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SMART INVESTIGATION OF DRUG-SUBSTRATE INTERACTIONS IN CLINICAL PHARMACOLOGY

Tristan BAGUET

First Master of Drug Development

Promotor

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SUMMARY

Drug development is very expensive and time-consuming. These burdens can be partially reduced by exclusively performing the essential drug-drug interaction studies. The Biopharmaceutics Drug Disposition Classification System (BDDCS), developed by Benet *et al.*, is assumed to be a roadmap for drug-drug interactions. BDDCS classifies compounds into 4 categories according to their solubility and extent of metabolism. It was developed as an extension to the Biopharmaceutical Classification System (BCS). The main goal for this master thesis is to explore the classification by BDDCS, its potential and to implement it as a tool during drug development at Janssen Pharmaceutica. The basis for the thesis is a survey of the Clinical Pharmacology & Biopharmaceutics reviews of 52 compounds that were recently approved by the FDA and EMA over the period 2011-2013.

Only pharmacokinetic interactions of other drugs on the approved compound as substrate were considered. Most of the interactions that were clinically relevant were found for BDDCS 1&2 compounds, and were metabolization related. A minority of the interactions were found for the BDDCS 3&4 compounds. The interactions with poorly metabolized compounds, excreted for more than 50% as parent compound, were transporter related. Two exceptions had metabolic interactions but the presumption is that these compounds are not poorly metabolized. Authorities did not use nor discuss BDDCS as a roadmap for DDI review.

In this thesis, a decision tree is proposed in order to implement BDDCS for the smart investigation of drug-substrate interactions. For compounds that are poorly metabolized, the focus should be on transporter-mediated drug interaction studies. Whereas for compounds that are extensively metabolized via cytochrome P-450 (CYP) and conjugation enzymes, the focus should be the enzyme related drug-drug interactions. For compounds that are primarily metabolized by non-CYP and, non-conjugation enzymes an alternative decision making is proposed in this thesis. For these drugs the BCS classification is to be used to predict the likelihood of transporter interactions. Highly permeable molecules are not expected to give clinically relevant interactions with transporters. Poorly permeable molecules are more likely to have transporter DDI on the compound as substrate.

SAMENVATTING

Geneesmiddelenontwikkeling kost zeer veel geld en is tijdrovend. Deze lasten kunnen gedeeltelijk verminderd worden door uitsluitend essentiële drug-drug interactie (DDI) studies te doen. Het Biopharmaceutics Drug Disposition Classification System (BDDCS), ontwikkeld door Benet *et al.*, is verondersteld een roadmap te zijn voor DDI's. BDDCS classificeert geneesmiddelen in 4 categorieën naargelang hun oplosbaarheid en mate van metabolisme. Het werd ontwikkeld als een uitbreiding op het Biopharmaceutical Classification System (BCS). Het voornaamste doel van deze thesis was om de BDDCS classificatie te verkennen en een implementatie als hulpmiddel gedurende geneesmiddelenontwikkeling bij Janssen Farmaceutica te maken. De basis voor deze thesis is een overzicht van de Clinical Pharmacology & Biopharmaceutics reviews van 52 geneesmiddelen die recent goedgekeurd zijn door de FDA en EMA tijdens de periode 2011-2013.

Enkel farmacokinetische interacties van het geneesmiddel als substraat werden beschouwd. De meeste klinisch relevant interacties zijn gevonden bij BDDCS 1&2 geneesmiddelen en waren metabolisatie gerelateerd. Een minderheid van de interacties zijn gevonden bij BDDCS 3&4 medicijnen. De interacties met geneesmiddelen, uitgescheiden voor meer dan 50% als moedermolecule, waren transporter gerelateerd. Twee uitzonderingen hadden metabole interacties, maar er zijn vermoedens dat deze geneesmiddelen toch in hoge mate gemetaboliseerd worden. Autoriteiten gebruikten noch bespraken BDDCS als roadmap voor DDI tijdens de reviews.

In deze thesis wordt een beslissingsboom voorgesteld om BDDCS te implementeren voor slimme onderzoeksstrategieën van geneesmiddel-substraat interacties. Voor geneesmiddelen die weinig gemetaboliseerd worden zou de focus op transporter gemedieerde geneesmiddelen interactie-studies moeten liggen. De focus, voor geneesmiddelen die extensief gemetaboliseerd worden via cytochroom P-450 (CYP) en conjugatie enzymen, zou moeten liggen op enzym gerelateerde DDI's. Voor geneesmiddelen die voornamelijk gemetaboliseerd worden via non-CYP en non-conjugatie enzymen moet de BCS classificatie gebruikt worden om de waarschijnlijkheid op transporter-interacties te voorspellen.

