#1

COMPLETE

Collector:	Email Invitation 1 (Email)
Started:	Tuesday, October 01, 2019 5:11:25 PM
Last Modified:	Tuesday, October 01, 2019 5:34:49 PM
Time Spent:	00:23:24
Email:	
IP Address:	

Page 1: I-PWG ADME Task Force Survey - August 2019

Q1 Please enter your unique individual Survey Monkey Code that was sent to you by Julian Arbuckle:

5351

Q2 What were the pharmaceutical R&D expenses of your company in 2018?

>4 $ Billion

Q3 What percentage of your pipeline is represented by small molecules:

Respondent skipped this question

Q4 What percentage of your pipeline is represented by therapeutic proteins, vaccines, or other types of compounds (not small molecule):

Respondent skipped this question

Q5 Do you typically conduct in vitro phenotyping studies to assess enzyme involvement in clearance of discovery or development compounds prior to phase 1 clinical studies?

Respondent skipped this question

Q6 Do you typically conduct in vitro phenotyping studies to assess transporter involvement in clearance of discovery or development compounds prior to Phase 1 clinical studies?

Respondent skipped this question

Q7 Which 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? Select all that apply.

Respondent skipped this question

Q8 Are there additional enzymes or transporters you would assess, given availability of appropriate and accurate in vitro tools? Please list.

Respondent skipped this question

Q9 What methods do you typically employ in preclinical studies to predict the fm (fraction metabolized) by particular enzymes? Please describe.	**Respondent skipped this question**
Q10 For which enzymes do you typically have high confidence in the estimated fm based on preclinical studies? None, or Please list.	**Respondent skipped this question**
Q11 If a compound is stable from stability assays using human liver microsomes or hepatocytes, but studies using recombinant enzymes suggest the compound is metabolized by a polymorphic enzyme, do you determine fm by the polymorphic enzyme?	**Respondent skipped this question**
Q12 If you answered "Yes" to Question 11 what are the in vitro tools?	**Respondent skipped this question**
Q13 What methods do you typically employ in preclinical studies to predict the ft (fraction transported) by particular transporters? Please describe.	**Respondent skipped this question**
Q14 For which transporters do you typically have high confidence in the estimated ft based on preclinical studies? None, or Please List	**Respondent skipped this question**
Q15 Have the preclinical strategies at your company failed to identify enzymes or transporters that were later (e.g. at the time of the human ADME study) determined to be clinically important?	**Respondent skipped this question**
Q16 If you answered "Yes" to Question 15 what was determined to be the reason these enzymes were missed as part of pre-clinical evaluations?	**Respondent skipped this question**
Q17 What percent of small-molecule compounds in your pipeline are metabolized or transported at least in part by CYP2D6?	**Respondent skipped this question**
Q18 What percent of small-molecule compounds in your pipeline are metabolized at least in part by CYP2C19?	**Respondent skipped this question**
Q19 What percent of small-molecule compounds in your pipeline are metabolized at least in part by CYP2C9?	**Respondent skipped this question**

Q20 What percent of small-molecule compounds in your pipeline are metabolized at least in part by UGT1A1?	**Respondent skipped this question**
Q21 What percent of small-molecule compounds in your pipeline are transported at least in part by SLCO1B1?	**Respondent skipped this question**
Q22 What percent of small-molecule compounds in your pipeline are transported at least in part by BCRP?	**Respondent skipped this question**
Q23 What percent of small-molecule compounds in your pipeline are transported at least in part by OCT1?	**Respondent skipped this question**
Q24 Do you use modeling and simulation tools to predict the impact of genetic variants in enzymes/transporters on compound disposition prior to clinical studies?	**Respondent skipped this question**
Q25 If you answered "Yes" to Question 24, please describe scenarios in which such tools may be used and what software is being used:	**Respondent skipped this question**
Q26 Does your company have decision criteria regarding drug candidate progression based on predicted involvement (%) of an enzyme or transporter with genetic variants that might impact clearance? Select all that apply.	**Respondent skipped this question**
Q27 If your company advances drug candidates with a predicted significant involvement of a polymorphic enzyme or transporter in clearance, are further pre-clinical studies performed to assess the risks?	**Respondent skipped this question**
Q28 If you answered "Yes" to Question 27 please describe (e.g. use of genotyped hepatocytes, recombinant systems expressing variant. Please include specific enzymes/transporters and alleles assayed using a given method.)	**Respondent skipped this question**
Q29 What gaps do you see in the ability to determine the impact of enzymes with genetic variants that might impact the drug development program using in vitro studies? Select all that apply.	**Respondent skipped this question**

Q30 What gaps do you see in the ability to determine the impact of transporters with genetic variants that might impact the drug development program using in vitro studies? Select all that apply.

Respondent skipped this question

#2

COMPLETE

Collector:	Email Invitation 1 (Email)
Started:	Thursday, October 03, 2019 5:46:59 PM
Last Modified:	Thursday, October 03, 2019 5:58:14 PM
Time Spent:	00:11:15
Email:	
IP Address:	

Page 1: I-PWG ADME Task Force Survey - August 2019

Q1 Please enter your unique individual Survey Monkey Code that was sent to you by Julian Arbuckle:	**Respondent skipped this question**
Q2 What were the pharmaceutical R&D expenses of your company in 2018?	**<1 $ Billion**
Q3 What percentage of your pipeline is represented by small molecules:	**<10%**
Q4 What percentage of your pipeline is represented by therapeutic proteins, vaccines, or other types of compounds (not small molecule):	**>75%**
Q5 Do you typically conduct in vitro phenotyping studies to assess enzyme involvement in clearance of discovery or development compounds prior to phase 1 clinical studies?	**No**
Q6 Do you typically conduct in vitro phenotyping studies to assess transporter involvement in clearance of discovery or development compounds prior to Phase 1 clinical studies?	**No**
Q7 Which 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? Select all that apply.	Other (please specify): nucleases, which is well understood already for the platform

Q8 Are there additional enzymes or transporters you would assess, given availability of appropriate and accurate in vitro tools? Please list.

No

Q9 What methods do you typically employ in preclinical studies to predict the fm (fraction metabolized) by particular enzymes? Please describe.

no applicable for RNA drugs

Q10 For which enzymes do you typically have high confidence in the estimated fm based on preclinical studies? None, or Please list.

NA

Q11 If a compound is stable from stability assays using human liver microsomes or hepatocytes, but studies using recombinant enzymes suggest the compound is metabolized by a polymorphic enzyme, do you determine fm by the polymorphic enzyme?

No

Q12 If you answered "Yes" to Question 11 what are the in vitro tools?

Respondent skipped this question

Q13 What methods do you typically employ in preclinical studies to predict the ft (fraction transported) by particular transporters? Please describe.

NA

Q14 For which transporters do you typically have high confidence in the estimated ft based on preclinical studies? None, or Please List

NA

Q15 Have the preclinical strategies at your company failed to identify enzymes or transporters that were later (e.g. at the time of the human ADME study) determined to be clinically important?

No

Q16 If you answered "Yes" to Question 15 what was determined to be the reason these enzymes were missed as part of pre-clinical evaluations?

