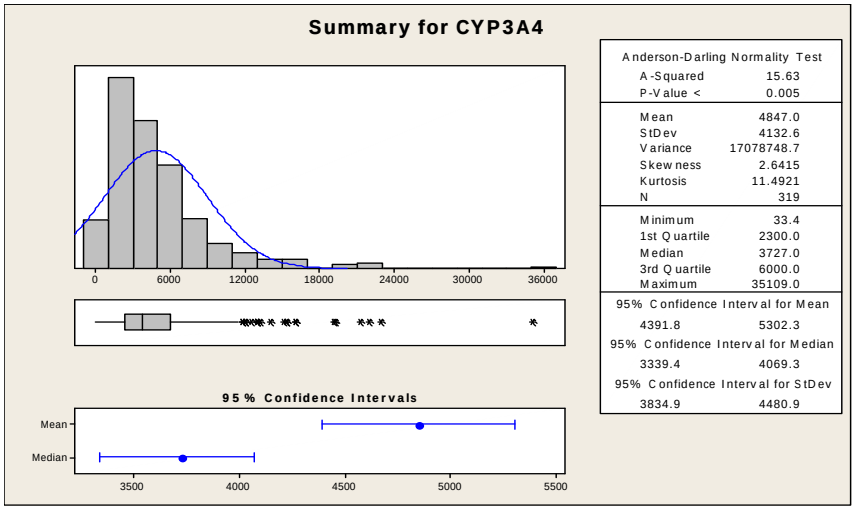
- CYP activities are not normally distributed; observed a skew to higher activities
- Distributions consistent with known phenotypes, for example,
  - Individuals induced for CYP3A and CYP1A2
  - Observe CYP2D6 poor metabolizers and ultrarapid metabolizers
- The assumption of normality is not valid with these skewed distributions
- Therefore, methods which require an assumption of a normal distribution can not be used to model variability in pooled HLM reagents
- The data needed to be normalized in order to use Coefficient of Variation (CV)

Monte Carlo Analysis

- One way to do this is through a Monte Carlo simulation
  - Monte Carlo simulations rely on repeated random samples of size N within a data set
  - The random numbers for the sample size n are drawn repeatedly for X number of trials
  - The distribution of the means and standard deviations of the simulations will be normal

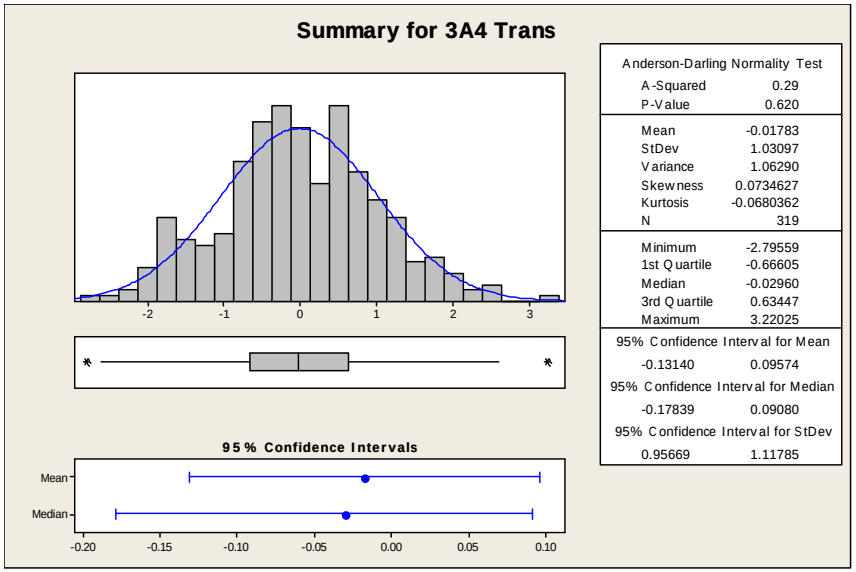
Example: CYP3A4

- The distribution for each CYP was found to be not normal, but rather logarithmic (lognormal)
- Monte Carlo simulations will generate a series of mean values which are expected to be normal



