Q2 What were the pharmaceutical R&D expenses of your company in 2011?

Answered: 13 Skipped: 4

ANSWER CHOICES	RESPONSES	
Less than 1 billion US dollars	23%	3
1-2 billion US dollars	15%	2
More than 2 billion US dollars	62%	8
TOTAL		13

Q3 What percentage of your pipeline is (please do not include the '%' sign):

Answered: 14 Skipped: 3

ANSWER CHOICES	AVERAGE NUMBER	TOTAL NUMBER	RESPONSES
Small molecules	59	831	14
Therapeutic proteins	43	475	11
Other (e.g., vaccines, etc)	16	94	6
Total Respondents: 14			

#	SMALL MOLECULES	DATE
1	25	10/9/2013 12:04 PM
2	40	10/7/2013 9:25 PM
3	41	10/3/2013 11:44 PM
4	25	10/3/2013 4:52 PM
5	70	9/27/2013 9:15 PM
6	100	9/27/2013 4:11 PM
7	60	9/26/2013 4:47 PM
8	50	9/26/2013 3:14 PM
9	100	9/26/2013 2:00 PM
10	100	9/24/2013 8:42 PM
11	75	9/24/2013 5:35 PM
12	70	9/23/2013 11:06 PM
13	50	9/18/2013 7:01 PM
14	25	9/13/2013 1:55 PM
#	THERAPEUTIC PROTEINS	DATE
1	75	10/9/2013 12:04 PM
2	50	10/7/2013 9:25 PM
3	59	10/3/2013 11:44 PM
4	75	10/3/2013 4:52 PM
5	25	9/27/2013 9:15 PM
6	30	9/26/2013 4:47 PM
7	50	9/26/2013 3:14 PM
8	16	9/24/2013 5:35 PM
9	20	9/23/2013 11:06 PM
10	50	9/18/2013 7:01 PM
11	25	9/13/2013 1:55 PM
#	OTHER (E.G., VACCINES, ETC)	DATE
1	10	10/7/2013 9:25 PM

2	5	9/27/2013 9:15 PM
3	10	9/26/2013 4:47 PM
4	9	9/24/2013 5:35 PM
5	10	9/23/2013 11:06 PM
6	50	9/13/2013 1:55 PM

Q4 What areas of expertise are represented by the contributor(s) to this survey (check all that apply)?

Answered: 17 Skipped: 0

ANSWER CHOICES	RESPONSES	
Pharmacogenetics/pharmacogenomics	71%	12
Drug metabolism and pharmacokinetics	88%	15
Clinical pharmacology	35%	6
Regulatory	6%	1
Pharmacovigilance	0%	0
Total Respondents: 17		

#	OTHER (PLEASE SPECIFY)	DATE
	There are no responses.	

Q5 Do you conduct in vitro phenotyping studies to test for potential polymorphic enzyme or transporter involvement in clearance of discovery or development compounds prior to phase 1 clinical studies?

Answered: 17 Skipped: 0

ANSWER CHOICES	RESPONSES	
No	18%	3
Yes	82%	14
TOTAL		17

Q6 Will recent FDA and EMA Guidances concerning pharmacogenetics influence future policy at your company for conducting in vitro studies to test for potential polymorphic enzyme or transporter involvement in clearance of discovery or development compounds?If you answer yes, how will these guidances influence internal policy?If you answer no, why will these guidances not influence internal policy?