Respondent skipped this question

Q17 What percent of small-molecule compounds in your pipeline are metabolized or transported at least in part by CYP2D6?

<10%

Q18 What percent of small-molecule compounds in your pipeline are metabolized at least in part by CYP2C19?

<10%

Q19 What percent of small-molecule compounds in your pipeline are metabolized at least in part by CYP2C9?	**<10%**
Q20 What percent of small-molecule compounds in your pipeline are metabolized at least in part by UGT1A1?	**<10%**
Q21 What percent of small-molecule compounds in your pipeline are transported at least in part by SLCO1B1?	**<10%**
Q22 What percent of small-molecule compounds in your pipeline are transported at least in part by BCRP?	**<10%**
Q23 What percent of small-molecule compounds in your pipeline are transported at least in part by OCT1?	**<10%**
Q24 Do you use modeling and simulation tools to predict the impact of genetic variants in enzymes/transporters on compound disposition prior to clinical studies?	**No**
Q25 If you answered "Yes" to Question 24, please describe scenarios in which such tools may be used and what software is being used:	**Respondent skipped this question**
Q26 Does your company have decision criteria regarding drug candidate progression based on predicted involvement (%) of an enzyme or transporter with genetic variants that might impact clearance? Select all that apply.	**No**
Q27 If your company advances drug candidates with a predicted significant involvement of a polymorphic enzyme or transporter in clearance, are further pre-clinical studies performed to assess the risks?	**No**
Q28 If you answered "Yes" to Question 27 please describe (e.g. use of genotyped hepatocytes, recombinant systems expressing variant. Please include specific enzymes/transporters and alleles assayed using a given method.)	**Respondent skipped this question**
Q29 What gaps do you see in the ability to determine the impact of enzymes with genetic variants that might impact the drug development program using in vitro studies? Select all that apply.	**Lack of in vitro models**

Q30 What gaps do you see in the ability to determine the impact of transporters with genetic variants that might impact the drug development program using in vitro studies? Select all that apply.	**Lack of in vitro models**

#3

COMPLETE

Collector:	Email Invitation 1 (Email)
Started:	Wednesday, October 09, 2019 1:04:14 PM
Last Modified:	Wednesday, October 09, 2019 1:37:31 PM
Time Spent:	00:33:17
Email:	
IP Address:	

Page 1: I-PWG ADME Task Force Survey - August 2019

Q1 Please enter your unique individual Survey Monkey Code that was sent to you by Julian Arbuckle:

We will not get 4M but Sam did not want us to remove anything either. He asked that we prioritize the most important items for the coming year (Keeping it at more like 2M or less)

Q2 What were the pharmaceutical R&D expenses of your company in 2018?	**<1 $ Billion**
Q3 What percentage of your pipeline is represented by small molecules:	**50-75%**
Q4 What percentage of your pipeline is represented by therapeutic proteins, vaccines, or other types of compounds (not small molecule):	**10-25%**
Q5 Do you typically conduct in vitro phenotyping studies to assess enzyme involvement in clearance of discovery or development compounds prior to phase 1 clinical studies?	**Yes**
Q6 Do you typically conduct in vitro phenotyping studies to assess transporter involvement in clearance of discovery or development compounds prior to Phase 1 clinical studies?	**Yes**

Q7 Which 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? Select all that apply.

CYP1A2,
CYP2B6,
CYP2C19,
CYP2C8,
CYP2C9,
CYP2D6,
CYP3A4,
AOX1,
SLCO1B1,
SLCO1B3,
UGT1A1,
UGT1A3,
UGT1A7,
UGT2B17,
UGT2B7,
CES1,
CES2

Q8 Are there additional enzymes or transporters you would assess, given availability of appropriate and accurate in vitro tools? Please list.

MDR1 and MRP2

Q9 What methods do you typically employ in preclinical studies to predict the fm (fraction metabolized) by particular enzymes? Please describe.

recombinant enzymes using the RAF method, inhibition with specific inhibitors in human hepatocytes or microsomes.

Q10 For which enzymes do you typically have high confidence in the estimated fm based on preclinical studies? None, or Please list.

CYP3A, CYP2C, CYP1A family of enzymes

Q11 If a compound is stable from stability assays using human liver microsomes or hepatocytes, but studies using recombinant enzymes suggest the compound is metabolized by a polymorphic enzyme, do you determine fm by the polymorphic enzyme?

Yes

Q12 If you answered "Yes" to Question 11 what are the in vitro tools?

recombinant enzymes if available.

Q13 What methods do you typically employ in preclinical studies to predict the ft (fraction transported) by particular transporters? Please describe.

Crypreserved human hepatocytes and overexpressing cells are used. Using OATP1B1 reference substrates the RAF method is used to predict in vivo CLint,all of test OATP1B1 substrate drugs from OATP1B1-transfected cells.

Q14 For which transporters do you typically have high confidence in the estimated ft based on preclinical studies? None, or Please List

OATP1B1 and OATP1B3

Q15 Have the preclinical strategies at your company failed to identify enzymes or transporters that were later (e.g. at the time of the human ADME study) determined to be clinically important?	**Yes**

Q16 If you answered "Yes" to Question 15 what was determined to be the reason these enzymes were missed as part of pre-clinical evaluations?

Lack of appropriate in vitro tools, Lack of knowledge about the extrahepatic or hepatic expression of enzymes.

Q17 What percent of small-molecule compounds in your pipeline are metabolized or transported at least in part by CYP2D6?	**<10%**
Q18 What percent of small-molecule compounds in your pipeline are metabolized at least in part by CYP2C19?	**<10%**
Q19 What percent of small-molecule compounds in your pipeline are metabolized at least in part by CYP2C9?	**10-25%**
Q20 What percent of small-molecule compounds in your pipeline are metabolized at least in part by UGT1A1?	**<10%**
Q21 What percent of small-molecule compounds in your pipeline are transported at least in part by SLCO1B1?	**25-50%**
Q22 What percent of small-molecule compounds in your pipeline are transported at least in part by BCRP?	**10-25%**

Q23 What percent of small-molecule compounds in your pipeline are transported at least in part by OCT1?	**10-25%**
Q24 Do you use modeling and simulation tools to predict the impact of genetic variants in enzymes/transporters on compound disposition prior to clinical studies?	**Yes**

Q25 If you answered "Yes" to Question 24, please describe scenarios in which such tools may be used and what software is being used:

We use Simcyp population simulator to explore the DDI in case of a polymorphic enzyme. This is only feasible if the frequency of the polymorphic population is available in the simulator.
We also use sensitivity analysis to understand the impact of the polymorphic enzyme on drug exposure and DDI.

Q26 Does your company have decision criteria regarding drug candidate progression based on predicted involvement (%) of an enzyme or transporter with genetic variants that might impact clearance? Select all that apply.	**Depends on the compound or therapeutic area (please describe further – fill in)**
Q27 If your company advances drug candidates with a predicted significant involvement of a polymorphic enzyme or transporter in clearance, are further pre-clinical studies performed to assess the risks?	**Yes**

Q28 If you answered "Yes" to Question 27 please describe (e.g. use of genotyped hepatocytes, recombinant systems expressing variant. Please include specific enzymes/transporters and alleles assayed using a given method.)