WORD OF THANKS

In the first place I would like to thank the University of Ghent and Janssen Pharmaceutica for giving me the opportunity to make my thesis at the company. It gave me a unique experience and gave me a first flavor of pharmaceutical sciences at industrial level.

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My girlfriend and friends for their moral support with my thesis.

Contents

Abbreviations

AKR: Aldo-keto reductase

AUC: Area under the Curve

BCS: Biopharmaceutics Classification System

BDDCS: Biopharmaceutics Drug Disposition Classification System

CHMP: Committee for Medicinal Products for Human Use

CYP: Cytochrome P450

DDI: Drug-Drug Interactions

EMA: European Medicine Agency

FDA: Food and Drug Administration

IV: Intravenous

NDA: New Drug Approval

NME: New Molecular Entity

PMS: Post marketing studies

UGT: Uridinediphosphate-glucuronosyltransferase

1 INTRODUCTION

The development of a new molecular entity takes 10 to 15 years and the costs vary from 500 million to 2000 million American dollar depending on the developing company and the therapeutic indication. Companies and authorities are continually searching for ways to reduce this burden on drug development. The investigation of drug-drug interactions (DDI) is one of the parts done in preclinical and clinical research to ensure a safe and efficacious treatment of patients during drug development and on the market after regulatory approval. Benet *et al.* believe that the Biopharmaceutical Drug Disposition Classification System (BDDCS) can predict mechanisms of DDI in an early stage of drug development. Hence saving time and resources by orienting drug development program in a smart way (2013 Profile Biopharmaceutical Research Industry, 2013) , (Adams, Van Brantner, 2006).

1.1 WHAT IS THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM?

Biopharmaceutics Classification System or BCS is a way to classify compounds with regard to their solubility and permeability. It was developed in 1995 by Amidon *et al.* when they recognized that solubility and permeability are the two main factors determining rate and extent of oral drug absorption (Amidon, Lennernas, Shah, Crison, 1995). Amidon divided drugs into 4 classes in accordance with their aqueous solubility and gastrointestinal permeability as depicted in figure 1-1. According to Benet most of the new molecular entities that are approved for market entry have a high molecular weight, are lipophilic and are poorly water soluble (Wu, Benet, 2005).

Class 1 High solubility High permeability	**Class 2** Low solubility High permeability
Class 3 High solubility Low permeability	**Class 4** Low solubility Low permeability

- Class 1: high solubility-high permeability
- Class 2: low solubility-high permeability
- Class 3: high solubility-low permeability
- Class 4: low solubility-low permeability

Figure 1-1: Biopharmaceutical Classification System (Benet, 2013)
BCS divides drugs into 4 categories according to their solubility and permeability

1.1.1 Solubility

The solubility of the compound of interest is always based on its highest dose strength. The FDA gives the following definition to highly soluble compounds. “A drug substance is considered *highly soluble* when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1-7.5.” (Guidance for Industry Guidance for Industry Waiver of In Vivo Bioavailability, 2000, pg 2) The 250 ml represents the volume of a glass of water that is drunk with oral administration of the compound during bioequivalence studies. The European authorities use the same directives. It is preferable that the drug is soluble over the entire pH-range (Guidance for Industry Guidance for Industry Waiver of In Vivo Bioavailability, 2000).

1.1.2 Permeability

Permeability can be determined by a direct or indirect way. Measuring the degree of absorption in a clinical study (e.g. human drug absorption study, mass-balance or absolute bio-availability study) is an indirect method. A direct method is performing a mass transfer across human intestinal membranes. Other, non-human, tests can be performed alternatively when demonstrated to be appropriate. The FDA gives following definition for highly permeable compounds. “A drug substance is considered to be highly permeable when the extent of absorption in humans is determined to be 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose.” (Guidance for Industry Waiver of In Vivo Bioavailability, 2000, pg. 2)

The extent of absorption can be determined by measuring the absolute bioavailability or by a mass balance study in healthy volunteers as recommended by the FDA.