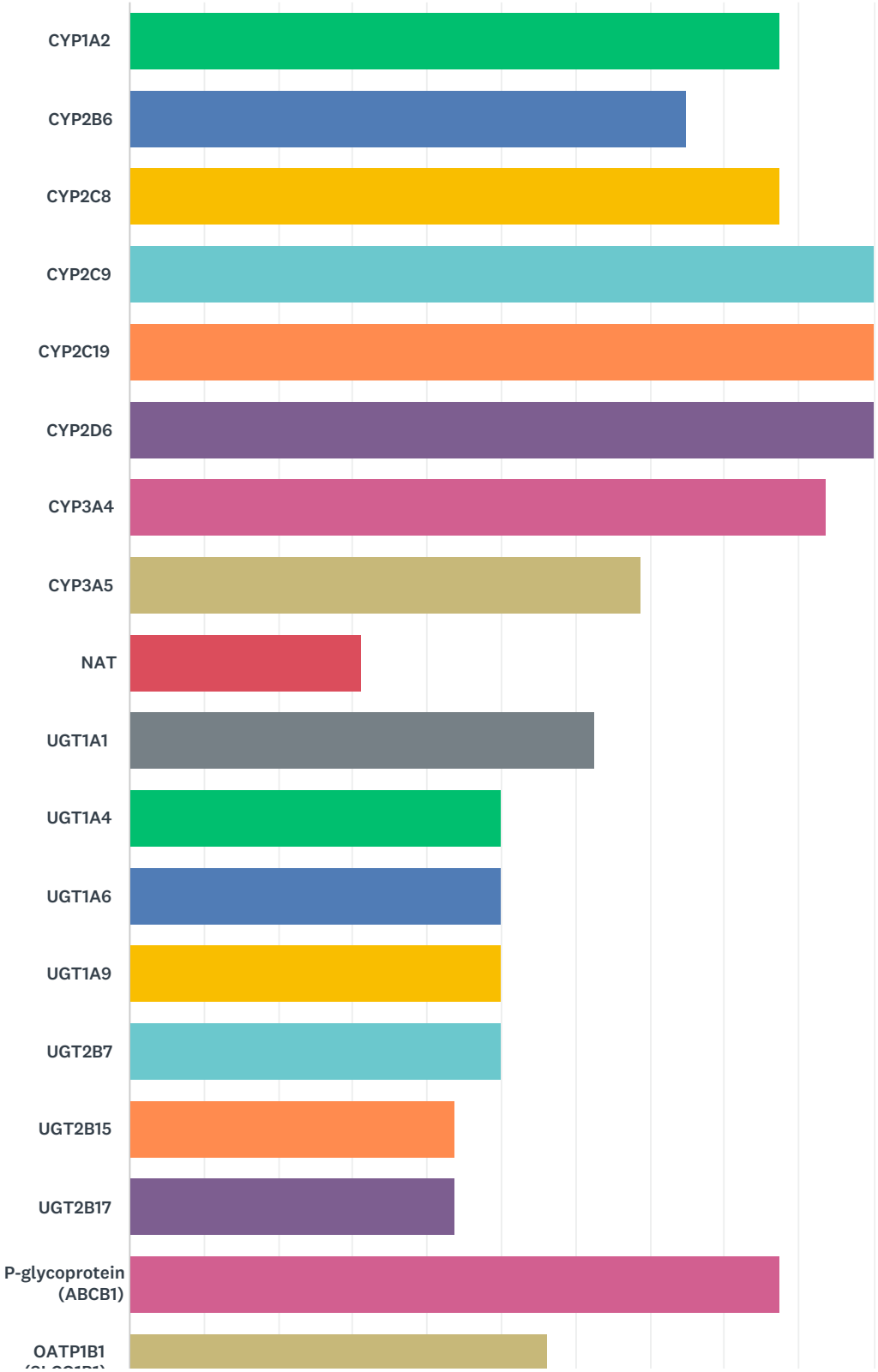
Answered: 17 Skipped: 0

ANSWER CHOICES	RESPONSES	
Yes	59%	10
No	41%	7
TOTAL		17

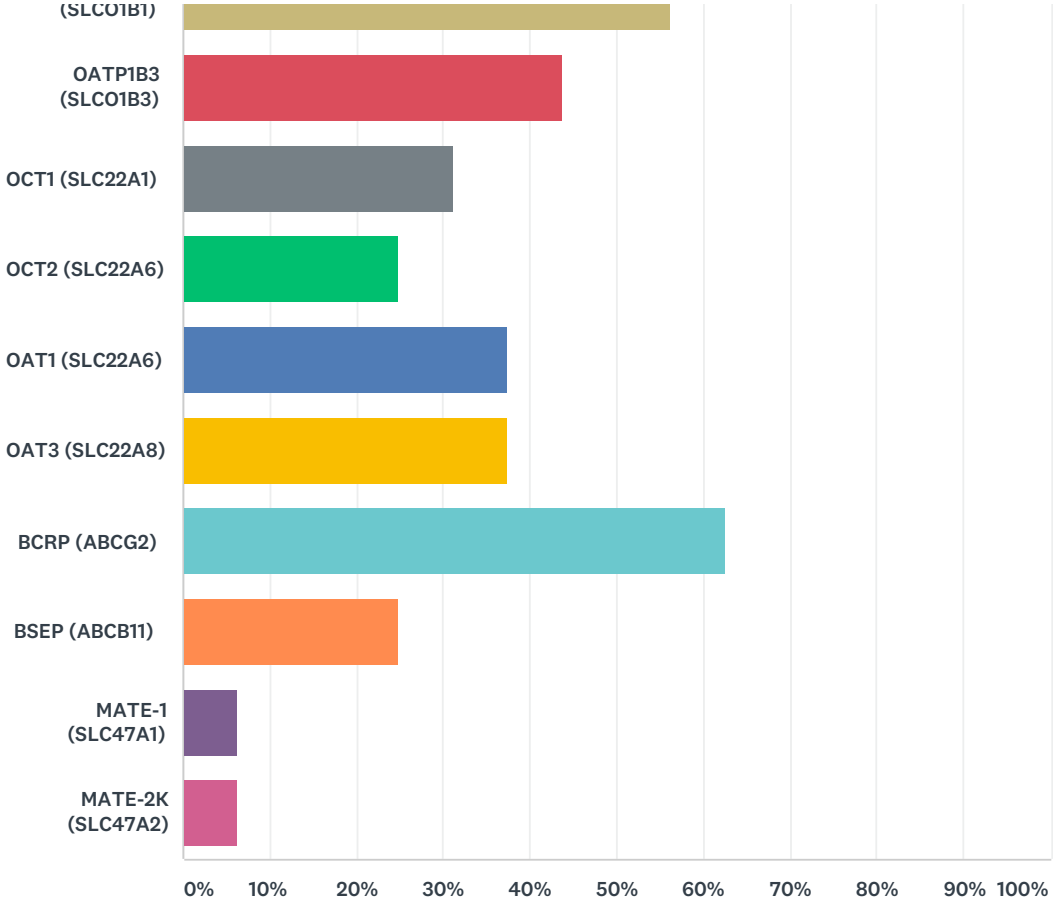
#	COMMENTS	DATE
1	not different from previous policy	10/9/2013 12:08 PM
2	FDA guidance	10/8/2013 9:50 PM
3	Company opinion is that regulatory guidances are being followed.	10/7/2013 9:26 PM
4	We have already assays in place to understand whether a polymorphic enzyme or transporter is involved in the metabolism and distribution of our compounds. We are already doing what the guidance suggests.	10/7/2013 3:58 PM
5	No major changes to the current practice, since in vitro studies for assessment of (polymorphic) enzymes or transporters were already done on a routine basis	9/27/2013 9:19 PM
6	More transporter work	9/27/2013 4:12 PM
7	The internal policy regarding enzymology and transporter pharmacogenetics is aligned with regulatory guidances.	9/26/2013 4:50 PM
8	resulted in in vitro phenotyping being competed sooner during drug development	9/26/2013 3:15 PM
9	Currently evaluation of internal processes in related to guidance on-going.	9/26/2013 2:00 PM
10	Will be used in conjunction with a Question Based Approach Tool that is provided to teams. In addition, there are guidance documents for phenotyping studies	9/24/2013 5:36 PM
11	on case by case basis, depending on whether the compound series has precedent historical data on polymorphic impact.	9/23/2013 11:06 PM
12	We follow the guidance ane establish the in vitro assays	9/18/2013 7:02 PM