We used recombinant systems that express the variant. Additionally we use PBPK modeling to understand the impact of these polymorphisms. These simulations are then used to make decisions on clinical study design, clinical pharmacology planning.

Q29 What gaps do you see in the ability to determine the impact of enzymes with genetic variants that might impact the drug development program using in vitro studies? Select all that apply.	**Lack of in vitro models** , **Inaccuracy of in vitro models** , **Impact of polymorphisms is not well characterized** , **Low turnover in vitro for certain compounds**
Q30 What gaps do you see in the ability to determine the impact of transporters with genetic variants that might impact the drug development program using in vitro studies? Select all that apply.	**Inaccuracy of in vitro models**

#4

COMPLETE

Collector:	Email Invitation 2 (Email)
Started:	Thursday, October 10, 2019 1:06:33 PM
Last Modified:	Thursday, October 10, 2019 1:22:51 PM
Time Spent:	00:16:17
Email:	
IP Address:	

Page 1: I-PWG ADME Task Force Survey - August 2019

Q1 Please enter your unique individual Survey Monkey Code that was sent to you by Julian Arbuckle:

3078

Q2 What were the pharmaceutical R&D expenses of your company in 2018?	**>4 $ Billion**
Q3 What percentage of your pipeline is represented by small molecules:	**50-75%**
Q4 What percentage of your pipeline is represented by therapeutic proteins, vaccines, or other types of compounds (not small molecule):	**25-50%**
Q5 Do you typically conduct in vitro phenotyping studies to assess enzyme involvement in clearance of discovery or development compounds prior to phase 1 clinical studies?	**Yes**
Q6 Do you typically conduct in vitro phenotyping studies to assess transporter involvement in clearance of discovery or development compounds prior to Phase 1 clinical studies?	**Yes**

Q7 Which 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? Select all that apply.

ABCB1,
ABCG2,
CYP1A2,
CYP2B6,
CYP2C18,
CYP2C19,
CYP2C8,
CYP2C9,
CYP2D6,
CYP3A4,
CYP3A5,
SLCO1B1,
SLCO1B3,
UGT1A1,
UGT1A3,
UGT1A4,
UGT1A6,
UGT1A7,
UGT1A8,
UGT1A9,
UGT1A10,
UGT2B4,
UGT2B15,
UGT2B17,
UGT2B7

Q8 Are there additional enzymes or transporters you would assess, given availability of appropriate and accurate in vitro tools? Please list.

none

Q9 What methods do you typically employ in preclinical studies to predict the fm (fraction metabolized) by particular enzymes? Please describe.

Recombinant enzymes and ISEF approaches for CYPs, human liver microsomes with specific inhibitors and inhibitory antibodies are used as well

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Q10 For which enzymes do you typically have high confidence in the estimated fm based on preclinical studies? None, or Please list.

All CYPs

Q11 If a compound is stable from stability assays using human liver microsomes or hepatocytes, but studies using recombinant enzymes suggest the compound is metabolized by a polymorphic enzyme, do you determine fm by the polymorphic enzyme? **Yes**

Q12 If you answered "Yes" to Question 11 what are the in vitro tools?

Hepatopac used to confirm metabolism

Q13 What methods do you typically employ in preclinical studies to predict the ft (fraction transported) by particular transporters? Please describe.

Not routinely used.

Q14 For which transporters do you typically have high confidence in the estimated ft based on preclinical studies? None, or Please List

none

Q15 Have the preclinical strategies at your company failed to identify enzymes or transporters that were later (e.g. at the time of the human ADME study) determined to be clinically important? **Yes**

Q16 If you answered "Yes" to Question 15 what was determined to be the reason these enzymes were missed as part of pre-clinical evaluations?

UGT2B17 – wasn’t routinely analyzed at the time

Q17 What percent of small-molecule compounds in your pipeline are metabolized or transported at least in part by CYP2D6? **<10%**

Q18 What percent of small-molecule compounds in your pipeline are metabolized at least in part by CYP2C19? **<10%**

Q19 What percent of small-molecule compounds in your pipeline are metabolized at least in part by CYP2C9? **<10%**

Q20 What percent of small-molecule compounds in your pipeline are metabolized at least in part by UGT1A1?	**<10%**
Q21 What percent of small-molecule compounds in your pipeline are transported at least in part by SLCO1B1?	**<10%**
Q22 What percent of small-molecule compounds in your pipeline are transported at least in part by BCRP?	**<10%**
Q23 What percent of small-molecule compounds in your pipeline are transported at least in part by OCT1?	**<10%**
Q24 Do you use modeling and simulation tools to predict the impact of genetic variants in enzymes/transporters on compound disposition prior to clinical studies?	**Yes**

Q25 If you answered "Yes" to Question 24, please describe scenarios in which such tools may be used and what software is being used:

SimCYP – simulate poor, normal and extensive metabolizers

Q26 Does your company have decision criteria regarding drug candidate progression based on predicted involvement (%) of an enzyme or transporter with genetic variants that might impact clearance? Select all that apply.	**Depends on the compound or therapeutic area (please describe further – fill in)**
Q27 If your company advances drug candidates with a predicted significant involvement of a polymorphic enzyme or transporter in clearance, are further pre-clinical studies performed to assess the risks?	**Yes**

Q28 If you answered "Yes" to Question 27 please describe (e.g. use of genotyped hepatocytes, recombinant systems expressing variant. Please include specific enzymes/transporters and alleles assayed using a given method.)

.) In select cases have determined intrinsic clearance in hepatocytes from pre-genotyped donors with CYP2C19*1/*1 (wild type) and CYP2C19*2/*2 as well as CYP2C19*3/*3 (poor metabolizer). Use of polymorphic enzymes is being considered, but not currently in use.

Q29 What gaps do you see in the ability to determine the impact of enzymes with genetic variants that might impact the drug development program using in vitro studies? Select all that apply.	**Low turnover in vitro for certain compounds** , Other (please specify): combination of enzymes+transporters

Q30 What gaps do you see in the ability to determine the impact of transporters with genetic variants that might impact the drug development program using in vitro studies? Select all that apply.	Other (please specify): Inaccuracy of in vitro models; Impact of polymorphisms is not well characterized; Other: contradictory clinical data for some transporters such as OCT1 and MDR1 P-gp)

#5

COMPLETE

Collector:	Email Invitation 3 (Email)
Started:	Friday, October 11, 2019 9:09:52 AM
Last Modified:	Friday, October 11, 2019 10:24:51 AM
Time Spent:	01:14:58
Email:	
IP Address:	

Page 1: I-PWG ADME Task Force Survey - August 2019

Q1 Please enter your unique individual Survey Monkey Code that was sent to you by Julian Arbuckle:

7755

Q2 What were the pharmaceutical R&D expenses of your company in 2018?	**<1 $ Billion**
Q3 What percentage of your pipeline is represented by small molecules:	**>75%**
Q4 What percentage of your pipeline is represented by therapeutic proteins, vaccines, or other types of compounds (not small molecule):	**<10%**
Q5 Do you typically conduct in vitro phenotyping studies to assess enzyme involvement in clearance of discovery or development compounds prior to phase 1 clinical studies?	**Yes**
Q6 Do you typically conduct in vitro phenotyping studies to assess transporter involvement in clearance of discovery or development compounds prior to Phase 1 clinical studies?	**No**
Q7 Which 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? Select all that apply.	**ABCB1,** **ABCG2,** **ABCB11,** **CYP1A1,** **CYP1A2,** **CYP2A6,** **CYP2B6,** **CYP2C18,**

CYP2C19,

CYP2C8,

CYP2C9,

CYP2D6,

CYP2E1,

CYP3A4,

CYP3A5,

FMO1,

FMO3,

AOX1,

NAT2,

SLC22A1,

SLCO1B1,

SLCO1B3,

SLCO2B1,

SULT1A1,

UGT1A1,

UGT1A3,

UGT1A4,

UGT1A5,

UGT1A6,

UGT1A7,

UGT1A8,

UGT1A9,

UGT1A10,

UGT2B4,

UGT2B15,

UGT2B17,

UGT2B7,

Other (please specify):

UGT2B10, MAOA, MAOB

Q8 Are there additional enzymes or transporters you would assess, given availability of appropriate and accurate in vitro tools? Please list.

Respondent skipped this question

Q9 What methods do you typically employ in preclinical studies to predict the fm (fraction metabolized) by particular enzymes? Please describe.

Recombinant enzymes and hepatocytes with specific inhibitor followed by in vitro-in vivo scaling

Q10 For which enzymes do you typically have high confidence in the estimated fm based on preclinical studies? None, or Please list.

None

Q11 If a compound is stable from stability assays using human liver microsomes or hepatocytes, but studies using recombinant enzymes suggest the compound is metabolized by a polymorphic enzyme, do you determine fm by the polymorphic enzyme?

No

Q12 If you answered "Yes" to Question 11 what are the in vitro tools?

Respondent skipped this question

Q13 What methods do you typically employ in preclinical studies to predict the ft (fraction transported) by particular transporters? Please describe.

NA

Q14 For which transporters do you typically have high confidence in the estimated ft based on preclinical studies? None, or Please List

NONE

Q15 Have the preclinical strategies at your company failed to identify enzymes or transporters that were later (e.g. at the time of the human ADME study) determined to be clinically important?

Respondent skipped this question

Q16 If you answered "Yes" to Question 15 what was determined to be the reason these enzymes were missed as part of pre-clinical evaluations?

Respondent skipped this question

Q17 What percent of small-molecule compounds in your pipeline are metabolized or transported at least in part by CYP2D6?

Respondent skipped this question

Q18 What percent of small-molecule compounds in your pipeline are metabolized at least in part by CYP2C19?

Respondent skipped this question

Q19 What percent of small-molecule compounds in your pipeline are metabolized at least in part by CYP2C9?	**Respondent skipped this question**
Q20 What percent of small-molecule compounds in your pipeline are metabolized at least in part by UGT1A1?	**Respondent skipped this question**
Q21 What percent of small-molecule compounds in your pipeline are transported at least in part by SLCO1B1?	**Respondent skipped this question**
Q22 What percent of small-molecule compounds in your pipeline are transported at least in part by BCRP?	**25-50%**
Q23 What percent of small-molecule compounds in your pipeline are transported at least in part by OCT1?	**Respondent skipped this question**
Q24 Do you use modeling and simulation tools to predict the impact of genetic variants in enzymes/transporters on compound disposition prior to clinical studies?	**No**
Q25 If you answered "Yes" to Question 24, please describe scenarios in which such tools may be used and what software is being used:	**Respondent skipped this question**
Q26 Does your company have decision criteria regarding drug candidate progression based on predicted involvement (%) of an enzyme or transporter with genetic variants that might impact clearance? Select all that apply.	**No**
Q27 If your company advances drug candidates with a predicted significant involvement of a polymorphic enzyme or transporter in clearance, are further pre-clinical studies performed to assess the risks?	**Respondent skipped this question**
Q28 If you answered "Yes" to Question 27 please describe (e.g. use of genotyped hepatocytes, recombinant systems expressing variant. Please include specific enzymes/transporters and alleles assayed using a given method.)	**Respondent skipped this question**

Q29 What gaps do you see in the ability to determine the impact of enzymes with genetic variants that might impact the drug development program using in vitro studies? Select all that apply.	**Inaccuracy of in vitro models** , **Impact of polymorphisms is not well characterized** , **Low turnover in vitro for certain compounds**
Q30 What gaps do you see in the ability to determine the impact of transporters with genetic variants that might impact the drug development program using in vitro studies? Select all that apply.	**Inaccuracy of in vitro models**

#6

COMPLETE

Collector:	Email Invitation 1 (Email)
Started:	Friday, October 11, 2019 4:50:24 PM
Last Modified:	Friday, October 11, 2019 8:07:25 PM
Time Spent:	03:17:00
Email:	f
IP Address:	

Page 1: I-PWG ADME Task Force Survey - August 2019

Q1 Please enter your unique individual Survey Monkey Code that was sent to you by Julian Arbuckle:

4099

Q2 What were the pharmaceutical R&D expenses of your company in 2018?	**<1 $ Billion**
Q3 What percentage of your pipeline is represented by small molecules:	**10-25%**
Q4 What percentage of your pipeline is represented by therapeutic proteins, vaccines, or other types of compounds (not small molecule):	**>75%**
Q5 Do you typically conduct in vitro phenotyping studies to assess enzyme involvement in clearance of discovery or development compounds prior to phase 1 clinical studies?	**Yes**
Q6 Do you typically conduct in vitro phenotyping studies to assess transporter involvement in clearance of discovery or development compounds prior to Phase 1 clinical studies?	**Yes**

Q7 Which 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? Select all that apply.

ABCB1,
ABCG2,
CYP1A2,
CYP2B6,
CYP2C19,
CYP2C8,
CYP2C9,
CYP2D6,
CYP3A4,
CYP3A5,
SLC22A6,
SLC22A8,
SLC47A1,
SLC47A2,
SLCO1B1,
SLCO1B3

Q8 Are there additional enzymes or transporters you would assess, given availability of appropriate and accurate in vitro tools? Please list.

Respondent skipped this question

Q9 What methods do you typically employ in preclinical studies to predict the fm (fraction metabolized) by particular enzymes? Please describe.

measuring substrate loss in individual cDNA expressed P450s

Q10 For which enzymes do you typically have high confidence in the estimated fm based on preclinical studies? None, or Please list.

None

Q11 If a compound is stable from stability assays using human liver microsomes or hepatocytes, but studies using recombinant enzymes suggest the compound is metabolized by a polymorphic enzyme, do you determine fm by the polymorphic enzyme?

No

Q12 If you answered "Yes" to Question 11 what are the in vitro tools?