- Mass balance studies are used to evaluate the fate of drug-related material. To identify the drug-related material the drug can be radiolabeled or unlabeled, stable isotopes can be implemented. When using radiolabeled drug it should be kept in mind that the drug recovery rarely is 100%. High oral absorption is assumed and calculated by the summation of drug related material in urine to the amount of metabolites present in the faeces. Due to the high variability of the results with mass balance studies this is not the most preferred method for

granting waivers for bioequivalence studies. One of the methods mentioned below may be favored (Roffey, Obach, Gedge, Smith, 2007).

- The absolute oral bioavailability is determined by comparing drug exposure after oral administration and intravenous administration. The result is expressed as the ratio $\frac{AUC\ oral\ administration}{AUC\ IV\ administration}$ normalized to the same administered dose.

Permeability can also be measured using intestinal permeability methods.

- Intestinal perfusion studies conducted *in vivo* in humans.
- Intestinal perfusion studies conducted *in vivo or in situ* in animal models.
- Permeation studies performed *in vitro* on human or animal tissues that are excised.
- Permeation studies *in vitro* using a cultured monolayer of epithelial cells.

Some of the permeability methods described above have different expression of transporters in comparison with human models. As a consequence drugs that are subject of active transport will receive a distorted value of permeability. The FDA recommends that trials with non-human models should be restricted to compounds transported exclusively by passive transport (Guidance for Industry Guidance for Industry Waiver of In Vivo Bioavailability, 2000).

Shugarts *et al.* made the remark that determining the permeability by measuring absolute bioavailability is not correct in perspective with the original definition of permeability. Bioavailability expresses the extent of absorption as where permeability expresses the rate of absorption. The two are not interchangeable. A substance can have a high permeability but a low bioavailability due to first pass metabolism (Shugarts *et al.*, 2009). The best permeability studies are thus those performed using the intestinal permeability methods (Guidance for Industry Waiver of In Vivo Bioavailability, 2000).

1.1.3 Biowaivers

When permeability and solubility of the drug substrate are combined with dissolution of the drug formulation, three major determinants of rate and extent of absorption are taken into account. It is within this framework that the authorities, FDA and EMA, acknowledge the BCS

classification to grant biowaivers. The grant of a biowaiver allows companies to switch between certain drug formulations without performing studies for *in vivo* bioavailability and bioequivalence.

Authorities consider a drug to have rapid dissolution when it is dissolved for more than 85% within 30 minutes. EMA adds that the compound dissolves very rapidly when the time period is less than 15 minutes.

The FDA gives biowaivers to substances that:

- Are highly soluble, highly permeable (BCS 1) and have rapid *in vitro* dissolution.
- Where the excipients are quantitatively the same in accordance to their function.
- Do not have a narrow therapeutic range.
- Are not intended to be absorbed in the oral cavity.

Prodrugs have extra remarks. The permeability of the prodrug or drug should be evaluated when the prodrug is converted respectively after or before intestinal membrane permeation. The dissolution and solubility of both drug and prodrug should be examined.

(Guidance for Industry Guidance for Industry Waiver of In Vivo Bioavailability, 2000)

The EMA is less strict and grants biowaivers to

- Compounds with high solubility and low or high permeability. Extra demands will be imposed for drugs with low permeability.
- In addition very rapid dissolution must have been demonstrated for both test as reference drug formulation.
- The excipients for BCS 3 compounds must be very similar, both quantitatively as qualitatively. For BCS 1 compounds it is enough to presume that the excipients do not change the bioavailability in a relevant way (Guideline on the Investigation of Bioequivalence, 2009).

1.2 BIOPHARMACEUTICAL DRUG DISPOSITION CLASSIFICATION SYSTEM

The Biopharmaceutical Drug Disposition Classification System or BDDCS was designed by Benet *et al.* as an extension of BCS. They observed that there was a link between permeability and degree of metabolization of the drug. It seemed that drugs with high permeability had a high extent of metabolism. A classification similar to figure 1-1 then can be made according to Benet *et al*. (Benet, Broccatelli, Oprea, 2011).

- BDDCS class 1: high solubility-high extent of metabolism
- BDDCS class 2: low solubility- high extent of metabolism
- BDDCS class 3: high solubility-low extent of metabolism
- BDDCS class 4: low solubility-low extent of metabolism

Class 1 and 2 are highly metabolized and therefore primarily eliminated by metabolism followed by excretion in faeces and/ or urine. Class 3 and 4 are poorly metabolized, and they are mainly excreted unchanged in faeces and/ or urine. The link between extent of metabolism and major route of elimination is showed in figures 1-2 and 1-3.