Q7 Which drug metabolism enzymes and transporters does your company test in vitro for their involvement in clearance of discovery or development compounds prior to phase 1 clinical studies?

Answered: 16 Skipped: 1



Preclinical activities to support clinical trial genotyping



ANSWER CHOICES	RESPONSES	
CYP1A2	88%	14
CYP2B6	75%	12
CYP2C8	88%	14
CYP2C9	100%	16
CYP2C19	100%	16
CYP2D6	100%	16
CYP3A4	94%	15
CYP3A5	69%	11
NAT	31%	5
UGT1A1	63%	10
UGT1A4	50%	8
UGT1A6	50%	8
UGT1A9	50%	8
UGT2B7	50%	8
UGT2B15	44%	7
UGT2B17	44%	7

P-glycoprotein (ABCB1)	88%	14
OATP1B1 (SLCO1B1)	56%	9
OATP1B3 (SLCO1B3)	44%	7
OCT1 (SLC22A1)	31%	5
OCT2 (SLC22A6)	25%	4
OAT1 (SLC22A6)	38%	6
OAT3 (SLC22A8)	38%	6
BCRP (ABCG2)	63%	10
BSEP (ABCB11)	25%	4
MATE-1 (SLC47A1)	6%	1
MATE-2K (SLC47A2)	6%	1
Total Respondents: 16		

#	OTHER (PLEASE SPECIFY)	DATE
1	Some others on case-by-case basis	10/7/2013 9:28 PM
2	Above are done more routinely, including FMOs. Other are on a case by case situation	10/7/2013 4:00 PM
3	MRP2 (ABCC2)	10/3/2013 11:45 PM
4	CYP1A1, CYP1B1, CYP2A6, CYP2C18, CYP2E1, CYP2J2, CYP4A11, CYP4F2, CYP4F3B, CYP4F12, FMO-1, FMO-3, FMO-5, UGT1A3, UGT1A7, UGT1A8, UGT1A10, UGT2B4, AO, OAT2, MAO A/B	9/27/2013 9:20 PM
5	MRP2 and NAT are rarely tested, but on a case-by-case basis when data implicates their invovlement as a significant CL mechanism; also test UGT1A3 and 1A5	9/26/2013 4:58 PM
6	CYP enzymes if extensive CYP-mediated metabolism identified in in vitro studies. Other metabolizing enzymes and transporters case by case.	9/26/2013 2:00 PM
7	(CYP3A5, FMO3, AO, esterases and transporters) are analyzed if expected to be involved in metabolism or transport	9/24/2013 5:39 PM
8	Prior to Phase I, UGT and transporter substrate studies are conducted case-by-case depending on preclinical data.	9/13/2013 1:56 PM

Q8 What in vitro system(s) do you use for phenotyping studies prior to phase 1? (check all that apply)