Respondent skipped this question

Q13 What methods do you typically employ in preclinical studies to predict the ft (fraction transported) by particular transporters? Please describe.

a polarized monolayer of
MDCK-II cells grown on permeable supports

Q14 For which transporters do you typically have high confidence in the estimated ft based on preclinical studies? None, or Please List

none

Q15 Have the preclinical strategies at your company failed to identify enzymes or transporters that were later (e.g. at the time of the human ADME study) determined to be clinically important?	**No**
Q16 If you answered "Yes" to Question 15 what was determined to be the reason these enzymes were missed as part of pre-clinical evaluations?	**Respondent skipped this question**
Q17 What percent of small-molecule compounds in your pipeline are metabolized or transported at least in part by CYP2D6?	**<10%**
Q18 What percent of small-molecule compounds in your pipeline are metabolized at least in part by CYP2C19?	**<10%**
Q19 What percent of small-molecule compounds in your pipeline are metabolized at least in part by CYP2C9?	**<10%**
Q20 What percent of small-molecule compounds in your pipeline are metabolized at least in part by UGT1A1?	**<10%**
Q21 What percent of small-molecule compounds in your pipeline are transported at least in part by SLCO1B1?	**<10%**
Q22 What percent of small-molecule compounds in your pipeline are transported at least in part by BCRP?	**10-25%**
Q23 What percent of small-molecule compounds in your pipeline are transported at least in part by OCT1?	**<10%**

Q24 Do you use modeling and simulation tools to predict the impact of genetic variants in enzymes/transporters on compound disposition prior to clinical studies?	**No**
Q25 If you answered "Yes" to Question 24, please describe scenarios in which such tools may be used and what software is being used:	**Respondent skipped this question**
Q26 Does your company have decision criteria regarding drug candidate progression based on predicted involvement (%) of an enzyme or transporter with genetic variants that might impact clearance? Select all that apply.	**No**
Q27 If your company advances drug candidates with a predicted significant involvement of a polymorphic enzyme or transporter in clearance, are further pre-clinical studies performed to assess the risks?	**No**
Q28 If you answered "Yes" to Question 27 please describe (e.g. use of genotyped hepatocytes, recombinant systems expressing variant. Please include specific enzymes/transporters and alleles assayed using a given method.)	**Respondent skipped this question**
Q29 What gaps do you see in the ability to determine the impact of enzymes with genetic variants that might impact the drug development program using in vitro studies? Select all that apply.	**Inaccuracy of in vitro models**, **Impact of polymorphisms is not well characterized**
Q30 What gaps do you see in the ability to determine the impact of transporters with genetic variants that might impact the drug development program using in vitro studies? Select all that apply.	**Lack of in vitro models**

#7

COMPLETE

Collector:	Email Invitation 1 (Email)
Started:	Friday, October 11, 2019 9:12:38 PM
Last Modified:	Friday, October 11, 2019 9:18:37 PM
Time Spent:	00:05:58
Email:	
IP Address:	

Page 1: I-PWG ADME Task Force Survey - August 2019

Q1 Please enter your unique individual Survey Monkey Code that was sent to you by Julian Arbuckle:

4001

Q2 What were the pharmaceutical R&D expenses of your company in 2018?	**>4 $ Billion**
Q3 What percentage of your pipeline is represented by small molecules:	**50-75%**
Q4 What percentage of your pipeline is represented by therapeutic proteins, vaccines, or other types of compounds (not small molecule):	**25-50%**
Q5 Do you typically conduct in vitro phenotyping studies to assess enzyme involvement in clearance of discovery or development compounds prior to phase 1 clinical studies?	**Yes**
Q6 Do you typically conduct in vitro phenotyping studies to assess transporter involvement in clearance of discovery or development compounds prior to Phase 1 clinical studies?	**Yes**
Q7 Which 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? Select all that apply.	**ABCB1,** **ABCB4,** **ABCC2,** **ABCG2,** **ABCB11,** **CYP1A1,** **CYP1A2,** **CYP2A6,**

CYP2B6,

CYP2C18,

CYP2C19,

CYP2C8,

CYP2C9,

CYP2D6,

CYP2E1,

CYP3A4,

CYP3A5,

DPYD,

FMO1,

FMO2,

FMO3,

FMO4,

FMO5,

AOX1,

GSTM1,

GSTP1,

GSTT1,

NAT1,

NAT2,

SLC15A2,

SLC22A1,

SLC22A2,

SLC22A6,

SLC22A8,

SLC47A1,

SLC47A2,

SLCO1B1,

SLCO1B3,

SLCO2B1,

SULT1A1,

TPMT,

UGT1A1,

UGT1A3,

UGT1A4,

UGT1A5,

UGT1A6,

UGT1A7,

UGT1A8,

UGT1A9,

UGT1A10,

UGT2B4,

UGT2B15,

UGT2B17,

UGT2B7,

CES1,

CES2

Q8 Are there additional enzymes or transporters you would assess, given availability of appropriate and accurate in vitro tools? Please list.

• CYP1B1, CYP2J2, CYP3A7, CYP4A11
• AOX vs XO (xanthine oxidase)
• EPHX1, EPHX2
• PON1, PON2, PON3
• SULT 1A2, 1A3, 1B1, 1E1, 2A1
• ADH, ALDH
• UGT2A1, UGT2B10, UGT2B11, UGT2B28
• OAT2, SLC22A7

Q9 What methods do you typically employ in preclinical studies to predict the fm (fraction metabolized) by particular enzymes? Please describe.

Primary evaluations are done by evaluating potential for NCE to be metabolized by recombinant enzymes in conjunction with chemical inhibitors (where selective chemical inhibitors are available or characterized).
• We are looking for agreement in methodology between recombinant enzymes and chemical inhibitor data. When no turnover (metabolite formation) is observed in recombinant enzymes, chemical inhibitor data are generally disregarded (potential for non-selective inhibition)
• Scaling of metabolism using RAF or ISEF is considered with caution since overprediction of certain routes from recombinant enzymes may occur (eg CYP3A4) and more weight is placed on chemical inhibitor data.
• In cases where metabolic CL fm estimations are less clear, additional approaches are employed such as (i) evaluation of metabolism in genotyped tissue fractions and/or (ii) a correlation analysis of metabolite formation in a range of individual human tissue donors with a large range in quantified protein of interest and/or catalytic activity.
• For AO or GSTs, yardstick approach is used to estimate from in vitro.

Q10 For which enzymes do you typically have high confidence in the estimated fm based on preclinical studies? None, or Please list.

There is generally high confidence in the overall metabolic CL fm estimations for CYP and UGTs. The level of confidence varies based on specific enzymes identified since chemical inhibitors are not well characterized for all enzymes.
• High confidence CYPs (1A2, 2C8, 2C9, 2C19, 2D6, 3A4, 3A5, 2B6)
• Low confidence CYPs (1A1, 1B1, 2A6, 2C18, 2E1, 2J2, 3A7, 4A11)
• High confidence UGTs (1A1, 1A3, 1A4, 1A6, 1A9, 2B7, 2B15)
• Low confidence UGTs (1A5, 1A7, 1A8, 1A10, 2B4, 2B17)
The confidence in overall identification of other contributing metabolic routes is generally high (eg SULT, CES, FMO, AOX, etc). However, assignment of metabolic CL fm estimations are lower confidence since IVIVE for these metabolic routes (and the appropriate CL scaling factors) are not as well advanced.