Class 1 High solubility High extent of metabolism	**Class 2** Low solubility High extent of metabolism
Class 3 High solubility Low extent of metabolism	**Class 4** Low solubility Low extent of metabolism

Figure 1-2: Biopharmaceutical Drug Disposition Classification System (Wu et al., 2005)

Class 1 Metabolism	**Class 2** Metabolism
Class 3 Renal and/or biliary elimination of unchanged drug	**Class 4** Renal and/or biliary elimination of unchanged drug

Figure 1-3: Predominant routes of drug elimination for drug substrates by BCS class (Wu et al., 2005)

1.2.1 Extent of metabolism

A drug is considered to have a high extent of metabolism when more than 70% of the drug is metabolized. When less than 30% is metabolized the drug is considered to be poorly metabolized. Benet *et al.* found that the number of drugs that have an extent of metabolism between 30% and 70% is very low. Consequently almost all drugs can be categorized following the criteria above. The factor solubility remains the same as in the BCS classification and has the same criteria. The difference in extent of metabolism between high vs. low permeability lies in the access that drugs have to metabolizing enzymes in hepatocytes. Highly permeable drugs can penetrate very easily into the hepatocytes. In addition they will easily be reabsorbed from the kidney lumen and the intestine. This provides multiple opportunities for the body to metabolize the drug. Poorly permeable compounds will not be reabsorbed in the same extent and will be more excreted as unchanged compound into urine or into the bile and faeces.

The change from BCS to BDDCS establishes an opportunity to predict the disposition for drugs that are categorized into one of the four classes possible. Furthermore it would increase the number of class 1 drugs that are appropriate for a biowaiver (Wu *et al.*, 2005). For investigators it is also easier to determine the major route of elimination than to determine the permeability. The following quote by Benet is very important for further sections of this thesis. "The matrix of drug metabolism in BDDCS is limited to the metabolic processes involving CYP450 and Phase 2 enzymes (such as glucuronidation and sulfation) that occur after drug absorption." (Chen, Amidon, Benet, Lennernas, Lawrence, 2011, pg. 1776)

1.2.2 Drug-drug interactions

The advantage that might be the most important and will be investigated in this thesis will be the possibility to predict DDI. In this thesis, drug-drug interactions are limited to interactions of the drug as a substrate. BDDCS can theoretically be used in an early stage of drug development to predict whether or not DDI related to metabolism or transporters are expected and will be relevant. The BDDCS does not say that every drug will undergo the DDI at the predicted mechanism. It just gives an idea in what direction scientists should search to find drug-drug interactions. Interactions at the metabolic pathways will especially occur to BDDCS

1&2 compounds. Interactions with transporters on the other hand could primarily find place with BDDCS 3&4 compounds (Biopharmaceutics Drug Disposition Classification System (BDDCS) – Its Impact and Application, 2013).

1.2.3 Transporters and predicting transporter effects

Drug transporters carry a molecule through the cell membrane. A transporter can transport a drug into the cell, uptake transporters, or can pump the compound out of the cell, efflux transporters. The Solute carrier transporter and Solute carrier organic anion transporter superfamilies represent the majority of uptake transporters involved in transport of xenobiotics. These transporters use a chemi-osmotic gradient as driving force and are not ATP dependent. The ATP-binding cassette superfamily represents the main part of the efflux transports. They use, in contrary to the uptake transporters, ATP as energy source (Shugarts, Benet, 2009).

It becomes more and more clear that transporters have a role in the pharmacokinetics of drugs that cannot be neglected. The point of interest here are transporters in the intestine, liver and kidneys in the context of drug disposition. Transporters can either regulate uptake or efflux of the molecule in organs. The importance of transporters on the disposition of an investigational drug can be predicted by the BDDCS class. Figure 1-5 illustrates the importance of transporters per BCS class but it also proves the importance of transporters per BDDCS class.

If knowledge exists which transporters influence the disposition of the drug, *in vivo* interaction studies can be conducted to investigate possible clinically relevant interactions. Figure 1-4 gives an overview of transporters selected on their clinical evidence on influencing drug disposition and/or side effects of medicines. Figure 1-4 helps to clarify the direction and location of transport. By combining figure 1-4 and 1-5 the importance of drug interaction at the specific transporter can be predicted (Giacomini, Huang, Tweedie DJ, & Benet, 2012).