Answered: 16 Skipped: 1

ANSWER CHOICES	RESPONSES	
Human liver microsomes with selective CYP inhibitors	100%	16
Recombinant human CYPs	94%	15
Human liver microsomes with selective UGT inhibitors	50%	8
Recombinant human UGTs	81%	13
Human hepatocytes for enzyme studies	69%	11
Established cell lines with one or more endogenously expressed transporter(s), such as Caco2	75%	12
Transfected cell lines with one or more expressed transporter(s)	81%	13
Membrane vesicles	69%	11
Human hepatocytes for transporter studies	44%	7
Total Respondents: 16		

#	OTHER IN VITRO ENZYME OR TRANSPORTER SYSTEMS (PLEASE SPECIFY ENZYMES OR TRANSPORTERS AND SYSTEMS)	DATE
1	CACO2	10/8/2013 9:51 PM
2	Most studies examining role of drug transporters in clearance are conducted during clinical development.	10/7/2013 9:31 PM
3	Pgp membrane vesicle assay if needed. SF9 transfected.	10/3/2013 11:47 PM
4	Engineered cells with genetic knockouts and those expressing recombinant UGTs or multiple recombinant transporters	9/27/2013 9:22 PM
5	carboxyl esterase and aldehyde dehydrogenase	9/26/2013 3:18 PM
6	anti-CYP inhibitory antibodies	9/24/2013 5:41 PM

Q9 Have you used in vitro systems expressing variants of polymorphic enzymes or transporters?

Answered: 16 Skipped: 1

ANSWER CHOICES	RESPONSES	
No	56%	9
Yes	44%	7
TOTAL		16

#	COMMENTS	DATE
1	Nothing recent	10/3/2013 11:47 PM
2	OATP1B1, CYP2D6, CYP2C9: difficult to get data for quantitative decision making as no data on Vmax can be obtained. HLM from individuals with homozygous or heterozygous with a null mutation would be needed.	9/24/2013 5:41 PM

Q10 If you have used in vitro systems expressing genetic variants of polymorphic enzymes and/or transporters, please specify which enzymes and transporters and which expression systems.

Answered: 8 Skipped: 9

#	RESPONSES	DATE
1	OATP1B1 variants in HEK293 cells; 2D6 poor/extensive metabolizers (microsomes)	10/7/2013 4:01 PM
2	CYP specifically 2C8 and 2C19	10/3/2013 11:47 PM
3	2C9, 2C19, UGT1A1, Pgp	10/1/2013 9:06 AM
4	Recombinant human CYPs (2C9, 2D6), recombinantly expressed human CYPs (supersomes)	9/27/2013 9:22 PM
5	Genotyped HLM (CYP1A1, 2B6, 2C9, 2C19, 2D6, 3A5; UGT1A1 and 2B7; NAT2), Recombinant enzymes (CYPs, UGTs, SULT)	9/26/2013 5:01 PM
6	CYP2C9, CYP2B6, CYP3A5, OATP1B1*15	9/26/2013 3:18 PM
7	OATP1B1, CYP2D6, CYP2C9 recombinant systems	9/24/2013 5:41 PM
8	HLM with variants in UGT1A1, UGT1A9, CYP3A5, CYP2D6, CYP2C8, CYP2C9, CYP2C19	9/13/2013 1:57 PM

Q11 What level of assay qualification/validation is typically used for in vitro enzyme or transporter assays when the data is used to determine whether to genotype subjects in phase 1 clinical studies?

Answered: 15 Skipped: 2

ANSWER CHOICES	RESPONSES	
High-throughput screening	0%	0
Later discovery with standardized protocol and limited controls)	47%	7
GLP-like (e.g., high number of claibration samples and replicates, positive and negative controls with characterized compounds)	47%	7
GLP	7%	1
Other	0%	0
TOTAL		15

#	OTHER (PLEASE SPECIFY)	DATE
1	occasionaly GLP is used, depending on the context	10/9/2013 12:14 PM
2	Depends. Sometimes "High-throughput screening"	10/3/2013 11:48 PM
3	Protocols are used instead of SOPs.	9/24/2013 5:42 PM
4	in-vitro data not used for genotyping decisions at phase 1.	9/23/2013 11:12 PM

Q12 When in vitro enzyme and transporter phenotyping data is used to include genotyping in phase 1 clinical studies, is a formal report written for regulatory submission?