Simulation Data are Normal

- The distribution of the means of the simulation data was found to be normal
- These means along with their standard deviations can now be used to calculate CVs for all CYPs
- Using CYP3A4 as an example



Monte Carlo Simulation Results (N=30)

	CYP1A2	CYP2B6	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Mean	637	50	2617	70	88	4847
Std Dev	519	87	1231	105	70	4133
CV isf Distribution was Normal	0.82	1.75	0.47	1.50	0.82	0.85
50 Monte Carlo (N=30)	**0.09**	**0.25**	**0.06**	**0.17**	**0.10**	**0.12**
100 Monte Carlo (N=30)	**0.07**	**0.13**	**0.03**	**0.11**	**0.06**	**0.07**
150 Monte Carlo (N=30)	**0.05**	**0.10**	**0.03**	**0.09**	**0.04**	**0.05**
200 Monte Carlo (N=30)	**0.04**	**0.06**	**0.02**	**0.07**	**0.03**	**0.03**

- CYP activity CV decreases as a function of the increase in pool size, and levels off after 100 donors where assay variability probably outweighs variability in the product
- **At 150 donors, product variability is less than or equal to assay variability—this is the point of diminishing returns**
- Accuracy of approach was tested with 50 donor pool

BD

Product Characterization Results

- We have manufactured 4 lots of a 50 donor pool
- The overall, observed variability for a 50 donor pool is the same as predicted by Monte Carlo simulations

CYP Form	4 lots 50-Donor Pool	
	Actual CV	Calculated CV
CYP1A2	0.15	0.09
CYP2B6	0.15	0.25
CYP2C9	0.13	0.06
CYP2C19	0.11	0.17
CYP2D6	0.14	0.10
CYP3A	0.06	0.12
	0.12	0.13