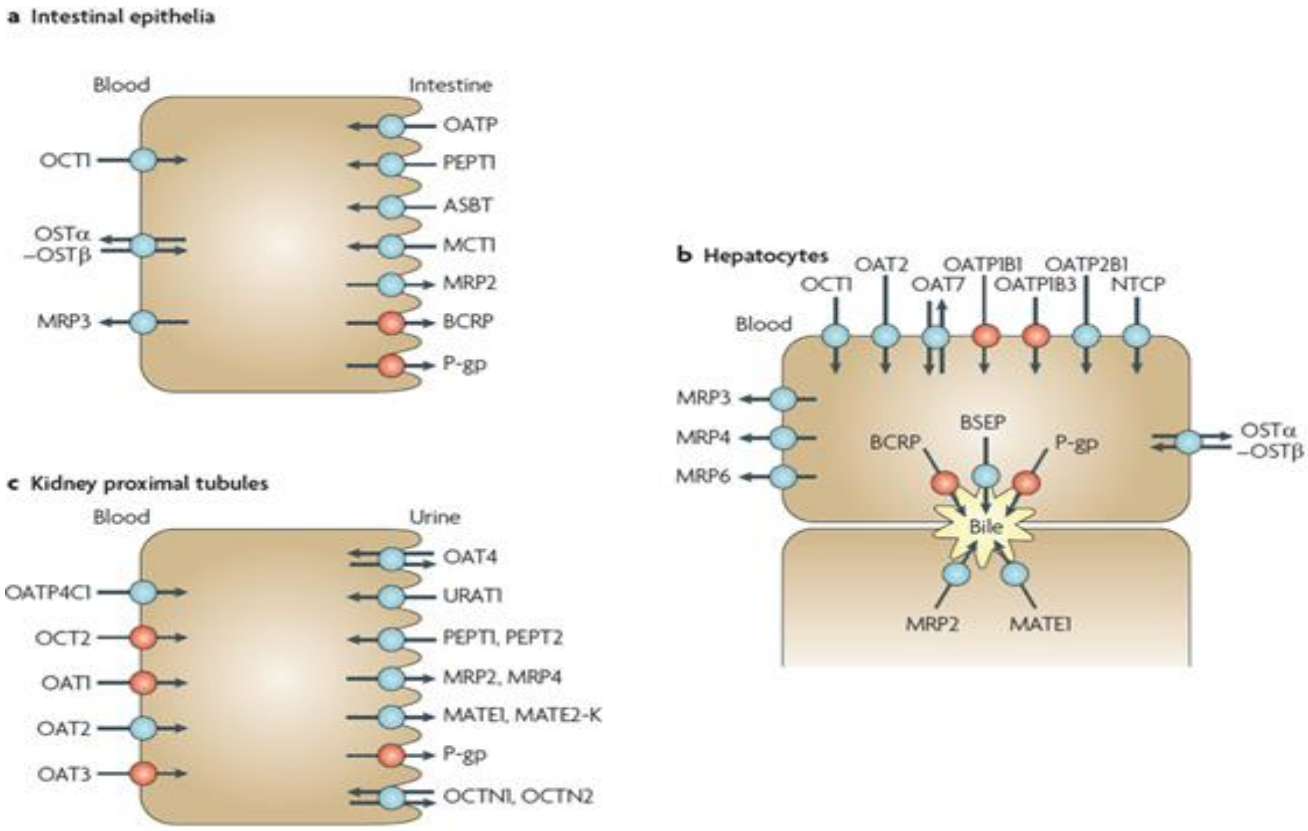

Figure 1-4: Most important transporters in intestinal epithelia, hepatocyte and kidney proximal tubes (Giacomini et al., 2012)

Class 1 Limited effect	**Class 2** Efflux transporters
Class 3 Uptake transports	**Class 4** Uptake and efflux transporters are important

Figure 1-5: Effect of transporters on drug disposition by BCS class (Wu et al., 2005)

- **Class 1 drugs**: Because they are highly soluble and highly permeable, BCS class 1 drugs do not have any problems penetrating the enterocytes. They do not need uptake transporters to get into the cell. Due to the rapid perfusion a high concentration in the enterocyte can be established and the efflux transporters get saturated. Hence absorption and efflux transporters play a limited role in the dissolution of the drug. The same applies to transporters in other tissues. Class 1 molecules can be substrates for transporters but their *in vivo* importance is negligible (Wu *et al.*, 2005).
- **Class 2 drugs**: These compounds are poorly soluble but have a high permeability. As a consequence they can rapidly diffuse into the cell. But due to their low solubility the concentrations inside the cell stay low. As the concentrations stay low neither efflux transporters nor intestinal enzymes become saturated.