Q11 If a compound is stable from stability assays using human liver microsomes or hepatocytes, but studies using recombinant enzymes suggest the compound is metabolized by a polymorphic enzyme, do you determine fm by the polymorphic enzyme?

Yes

Q12 If you answered "Yes" to Question 11 what are the in vitro tools?

No compounds are considered truly metabolically stable unless elimination is confirmed as other (eg exclusively renal).
Sensitive LC/MS/MS techniques generally allow identification of metabolites with slow formation rates. Phenotyping of low turnover compounds may be challenging, but utilization of metabolite formation in human hepatocyte relay assays in the presence of chemical inhibitors could inform the metabolic CL fm estimations. Metabolite formation rates in the genotyped tissue fractions could also be employed.

Q13 What methods do you typically employ in preclinical studies to predict the ft (fraction transported) by particular transporters? Please describe.

Single transfects and primary human hepatocytes with selective inhibitors

---

Q14 For which transporters do you typically have high confidence in the estimated ft based on preclinical studies? None, or Please List

OCT1 and NTCP. OATPs vs non-OATPs in human hepatocytes.

Q15 Have the preclinical strategies at your company failed to identify enzymes or transporters that were later (e.g. at the time of the human ADME study) determined to be clinically important?

Yes

Q16 If you answered "Yes" to Question 15 what was determined to be the reason these enzymes were missed as part of pre-clinical evaluations?

Inability of evaluated tissue fractions to generate all the human metabolites (eg incomplete metabolic picture or extrahepatic metabolite formation).
• Insufficient evaluation of non-CYP enzymes in phenotyping.
• Underprediction of in vivo human CL for certain metabolic routes due to lack in IVIVE (eg AOX, esterases, etc).
• Previous use of screening r-CYP phenotyping – since strategy corrected with learnings.

Q17 What percent of small-molecule compounds in your pipeline are metabolized or transported at least in part by CYP2D6?	**10-25%**
Q18 What percent of small-molecule compounds in your pipeline are metabolized at least in part by CYP2C19?	**10-25%**
Q19 What percent of small-molecule compounds in your pipeline are metabolized at least in part by CYP2C9?	**10-25%**
Q20 What percent of small-molecule compounds in your pipeline are metabolized at least in part by UGT1A1?	**<10%**
Q21 What percent of small-molecule compounds in your pipeline are transported at least in part by SLCO1B1?	**10-25%**
Q22 What percent of small-molecule compounds in your pipeline are transported at least in part by BCRP?	**25-50%**
Q23 What percent of small-molecule compounds in your pipeline are transported at least in part by OCT1?	**<10%**
Q24 Do you use modeling and simulation tools to predict the impact of genetic variants in enzymes/transporters on compound disposition prior to clinical studies?	**Yes**

Q25 If you answered "Yes" to Question 24, please describe scenarios in which such tools may be used and what software is being used:

In cases where polymorphic enzymes contribute to <25% of the metabolic CL fm or CL fm, limited if any evaluations are generally considered. In cases where metabolic CL fm or CL fm exceeds 25% and particularly 50%, the impact of genotype on overall CL is considered in conjunction with special scenarios (eg CYP2C19 poor metabolizer co-administered a CYP3A inhibitor). We use Simcyp as the preferred PBPK modeling tool. Generally, the questions are if human exposure in poor metabolizer subjects would still be within TI safety margins and/or if co-medications should be excluded in initial clinical trials until in vivo involvement of polymorphic CL is more fully elucidated.

Q26 Does your company have decision criteria regarding drug candidate progression based on predicted involvement (%) of an enzyme or transporter with genetic variants that might impact clearance? Select all that apply.

Depends on the compound or therapeutic area (please describe further – fill in)

,

Other (please specify):

In general, the aim is to identify molecules where less than 50% of the CL involves a polymorphic enzyme or transporter. In certain cases, it is easier to minimize routes (eg no enzyme for CYP2D6), whereas reduced function enzymes may be less critically evaluated (eg CYP2C9, CYP2C19) and requires further experimentation. In other cases, impact of polymorphic transporters would be implied (eg OATP1B1 when targeting the liver) and is evaluated with impact on PK variability and patient safety. This strategy also includes assessment in genotyped/phenotyped microsomes.

Q27 If your company advances drug candidates with a predicted significant involvement of a polymorphic enzyme or transporter in clearance, are further pre-clinical studies performed to assess the risks?

Yes

Q28 If you answered "Yes" to Question 27 please describe (e.g. use of genotyped hepatocytes, recombinant systems expressing variant. Please include specific enzymes/transporters and alleles assayed using a given method.)

In general, we would evaluate genotyped human liver microsomes (more donors are readily available) and sometimes genotyped hepatocytes (less donors available). We have not used variant expressed enzymes. Primary evaluations include CYPs (eg 2C9, 2C19, 2D6, 3A5), SLCO1B1, and UGTs (eg 1A1) where clinically significant polymorphisms are known.

Q29 What gaps do you see in the ability to determine the impact of enzymes with genetic variants that might impact the drug development program using in vitro studies? Select all that apply.

Impact of polymorphisms is not well characterized ,

Lack of resources ,

Other (please specify):

PBPK models are not fully developed and verified to model clinical significance (PK) of certain polymorphisms (eg CYP2C19). In other cases (eg OATP, CYP3A5), PK variability may increase but may not impact clinical outcome or efficacy (PD) and altered PK variability may not require therapeutic dose adjustments. More clinical data relating genotype with PK variability and outcome are required, eg it is well understood that PK could be impacted by polymorphic CYP2C19 expression, but the exact impact of each polymorphism on PK (eg percentage reduction in PM metabolic rate) is less clearly understood. In addition, difficulties of low turnover and understanding the full impact of polymorphisms (genotype-phenotype translation).

Q30 What gaps do you see in the ability to determine the impact of transporters with genetic variants that might impact the drug development program using in vitro studies? Select all that apply.

Other (please specify):

The clinical impact of transporter pharmacogenomics on patient safety and therapeutic drug efficacy is less clear (eg OATP variants impact PK variability and safety of simvastatin and has no impact of efficacy of atorvastatin). Clinical studies with genotype as covariate relating PK variability (potential safety marker) as well as clinical efficacy (outcome) are required to advance the field. Instead of all bottom-up, more top-down data are required to eventually meet with a middle-out approach and help to context the value of in vitro tool evaluations in the preclinical phases of drug discovery and development.