Answered: 15 Skipped: 2

ANSWER CHOICES	RESPONSES	
Yes	60%	9
No	40%	6
TOTAL		15

#	COMMENTS	DATE
1	Lately we have not had cases where defined ADME genotyping has been included in P1. We do collect DNA samples and perform genotyping retrospectively if needed.	9/26/2013 2:00 PM
2	o Typically we do not do in-vitro phenotyping to investigate genotyping before phase 1	9/23/2013 11:12 PM

Q13 Please specify modeling and simulation software used with in vitro data to support phase 1 clinical studies (check all that apply):

Answered: 16 Skipped: 1

ANSWER CHOICES	RESPONSES	
Static modeling, using general pharmacokinetic equations	81%	13
DDI Predict	25%	4
PK-Sim	0%	0
DDI Predict	0%	0
SimCYP	81%	13
GastroPlus	81%	13
Total Respondents: 16		

#	OTHER (PLEASE SPECIFY)	DATE
	There are no responses.	

Q14 What in vitro parameters do you use to predict the impact of a polymorphic enzyme or transporter on drug clearance? (check all that apply)

Answered: 15 Skipped: 2

ANSWER CHOICES	RESPONSES	
Relative activity or expression factors (RAF or REF) or intersystem extrapolation factors (ISEF) values with recombinant CYPs	87%	13
% inhibition by selective CYP inhibitors in human liver microsomes (HLM)	93%	14
Relative activity or expression factors (RAF or REF) or intersystem extrapolation factors (ISEF) with recombinant UGTs	40%	6
% inhibition with selective UGT inhibitors in human liver microsomes (HLM)	60%	9
Active versus passive uptake in system with relevant transporter(s)	80%	12
% inhibition by selective transporter inhibitors	87%	13
Transporter Jmax (Vmax) and Km determination	33%	5
Total Respondents: 15		

#	OTHER (PLEASE SPECIFY)	DATE
1	Other	10/8/2013 9:52 PM
2	Correlation anlaysis (genotype vs metabolic CL) with genotyped human liver microsomes	9/26/2013 5:07 PM
3	Km, Vmax for a metabolite that is formed via a known enzymatic pathway	9/13/2013 1:58 PM

Q15 Please describe or cite key publications describing modeling and simulation approaches that are used to include genotyping into phase 1 clinical studies

Answered: 7 Skipped: 10

#	RESPONSES	DATE
1	regulatory guidelines and KOL publications	10/9/2013 12:18 PM
2	X Chu, K Korzekwa, R Elsby, et al ; on behalf of the International Transporter Consortium. Intracellular Drug Concentrations and Transporters: Measurement, Modeling, and Implications for the Liver Clinical Pharmacology & Therapeutics (2013); 94 1, 126–141. Watanabe, T., Kusuhara, H., Maeda, K., Shitara, Y. & Sugiyama, Y. Physiologically based pharmacokinetic modeling to predict transporter-mediated clearance and distribution of pravastatin in humans. J. Pharmacol. Exp. Ther. (2009); 328, 652–662. Fan J, Chen S, Chow EC, Pang KS. PBPK modeling of intestinal and liver enzymes and transporters in drug absorption and sequential metabolism. Curr Drug Metab. 2010 Nov;11(9):743-61.	10/3/2013 11:49 PM
3	Goutelle S, Bourguignon L, Bleyzac N, Berry J, Clavel-Grabit F, and Tod M (2013) In vivo quantitative prediction of the effect of gene polymorphisms and drug interactions on drug exposure for CYP2C19 substrates. The AAPS journal 15:415-426. Y. Chen, L. Liu, K. Nguyen, and A. Fretland, Utility of Intersystem Extrapolation Factors in Early Reaction Phenotyping and the Quantitative Extrapolation of Human Liver Microsomal Intrinsic Clearance Using Recombinant Cytochromes P450, DMD 39:373–382, 2011 (Demonstrates the predictive success of rhCYPs for estimating the fraction of total CL via each isoform)	9/26/2013 5:07 PM
4	-	9/26/2013 2:00 PM
5	None	9/24/2013 5:44 PM
6	None	9/23/2013 11:15 PM
7	Rodrigues AD. (1999) Integrated cytochrome P450 reaction phenotyping: attempting to bridge the gap between cDNA-expressed cytochromes P450 and native human liver microsomes. Biochem. Pharmacol., 57 (5), 465-480.	9/13/2013 1:58 PM

Q16 In general, how predictive have models using in vitro data been when compared to clinical experience?

Answered: 11 Skipped: 6

ANSWER CHOICES	RESPONSES	
Predictive within 2-fold	45%	5
Prediction differs from actual value(s) by greater than 2-fold	27%	3
Predictive within 2-fold for some enzymes or transporters	27%	3
TOTAL		11

#	COMMENTS (PLEASE PROVIDE MORE DETAIL)	DATE
1	case by case	10/9/2013 12:18 PM
2	In general, predictions are more often within 2-fold, but not always. Why or why not is usually not clear. Especially difficult with slowly metabolized/low clearance compounds.	10/7/2013 9:35 PM
3	Predictions are best for compounds where hepatic metabolism is the predominant elimination pathway. Contribution of transporters and extra-hepatic metabolism decreases predictability.	9/27/2013 9:24 PM
4	Not enough experience to make a statement	9/26/2013 2:00 PM
5	Limited experience makes assessment difficult.	9/24/2013 5:44 PM
6	to our knowledge within 2-fold for perpetrator of DDI (ref: Shardlow.C and al. “Impact of Physiologically-based Pharmacokinetic Modelling and Simulation in Drug Development”, Drug Metab Dispos dmd.113.052803; published ahead of print September 5, 2013, doi:10.1124/dmd.113.052803	9/23/2013 11:15 PM
7	in general predictions are within 2-4 fold, but for some drugs the prediction is better (within 2-fold)	9/13/2013 1:58 PM

Q17 Does your company have decision criteria regarding drug candidate progression based on predicted involvement (%) of a polymorphic enzyme or transporter in drug clearance?