  Note: A lot of drugs are substrate for both CYP3A and P-gp, see 1.2.4: enzyme metabolism-transporter interplay (Wu *et al.*, 2005).
- **Class 3 drugs**: Molecules with high solubility and low permeability. Because of their low permeability it is hard for the drug to enter the cell without the help of transports. Efflux transporters might also be important as these poor permeable compounds are not able to create high enough intracellular concentrations to saturate efflux transporters (Wu *et al.*, 2005).
- **Class 4 drugs**: With their low solubility and low permeability these compounds can be substrate for both uptake as efflux transporters. Some of these molecules are misclassified as their solubility was measured in aqueous medium. In fact their solubility in the intestine can be higher due to the presence of bile acids (Wu *et al.*, 2005).

Table 1-1 and 1-2 are made by Shugarts and Benet and give an idea of the expected effect on the AUC of a substrate dependent on the location of the transporter in the intestine and liver.

Table 1-1: Predicted effect of interaction at intestinal drug transporters on exposure (AUC) of BDDCS class (Shugarts *et al.*, 2009)

BDDCS class	1	2	3	4
Inhibition				
Apical[a] Uptake	⟺	⟺	↓	↓
Apical efflux	⟺	↑	↑	↑
Basolateral[b] Uptake	⟺	?	↑	↑
Basolateral Efflux	⟺	?	↓	↓
Induction				
Apical Uptake	⟺	⟺	↑	↑
Apical efflux	⟺	↓	↓	↓
Basolateral Uptake	⟺	?	↓	↓
Basolateral Efflux	⟺	?	↑	↑

[a] The side of a cell that faces the lumen

[b] The side of a cell that faces the blood

Table 1-2: Predicted effect of interaction at hepatic drug transporters on exposure (AUC) by BDDCS class (Shugarts *et al.*, 2009)

BDDCS class	1	2	3	4
Inhibition				
Apical efflux	⟺	↓	↑	↑
Basolateral uptake	⟺	↑	↑	↑
Basolateral efflux	⟺	↓	↓	↓
Induction				
Apical efflux	⟺	↑	↓	↓
Basolateral Uptake	⟺	↓	↓	↓
Basolateral efflux	⟺	↑	↑	↑

1.2.4 Enzyme metabolism-transporter interplay

It is possible that there is some kind of interplay between the transport and metabolization of a drug. If a compound is a substrate of a transporter this can affect the access to the metabolizing enzymes. The most commonly known interplay is that between CYP3A4 and P-gp in the intestinal wall. P-gp is believed to be a defense mechanism against xenobiotics.

The transporter pumps foreign substances out of the body in an active manner, as so preventing damage. The remarkable interplay between P-gp and CYP3A4 is a consequence of the overlap in substrate selectivity, tissue localization and coinducibility.

The P-gp transporter can control the access to the intestinal enterocyte. When a substrate diffuses into the enterocyte it can be extruded back into the lumen by the P-gp. When this process of diffusion and extrusion happens repeatedly there are several opportunities to metabolize the drug. As a consequence the absorption is delayed and there is an increased degree of metabolization of the drug (Cummins, Jacobsen, & Benet, 2002).

1.3 REGULATORY GUIDELINES ON ACCELERATED APPROVAL REQUIREMENTS

The FDA allows that some drugs, under certain conditions, are approved along with accelerated approval requirements. The goal is to shorten the duration of registration for medicines against life threatening diseases. This provides earlier access of promising therapy to patients. Disadvantage is that the accelerated approval may create a safety risk. Therefore accelerated approvals are only given to drugs whose indications are serious conditions where the medical needs are unmet.

The therapeutic activity must be well funded. Since tests on decrease of mortality/ morbidity cannot be performed other evidence should be provided in such accelerated approvals. The effect on a surrogate endpoint can be a good predictor for mortality/morbidity. For example, the sponsor can measure the result on a clinical endpoint that can be measured more rapidly than mortality/morbidity.