#8

COMPLETE

Collector:	Email Invitation 1 (Email)
Started:	Monday, October 14, 2019 8:57:28 PM
Last Modified:	Monday, October 14, 2019 9:21:41 PM
Time Spent:	00:24:12
Email:	
IP Address:	

Page 1: I-PWG ADME Task Force Survey - August 2019

Q1 Please enter your unique individual Survey Monkey Code that was sent to you by Julian Arbuckle:

2088

Q2 What were the pharmaceutical R&D expenses of your company in 2018?	**>4 $ Billion**
Q3 What percentage of your pipeline is represented by small molecules:	**25-50%**
Q4 What percentage of your pipeline is represented by therapeutic proteins, vaccines, or other types of compounds (not small molecule):	**50-75%**
Q5 Do you typically conduct in vitro phenotyping studies to assess enzyme involvement in clearance of discovery or development compounds prior to phase 1 clinical studies?	**Yes**
Q6 Do you typically conduct in vitro phenotyping studies to assess transporter involvement in clearance of discovery or development compounds prior to Phase 1 clinical studies?	**Yes**

Q7 Which 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? Select all that apply.

ABCB1,

ABCG2,

CYP1A2,

CYP2B6,

CYP2C19,

CYP2C8,

CYP2C9,

CYP2D6,

CYP2E1,

CYP3A4,

CYP3A5,

SLCO1B1,

SLCO1B3,

Other (please specify):
CYP2J2

Q8 Are there additional enzymes or transporters you would assess, given availability of appropriate and accurate in vitro tools? Please list.

Respondent skipped this question

Q9 What methods do you typically employ in preclinical studies to predict the fm (fraction metabolized) by particular enzymes? Please describe.

. parent compound disappearance using recombinant human cytochrome P450s
. human hepatocytes with and without ABT

Q10 For which enzymes do you typically have high confidence in the estimated fm based on preclinical studies? None, or Please list.

Cytochrome P450s

Q11 If a compound is stable from stability assays using human liver microsomes or hepatocytes, but studies using recombinant enzymes suggest the compound is metabolized by a polymorphic enzyme, do you determine fm by the polymorphic enzyme?

Yes

Q12 If you answered "Yes" to Question 11 what are the in vitro tools?

Use relative activity factors (RAF) approach when assessing parent compound disappearance using recombinant human cytochrome P450s.

Q13 What methods do you typically employ in preclinical studies to predict the ft (fraction transported) by particular transporters? Please describe.

None

Q14 For which transporters do you typically have high confidence in the estimated ft based on preclinical studies? None, or Please List

none

Q15 Have the preclinical strategies at your company failed to identify enzymes or transporters that were later (e.g. at the time of the human ADME study) determined to be clinically important?	**Yes**

Q16 If you answered "Yes" to Question 15 what was determined to be the reason these enzymes were missed as part of pre-clinical evaluations?

. Low clearance compounds in vitro studies

Q17 What percent of small-molecule compounds in your pipeline are metabolized or transported at least in part by CYP2D6?	**<10%**
Q18 What percent of small-molecule compounds in your pipeline are metabolized at least in part by CYP2C19?	**<10%**
Q19 What percent of small-molecule compounds in your pipeline are metabolized at least in part by CYP2C9?	**<10%**
Q20 What percent of small-molecule compounds in your pipeline are metabolized at least in part by UGT1A1?	**10-25%**
Q21 What percent of small-molecule compounds in your pipeline are transported at least in part by SLCO1B1?	**<10%**
Q22 What percent of small-molecule compounds in your pipeline are transported at least in part by BCRP?	**25-50%**
Q23 What percent of small-molecule compounds in your pipeline are transported at least in part by OCT1?	**<10%**

Q24 Do you use modeling and simulation tools to predict the impact of genetic variants in enzymes/transporters on compound disposition prior to clinical studies?	**No**
Q25 If you answered "Yes" to Question 24, please describe scenarios in which such tools may be used and what software is being used:	**Respondent skipped this question**
Q26 Does your company have decision criteria regarding drug candidate progression based on predicted involvement (%) of an enzyme or transporter with genetic variants that might impact clearance? Select all that apply.	**No**
Q27 If your company advances drug candidates with a predicted significant involvement of a polymorphic enzyme or transporter in clearance, are further pre-clinical studies performed to assess the risks?	**No**
Q28 If you answered "Yes" to Question 27 please describe (e.g. use of genotyped hepatocytes, recombinant systems expressing variant. Please include specific enzymes/transporters and alleles assayed using a given method.)	**Respondent skipped this question**
Q29 What gaps do you see in the ability to determine the impact of enzymes with genetic variants that might impact the drug development program using in vitro studies? Select all that apply.	**Inaccuracy of in vitro models** , **Low turnover in vitro for certain compounds** , Other (please specify): Scaling factors are not well characterized.
Q30 What gaps do you see in the ability to determine the impact of transporters with genetic variants that might impact the drug development program using in vitro studies? Select all that apply.	Other (please specify): Scaling factors are not well characterized.

#9

COMPLETE

Collector:	Email Invitation 1 (Email)
Started:	Friday, October 25, 2019 1:19:18 PM
Last Modified:	Friday, October 25, 2019 1:27:01 PM
Time Spent:	00:07:43
Email:	
IP Address:	

Page 1: I-PWG ADME Task Force Survey - August 2019

Q1 Please enter your unique individual Survey Monkey Code that was sent to you by Julian Arbuckle:

5965

Q2 What were the pharmaceutical R&D expenses of your company in 2018?	**1-4 $ Billion**
Q3 What percentage of your pipeline is represented by small molecules:	**50-75%**
Q4 What percentage of your pipeline is represented by therapeutic proteins, vaccines, or other types of compounds (not small molecule):	**<10%**
Q5 Do you typically conduct in vitro phenotyping studies to assess enzyme involvement in clearance of discovery or development compounds prior to phase 1 clinical studies?	**Yes**
Q6 Do you typically conduct in vitro phenotyping studies to assess transporter involvement in clearance of discovery or development compounds prior to Phase 1 clinical studies?	**Yes**

Q7 Which 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? Select all that apply.

ABCB1,
ABCG2,
CYP1A1,
CYP2B6,
CYP2C18,
CYP2C19,
CYP2C8,
CYP2C9,
CYP2D6,
CYP3A4,
NAT1,
SLC15A2,
SLC22A2,
SLC22A6,
SLCO2B1,
UGT1A1,
UGT1A3,
UGT2B4,
UGT2B7,
CES1,
CES2

Q8 Are there additional enzymes or transporters you would assess, given availability of appropriate and accurate in vitro tools? Please list.

no

Q9 What methods do you typically employ in preclinical studies to predict the fm (fraction metabolized) by particular enzymes? Please describe.

in vitro metabolism studies

Q10 For which enzymes do you typically have high confidence in the estimated fm based on preclinical studies? None, or Please list.

CYPs

Q11 If a compound is stable from stability assays using human liver microsomes or hepatocytes, but studies using recombinant enzymes suggest the compound is metabolized by a polymorphic enzyme, do you determine fm by the polymorphic enzyme? **Yes**

Q12 If you answered "Yes" to Question 11 what are the in vitro tools?

microsomes, rCYPs

Q13 What methods do you typically employ in preclinical studies to predict the ft (fraction transported) by particular transporters? Please describe.