Answered: 16 Skipped: 1

ANSWER CHOICES	RESPONSES	
No	13%	2
Yes, ≥25%	0%	0
Yes, ≥50%	13%	2
Case-by-case	75%	12
TOTAL		16

#	COMMENTS	DATE
1	Difficult to estimate metabolic and systemic clearance using in vitro models only.	10/7/2013 9:35 PM
2	In certain therapeutic areas, less stringent selection criteria are used (i.e., greater than 50-60% CL by a polymorphic route may be acceptable).	9/26/2013 5:07 PM

Q18 What is your company's general policy on genotyping drug metabolism enzymes and transporters in phase 1 subjects?

Answered: 17 Skipped: 0

ANSWER CHOICES	RESPONSES	
Genotype routinely, independent of in vitro data	12%	2
Genotype only when in vitro data suggests involvement of a polymorphic enzyme or transporter	24%	4
Genotype when high pharmacokinetic variability is observed in phase 1 clinical trials	65%	11
TOTAL		17

#	OTHER (PLEASE SPECIFY)	DATE
1	and in case in-vitro data suggest polymorphic protein involvement	10/9/2013 12:26 PM
2	or genotype when high pharmacokinetic variability is observed in phase 1 clinical trials	10/7/2013 4:09 PM
3	On a case-by-case basis, genotyping may be pursued in Phase 1 when in vitro data suggests involvement of a polymorphic pathway and we would like to relate exposure (phenotype) to genotype.	9/26/2013 5:13 PM
4	Both situationsindepndantly trigger genotyping in vitro data support involvement and high PK variability	9/24/2013 5:50 PM
5	If assets have committed to medicine development	9/23/2013 11:21 PM
6	GEnotype when clinical studies indicate polymorphic enzyme or transporter are involved in drug disposition	9/18/2013 7:24 PM

Q19 In interpreting the relevance of polymorphism data for a discovery or development program, do you consider disease indication and/or frequently co-administered drugs (e.g., statins)? (check all that apply)

Answered: 14 Skipped: 3

ANSWER CHOICES	RESPONSES	
Non-oncology indications considered	64%	9
Oncology indication considered	64%	9
Co-administered drugs for non-oncology indications considered	93%	13
Co-administered drugs for oncology indication considered	79%	11
Total Respondents: 14		

#	COMMENTS	DATE
1	This is driven by the literature and not specifically to a TA.	10/3/2013 11:49 PM
2	Had trouble understanding this question but the relvance is considered with multiple factors for any program	9/24/2013 5:50 PM
3	All apply but only at later stage in development, when phenotyping data are available	9/23/2013 11:21 PM

Q20 Has in vitro data influenced a decision to genotype subjects during phase 1 clinical studies in the past three years?

Answered: 17 Skipped: 0

ANSWER CHOICES	RESPONSES	
Yes	59%	10
No	41%	7
TOTAL		17

#	COMMENTS	DATE
1	Genotyping is done routinely in all phase 1 studies, independent of in vitro data.	10/7/2013 9:38 PM
2	Most commonly, in vitro data has indicated no polymorphically expressed enzyme contributing to >50% of total CL, influencing the lack of need to genotype in phase 1 studies. There have only been a few programs going forward with this liability. Genotyping of hepatic uptake transporters to characterize PK variability based on in vitro data indicating active uptake has occurred.	9/26/2013 5:13 PM

Q21 If you indicated that preclinical data has influenced a decision to genotype subjects during phase 1 in the past three years, in how many programs?

Answered: 12 Skipped: 5

ANSWER CHOICES	RESPONSES	
1-3 programs	50%	6
>3 programs	50%	6
TOTAL		12

Q22 Please list enzymes or transporters that have been genotyped in subjects during phase 1 based on in vitro data:

Answered: 10 Skipped: 7

#	RESPONSES	DATE
1	CYP2D6, NAT2	10/9/2013 12:26 PM
2	CYP2A6 CYP2B6 CYP2C9 CYP2C19 CYP2D6 Other phase I enzyme EPHX1/2 UGT1A1 Other phase II enzyme UGT1A9 / UGT2B4 / UGT2B7 / UGT2B15 OATP1B1 MDR1 CYP3A4 CYP3A5 SLCO1B1 SLCO2B1 SLCO1B3 SLC10A1 ABCG2	10/7/2013 4:09 PM
3	pGP and BCRP	10/3/2013 11:49 PM
4	NAT2, CYP2D6, CYP1A2	10/3/2013 4:53 PM
5	Chip genotyping of the complete set of relevant enzymes and transporters, with a special focus on CYP2C9, CYP2C19, CYP3A5, CYP2D6 and OATP1B1 depending on in vitro data.	9/27/2013 9:27 PM
6	CYP2C19, CYP3A5, OATP1B1	9/26/2013 5:13 PM
7	CYP2C9 and CYP2C19	9/26/2013 3:18 PM
8	Frequently will use DMET Chip some specific analyses have focused on OATP1B1/3 BSEP PGP MRP2) CYP2D6 UGT2B17 CYP2D6 CYP2C9 CYP2C19 UGT1A1	9/24/2013 5:50 PM
9	NAT2 and CYP2D6	9/18/2013 7:24 PM
10	UGT1A1, CYP2B6, CYP2C19, CYP2D6, 2C9	9/13/2013 1:59 PM

Q23 If clinical studies have been conducted with individuals with characterized genotype, what was the primary rationale?

Answered: 17 Skipped: 0

ANSWER CHOICES	RESPONSES	
This has not been done	29%	5
To include or exclude individuals from a clinical study	41%	7
To investigate pharmacokinetic variability	76%	13
To investigate efficacy	12%	2
To investigate safety	29%	5
Total Respondents: 17		

#	OTHER (PLEASE SPECIFY)	DATE
1	after phase 1	9/23/2013 11:21 PM

Q24 Have the preclinical strategies at your company been sufficient to identify polymorphic enzymes or transporters that were determined to be clinically important?

Answered: 14 Skipped: 3

ANSWER CHOICES	RESPONSES	
Yes	86%	12
No	14%	2
TOTAL		14

#	PLEASE SUMMARIZE EXPERIENCES	DATE
1	although at advance developmental stages	10/9/2013 12:28 PM
2	Routine genotyping of phase 1 subjects, independent of in vitro data, allows relatively fast examination of possible polymorphic metabolism or transport resulting in high PK variability.	10/7/2013 9:46 PM
3	Insufficient data and resources	10/3/2013 11:49 PM
4	For several projects, a contribution of polymorphic enzymes was predicted by in vitro data and later confirmed in clinical trials	9/27/2013 9:30 PM
5	We never went far enough to answer this question	9/27/2013 4:18 PM
6	Not enough experience to make a statement	9/26/2013 2:01 PM
7	In most cases for CYP enzymes sufficient, less precise for transporters and UGTs.	9/24/2013 5:51 PM
8	o Please summarize experiences there have been cases where despite some preclinical effort there has been PK variability in the clinic subsequently prescribe to polymorphic enzyme contributions to metabolism	9/13/2013 2:00 PM

Q25 Have the preclinical strategies at your company failed to identify polymorphic enzymes or transporters that were determined to be clinically important?

Answered: 14 Skipped: 3

ANSWER CHOICES	RESPONSES	
Yes	43%	6
No	57%	8
TOTAL		14

#	PLEASE SUMMARIZE EXPERIENCES (E.G., POOR COMPOUND SOLUBILITY; SLOW METABOLIC TURNOVER; PATHWAY NOT OBSERVED IN VITRO; ETC)	DATE
1	Poor solubility and slow metabolic turnover make determination of Fm difficult. A couple of examples where tested drug concentrations were too high, resulting in missed identification of the role of a polymorphic enzyme.	10/7/2013 9:46 PM
2	Insufficient data and resources	10/3/2013 11:49 PM
3	pathway not observed in microsomes	9/27/2013 9:30 PM
4	We never went far enough to answer this question	9/27/2013 4:18 PM
5	Km differences underestimated importance of CYP2D6 in the in vitro assays	9/26/2013 5:17 PM
6	We have seen higher variability than expected due to various reasons, at least partially due to poor compound solubility	9/26/2013 2:01 PM
7	Effect that an enzyme can have on exposure is not always known. In addition, phenotyping tools are not always available (e.g. UGTs).	9/24/2013 5:51 PM

Q26 What gaps do you see in the ability to determine the impact of polymorphic enzymes or transporters using in vitro studies?