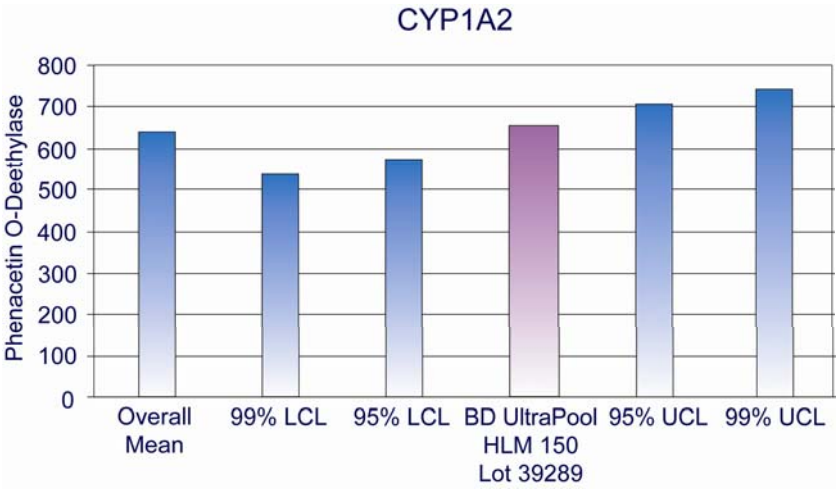
BD UltraPool HLM 150—Design

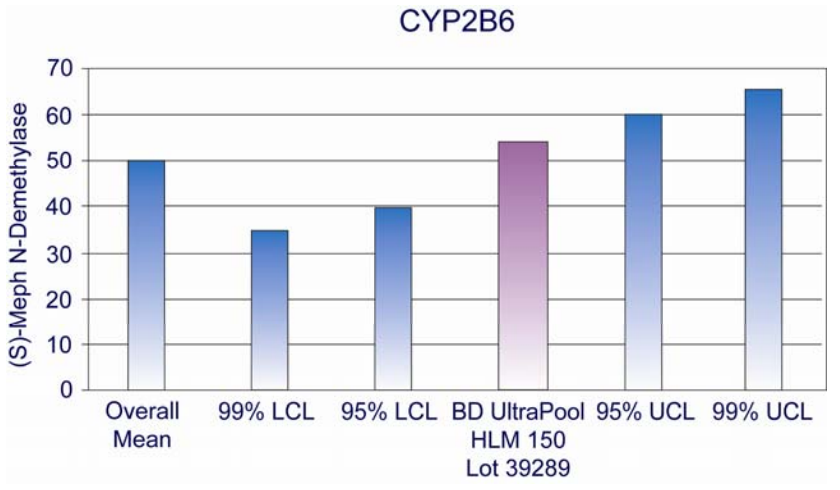
- 150 Donors—75 males, 75 females, random selection, adults, eliminate donors with elevated P420 or with an inadequate amount of tissue available
  - >100,000 vials from the same group of donors.
- HLM (cat. no. 452117), S9 (cat. no. 452116), and cytosol (cat. no. 452115) available from the same donor composition
  - Standard fill sizes as catalog products including, Easy-Count Box for HLM (cat. no. 452118)
  - Custom fill sizes available
- Product launched with same QC assays as our 50 donor pool
  - Supplemental data will be added—full kinetics for the major drug metabolizing CYPs and expanded CYP Western blotting

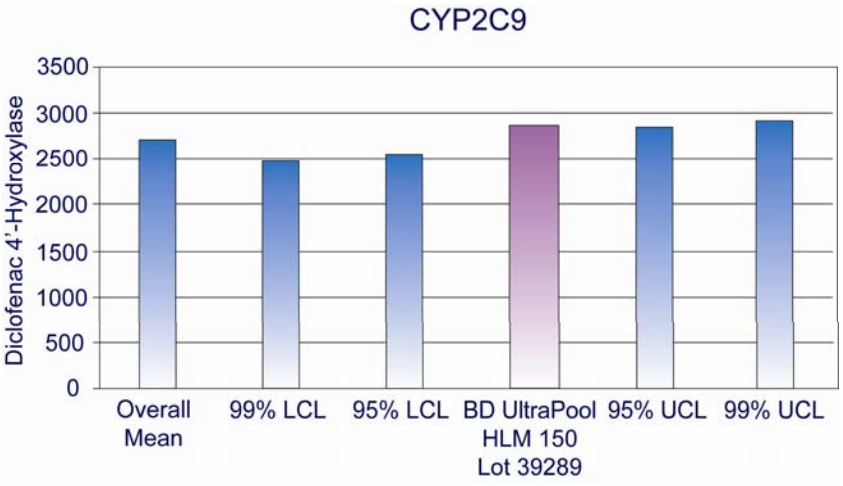
How did we do with the first Lot?