CACO2 cells

Q14 For which transporters do you typically have high confidence in the estimated ft based on preclinical studies? None, or Please List

none

Q15 Have the preclinical strategies at your company failed to identify enzymes or transporters that were later (e.g. at the time of the human ADME study) determined to be clinically important? **No**

Q16 If you answered "Yes" to Question 15 what was determined to be the reason these enzymes were missed as part of pre-clinical evaluations?

na

Q17 What percent of small-molecule compounds in your pipeline are metabolized or transported at least in part by CYP2D6? **10-25%**

Q18 What percent of small-molecule compounds in your pipeline are metabolized at least in part by CYP2C19? **<10%**

Q19 What percent of small-molecule compounds in your pipeline are metabolized at least in part by CYP2C9? **<10%**

Q20 What percent of small-molecule compounds in your pipeline are metabolized at least in part by UGT1A1? **<10%**

Q21 What percent of small-molecule compounds in your pipeline are transported at least in part by SLCO1B1? **<10%**

Q22 What percent of small-molecule compounds in your pipeline are transported at least in part by BCRP?	**<10%**
Q23 What percent of small-molecule compounds in your pipeline are transported at least in part by OCT1?	**10-25%**
Q24 Do you use modeling and simulation tools to predict the impact of genetic variants in enzymes/transporters on compound disposition prior to clinical studies?	**No**

Q25 If you answered "Yes" to Question 24, please describe scenarios in which such tools may be used and what software is being used:

na

Q26 Does your company have decision criteria regarding drug candidate progression based on predicted involvement (%) of an enzyme or transporter with genetic variants that might impact clearance? Select all that apply.	**No**
Q27 If your company advances drug candidates with a predicted significant involvement of a polymorphic enzyme or transporter in clearance, are further pre-clinical studies performed to assess the risks?	**Yes**

Q28 If you answered "Yes" to Question 27 please describe (e.g. use of genotyped hepatocytes, recombinant systems expressing variant. Please include specific enzymes/transporters and alleles assayed using a given method.)

major isozymes

Q29 What gaps do you see in the ability to determine the impact of enzymes with genetic variants that might impact the drug development program using in vitro studies? Select all that apply.	**Lack of in vitro models** , **Inaccuracy of in vitro models** , **Impact of polymorphisms is not well characterized**
Q30 What gaps do you see in the ability to determine the impact of transporters with genetic variants that might impact the drug development program using in vitro studies? Select all that apply.	**Lack of in vitro models**

#10

COMPLETE

Collector:	Email Invitation 1 (Email)
Started:	Tuesday, November 05, 2019 7:32:46 PM
Last Modified:	Tuesday, November 05, 2019 7:38:23 PM
Time Spent:	00:05:37
Email:	
IP Address:	

Page 1: I-PWG ADME Task Force Survey - August 2019

Q1 Please enter your unique individual Survey Monkey Code that was sent to you by Julian Arbuckle:

1744

Q2 What were the pharmaceutical R&D expenses of your company in 2018?	**>4 $ Billion**
Q3 What percentage of your pipeline is represented by small molecules:	**50-75%**
Q4 What percentage of your pipeline is represented by therapeutic proteins, vaccines, or other types of compounds (not small molecule):	**25-50%**
Q5 Do you typically conduct in vitro phenotyping studies to assess enzyme involvement in clearance of discovery or development compounds prior to phase 1 clinical studies?	**Yes**
Q6 Do you typically conduct in vitro phenotyping studies to assess transporter involvement in clearance of discovery or development compounds prior to Phase 1 clinical studies?	**Yes**

Q7 Which 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? Select all that apply.	**ABCB1,** **CYP1A2,** **CYP2B6,** **CYP2C19,** **CYP2C8,** **CYP2C9,** **CYP2D6,** **CYP3A4,** **CYP3A5,** **NAT1,** **NAT2,** **SULT1A1,** **UGT1A1**

Q8 Are there additional enzymes or transporters you would assess, given availability of appropriate and accurate in vitro tools? Please list.

Aldehyde oxidase
beta-oxidation

Q9 What methods do you typically employ in preclinical studies to predict the fm (fraction metabolized) by particular enzymes? Please describe.

ADME study

Q10 For which enzymes do you typically have high confidence in the estimated fm based on preclinical studies? None, or Please list.

CYP3A4

Q11 If a compound is stable from stability assays using human liver microsomes or hepatocytes, but studies using recombinant enzymes suggest the compound is metabolized by a polymorphic enzyme, do you determine fm by the polymorphic enzyme?	**No**
Q12 If you answered "Yes" to Question 11 what are the in vitro tools?	**Respondent skipped this question**

Q13 What methods do you typically employ in preclinical studies to predict the ft (fraction transported) by particular transporters? Please describe.

none

Q14 For which transporters do you typically have high confidence in the estimated ft based on preclinical studies? None, or Please List

no

Q15 Have the preclinical strategies at your company failed to identify enzymes or transporters that were later (e.g. at the time of the human ADME study) determined to be clinically important?	**No**
Q16 If you answered "Yes" to Question 15 what was determined to be the reason these enzymes were missed as part of pre-clinical evaluations?	**Respondent skipped this question**
Q17 What percent of small-molecule compounds in your pipeline are metabolized or transported at least in part by CYP2D6?	**10-25%**
Q18 What percent of small-molecule compounds in your pipeline are metabolized at least in part by CYP2C19?	**10-25%**
Q19 What percent of small-molecule compounds in your pipeline are metabolized at least in part by CYP2C9?	**10-25%**
Q20 What percent of small-molecule compounds in your pipeline are metabolized at least in part by UGT1A1?	**25-50%**
Q21 What percent of small-molecule compounds in your pipeline are transported at least in part by SLCO1B1?	**<10%**
Q22 What percent of small-molecule compounds in your pipeline are transported at least in part by BCRP?	**25-50%**
Q23 What percent of small-molecule compounds in your pipeline are transported at least in part by OCT1?	**10-25%**
Q24 Do you use modeling and simulation tools to predict the impact of genetic variants in enzymes/transporters on compound disposition prior to clinical studies?	**Yes**

Q25 If you answered "Yes" to Question 24, please describe scenarios in which such tools may be used and what software is being used:

pediatrics, simcyp

Q26 Does your company have decision criteria regarding drug candidate progression based on predicted involvement (%) of an enzyme or transporter with genetic variants that might impact clearance? Select all that apply.	**No**
Q27 If your company advances drug candidates with a predicted significant involvement of a polymorphic enzyme or transporter in clearance, are further pre-clinical studies performed to assess the risks?	**No**
Q28 If you answered "Yes" to Question 27 please describe (e.g. use of genotyped hepatocytes, recombinant systems expressing variant. Please include specific enzymes/transporters and alleles assayed using a given method.)	**Respondent skipped this question**
Q29 What gaps do you see in the ability to determine the impact of enzymes with genetic variants that might impact the drug development program using in vitro studies? Select all that apply.	**Inaccuracy of in vitro models**, **Impact of polymorphisms is not well characterized**
Q30 What gaps do you see in the ability to determine the impact of transporters with genetic variants that might impact the drug development program using in vitro studies? Select all that apply.	**Inaccuracy of in vitro models**