Answered: 12 Skipped: 5

#	RESPONSES	DATE
1	Lack of in vitro models for the breadth of enzymes and transporters. Predictability of in vitro data is sometimes limited. Better tools and understanding to increase predictability from in vitro to clinical is needed.	10/7/2013 9:46 PM
2	Resources	10/3/2013 11:49 PM
3	It is difficult to estimate the contribution of polymorphic transporters or extrahepatic enzymes to total elimination; Not all polymorphisms are known	9/27/2013 9:30 PM
4	Not enough experience	9/27/2013 4:18 PM
5	Translation of in vitro fraction metabolized or transported (fm) data to in vivo fm; Compounded impact may be due to a lack of understanding of in vitro and/or in vivo enzyme or transporter abundance Lack of isoforms-selective chemical inhibitors for many enzymes and transporters Literature reports of attempts to determine the functional impact of transporter SNPs through in vitro studies with transfected cells has been inconclusive and contradictory. Even for the polymorphisms known to impact PK from clinical trials, unclear whether protein expression, cell-trafficking or function (e.g. altered Km) is the molecular basis. Timing of radiolabeled ADME studies (ie, late in development) to define primary CL mechanisms/routes	9/26/2013 5:17 PM
6	clearance pathways in early stage of drug development program	9/26/2013 3:19 PM
7	Lack of translational experience of in vitro findings to human/patients	9/26/2013 2:01 PM
8	variability in extrapolating the data to clinic	9/24/2013 8:50 PM
9	Recombinant polymorphic enzymes are not always available or HLM from genetic polymorphic livers not always available to determine the impact. Immature state of bottom up approaches for transporters. Quantitation of non-CYP enzymes and transporters. Determination of free intracellular drug concentrations.	9/24/2013 5:51 PM
10	The biggest gap is lacking of knowledge or understanding on clinical relevance for some polymorphic enzymes or transporters.	9/23/2013 11:22 PM
11	The impact of the polymorphic enzymes or transporters on drug disposition in clinic depends on the RAF of the enzymes/transporters. Due to the lack of specific inhibitor/substrate (at least for transporters), it may not be possible to determine the RAF	9/18/2013 7:26 PM
12	Difficulty assessing compounds that are poorly turned over in vitro, not having specific inhibitors for certain enzymes/transporters, difficulty in doing IVIVC for some enzymes transporters	9/13/2013 2:00 PM

Q27 Based on your experience, please rank human enzyme or transporter polymorphisms in terms of their clinical relevance

Answered: 16 Skipped: 1

	VERY RELEVANT	RELEVANT	SOMEWHAT RELEVANT	NOT RELEVANT	I DO NOT KNOW	TOTAL
CYP1A2	0% 0	13% 2	47% 7	33% 5	7% 1	15
CYP2B6	0% 0	40% 6	53% 8	7% 1	0% 0	15
CYP2C8	7% 1	47% 7	33% 5	7% 1	7% 1	15
CYP2C9	47% 7	47% 7	7% 1	0% 0	0% 0	15
CYP2C19	60% 9	40% 6	0% 0	0% 0	0% 0	15
CYP2D6	87% 13	13% 2	0% 0	0% 0	0% 0	15
CYP3A4	20% 3	0% 0	47% 7	27% 4	7% 1	15
CYP3A5	7% 1	47% 7	47% 7	0% 0	0% 0	15
NAT	0% 0	38% 6	38% 6	6% 1	19% 3	16
UGT1A1	67% 10	27% 4	0% 0	0% 0	7% 1	15
UGT1A4	0% 0	13% 2	33% 5	20% 3	33% 5	15
UGT1A6	0% 0	20% 3	20% 3	27% 4	33% 5	15
UGT1A9	0% 0	20% 3	27% 4	20% 3	33% 5	15
UGT2B7	20% 3	7% 1	27% 4	20% 3	27% 4	15
UGT2B15	7% 1	20% 3	20% 3	20% 3	33% 5	15
UGT2B17	13% 2	20% 3	7% 1	27% 4	33% 5	15
P-glycoprotein (ABCB1)	20% 3	27% 4	33% 5	13% 2	7% 1	15
OATP1B1 (SLCO1B1)	47% 7	47% 7	0% 0	0% 0	7% 1	15
OATP1B3 (SLCO1B3)	0% 0	27% 4	47% 7	13% 2	13% 2	15
OCT1 (SLC22A1)	0% 0	13% 2	67% 10	0% 0	20% 3	15

OCT2 (SLC22A2)	7% 1	7% 1	67% 10	0% 0	20% 3	15
OAT1 (SLC22A6)	0% 0	7% 1	29% 4	36% 5	29% 4	14
OAT3 (SLC22A8)	0% 0	7% 1	36% 5	36% 5	21% 3	14
BCRP(ABCG2)	20% 3	33% 5	27% 4	0% 0	20% 3	15
BSEP(ABCB11)	0% 0	7% 1	53% 8	20% 3	20% 3	15
MATE-1(SLC47A1)	7% 1	0% 0	50% 7	0% 0	43% 6	14
MATE-2K(SLC47A2)	7% 1	0% 0	43% 6	0% 0	50% 7	14

#	OTHER GENES? (PLEASE SPECIFY)	DATE
1	Any one can be relevant for examples, depends on to % of metabolism /transport through a certain pathway frequency of non functional variants etc	9/24/2013 5:57 PM

Q28 Thank you for your help!

Answered: 1 Skipped: 16

#	RESPONSES	DATE
1	THANK YOU	9/24/2013 8:53 PM