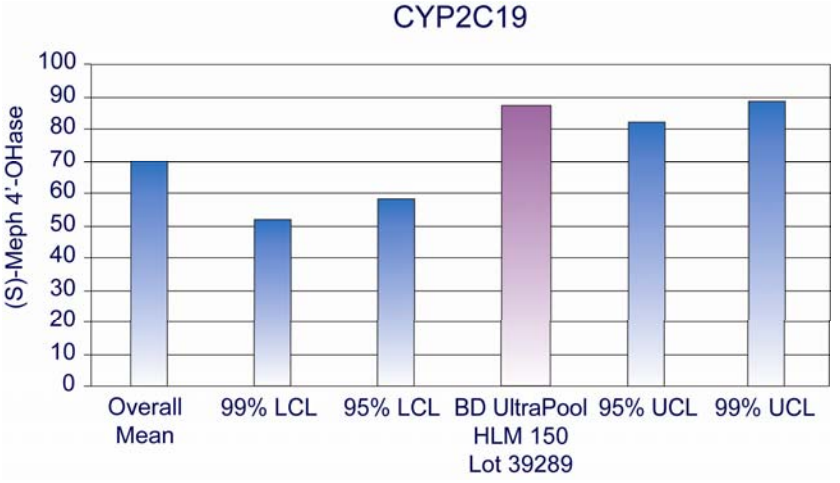
BD

Modeled versus Lot 39289

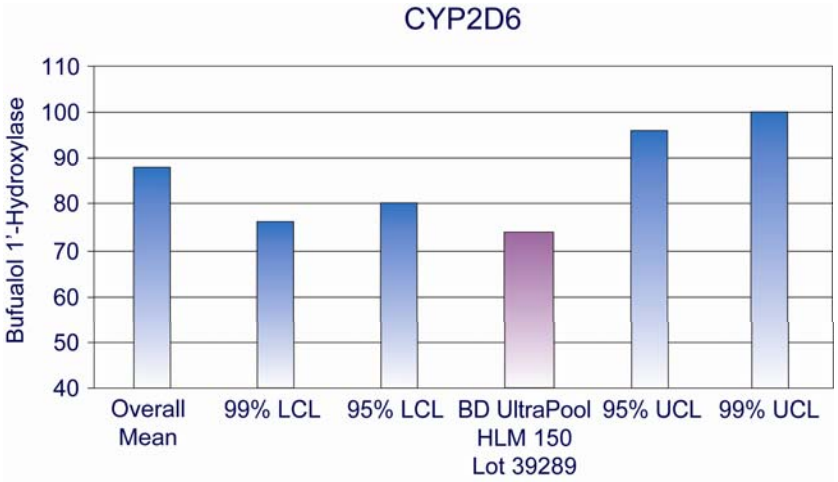


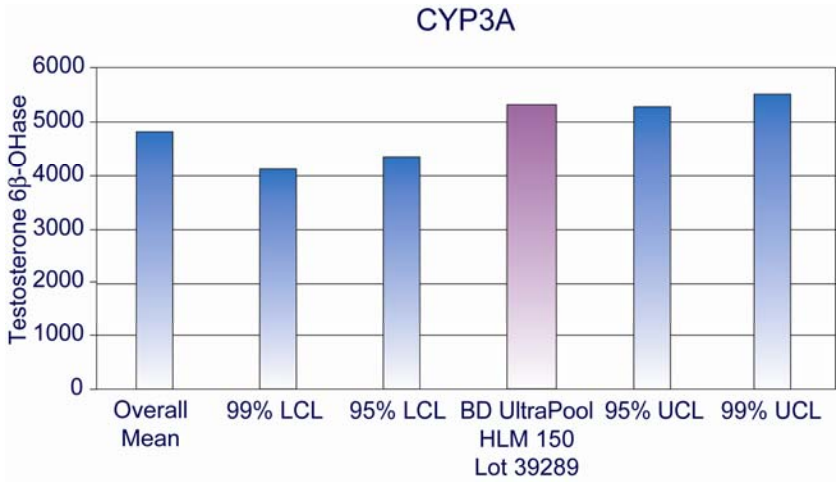






Modeled versus Lot 39289 (cont'd)





- Assay activities are in good agreement with the modeled activity and variability
- We predict that assay variability > product variability

BD UltraPool HLM 150—Recap

- Supported by scientific analyses of our historical data on HLM prepared from > 300 donors
- Designed to:
  - Bring reagent variability to level which is less than typical *in vitro* ADME assay variability
    - For the most important CYPs, CV $\leq$ 0.05
  - Represent the population average
  - Address gender bias among organ donor livers
  - Address age-related change in CYPs
  - Use livers which do not show evidence of improper handling and where considerable tissue was available
- Supported by pooled S9 and cytosol from the same donor set
- Use with confidence now and for years into the future!

Questions?

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