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			

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		

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

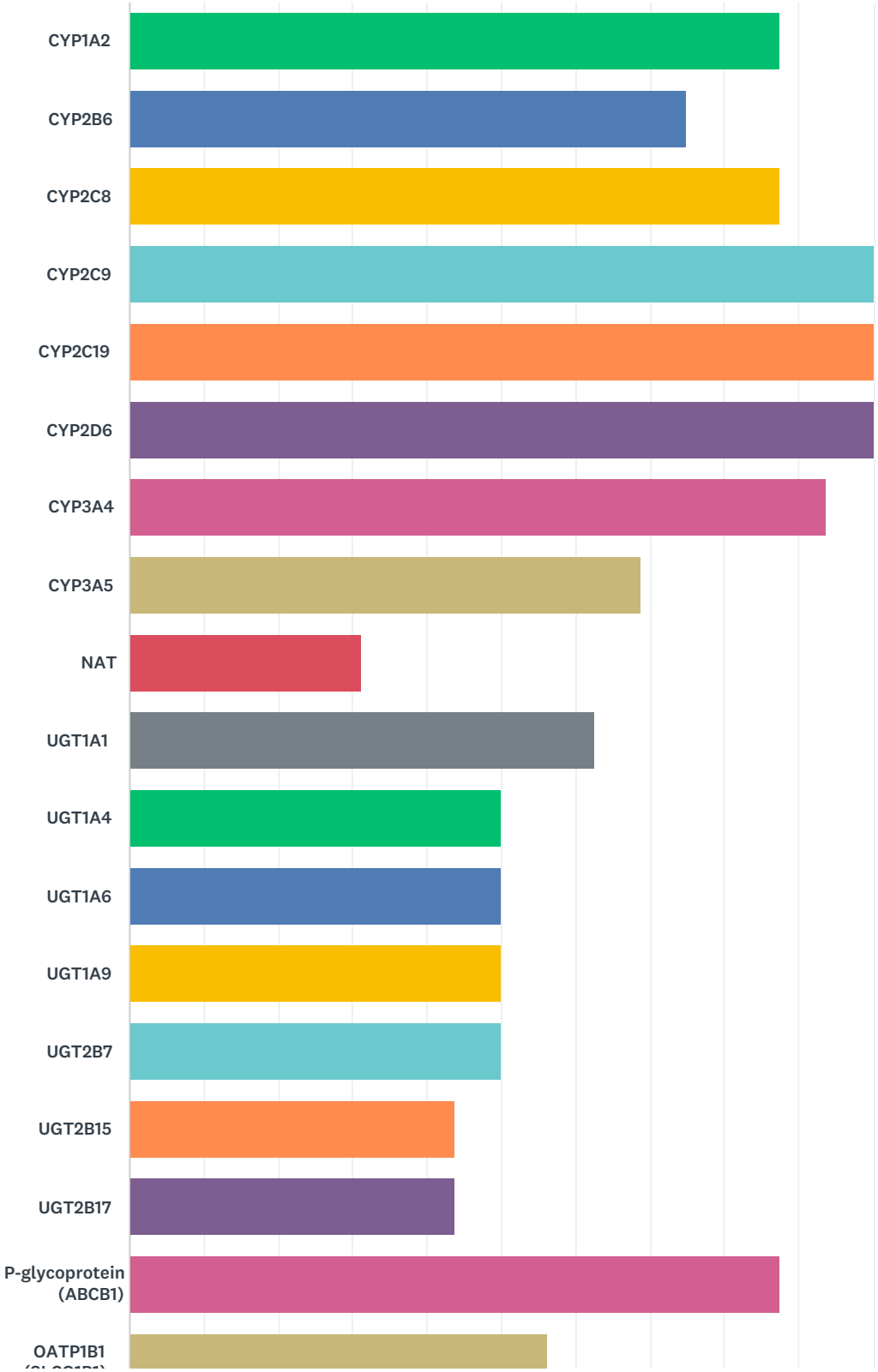
Q6 Will recent FDA and EMA Guidances concerning pharmacogenetics influence future policy at your company for conducting in vitro studies to test for potential polymorphic enzyme or transporter involvement in clearance of discovery or development compounds?If you answer yes, how will these guidances influence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

Answered: 17 Skipped: 0

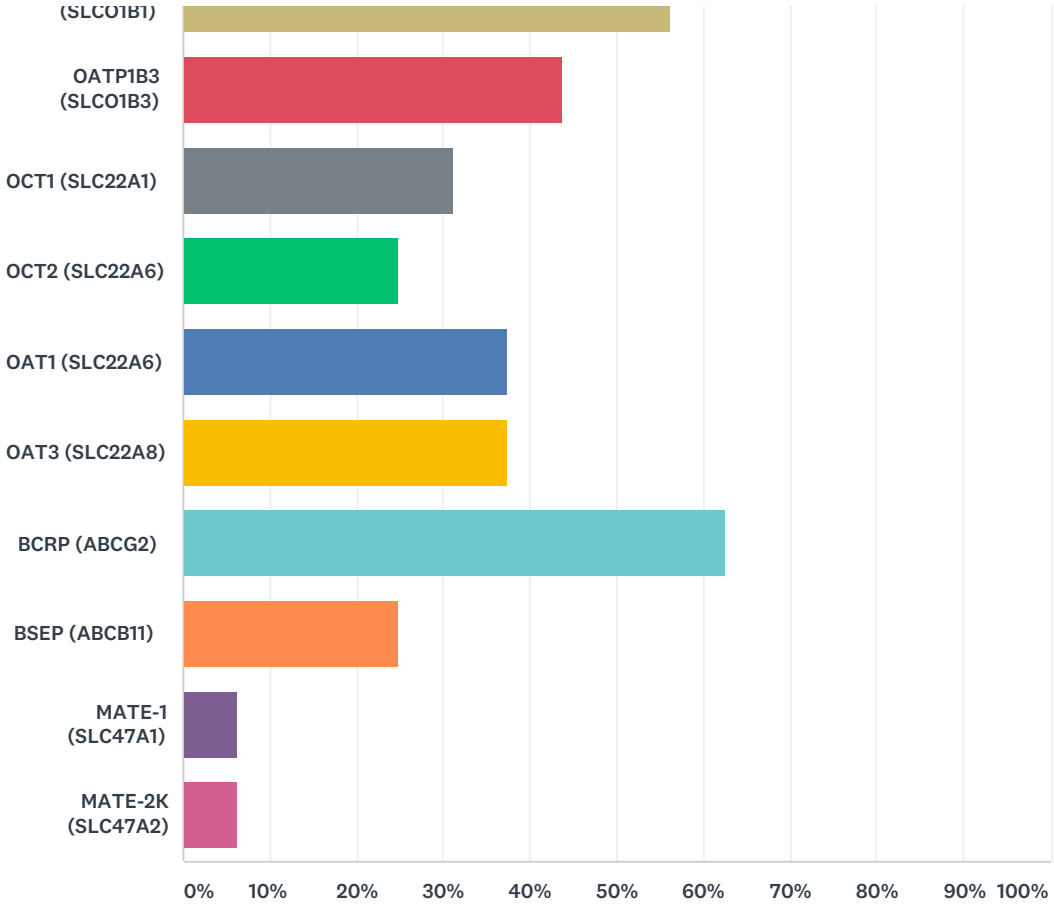
ANSWER CHOICES	RESPONSES	
Yes	59%	10
No	41%	7
TOTAL		17

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		

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		

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

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

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

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

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		

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		

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

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

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

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

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		

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

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

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		

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

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

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

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

Q28 Thank you for your help!

Answered: 1 Skipped: 16