Requirements that are imposed to get the accelerated approval are postmarketing confirmatory trials. For example the beneficial clinical effect on mortality/morbidity must be demonstrated. *In vivo* interaction studies must be performed. These confirmatory trials can be satisfying or not. When the results satisfy the authorities they will terminate the requirements. If the results are not satisfying, for example there is not the ultimate beneficial effect, the product can be withdrawn from the market (Guidance for Industry – Expedited Programs for Serious Conditions – Drugs and Biologics, 2013).

2 OBJECTIVES

One of the purposes of the BDDCS classification system developed by Leslie Benet was to provide a roadmap towards the most appropriate preclinical and clinical pharmacokinetic investigations in drug research and drug development. According to Benet, a BDDCS roadmap would help to predict drug disposition and interactions in an early stage of drug development. In addition it would help to guide drug-drug interaction investigation strategies. This includes prioritizing specific DDI investigation and assessing the risk of clinically relevant drug-drug interaction during drug development and postmarketing in patients.

A first objective of this thesis is to explore drug classification according to BDDCS and see if it has a value for smart drug research and development.

A second objective is to look at what efforts pharmaceutical companies have done during recent drug development. These efforts are reflected in their regulatory submissions to obtain regulatory approval for market entry. The focus of this thesis is on metabolic drug-drug interactions and interactions with drug transporters because information on the latter type of drug-drug interactions appears to be scarce. The last few years the importance of transporters became clearer and the authorities seem to demand more information in registration files concerning transporters. The survey in this thesis may provide deeper insight in the regulatory position about the submitted drug interaction information by various pharmaceutical companies over the period 2011-2013.

The last objective is to summarize the lessons learned for future guidance and possible implementation of a BDDCS based R&D roadmap at Janssen.

3 MATERIALS AND METHODS

3.1 MATERIALS

In order to gain enough study material to investigate the objectives the new drug applications (NDA) from 2011 until 2013 were collected. These NDA's were obtained from the FDA site (Drugs@FDA, 2014). The Clinical Pharmacology Biopharmaceutics review was the relevant part of the NDA with respect to our goals. As mentioned before most information came from the FDA website. The data was also checked with the EMA website (European public assessment reports, 2014).

3.2 METHODS

3.2.1 Survey of FDA Clinical pharmacology & Biopharmaceutics drug reviews

Fifty-two reviews of new drug approvals were examined as a foundation for this thesis. These 52 NDA's take into account all small molecules for oral administration that were approved by the FDA in the period 2011-2013. Large molecules, like antibodies, are left out of this survey. BCS and BDDCS only apply to orally administered drugs, drugs with other routes of administration were not added to the dataset.

For each drug the BCS class, major pathway of elimination, the drug's metabolization pathways, transporters of the drug and clinically relevant interactions were noted. BDDCS class was determined by evaluating the percentage metabolized or the major pathway of elimination. More details about every parameter are given in table 3-1.

Table 3-1: Explanation about collected parameters from this survey

BCS-class	The BCS class was obtained by two ways. Either it was explicitly mentioned under the subsection General Biopharmaceutics or it was derived from characteristics in the review. For example the sponsor of Eslicarbazepine Acetate deleted the BCS class. From the characteristics low aqueous solubility and high bioavailability the molecule was classified as BCS class 2.
BDDCS-class	The BDDCS class of a drug was given based on its way of elimination. If the drug was excreted for >70% as a metabolite the compound was considered to be highly metabolized. BDDCS classification was in majority of the cases determined based on mass balance studies. Whenever recovery of radiolabeled ligand was not 100%, normalization was done. This allowed determining the total percentage unchanged drug. Comparing BDDCS to BCS could serve as a confirmation.
Major route of elimination	Gives the major route of elimination of a drug. This was determined in mass balance studies.
Metabolic pathways (substrate)	Mentions metabolic pathways of the investigational drug. When the possibility for interactions with these pathways is suspected further *in vivo* studies are conducted. The data proposing the metabolic scheme comes from *in vitro* experiments.
Probes used for metabolism DDI studies	Drugs used *in vivo* to investigate metabolism related drug-drug interactions.
Transporters (substrate)	Mentions transporters of the investigational drug. When the possibility for interactions with these transporters is suspected further *in vivo* studies are conducted. The data suggesting these transporters come from *in vitro* experiments.

Table 3-1: Explanation about collected parameters from the drugs part 2

Probes used in transporter DDI studies	Drugs used *in vivo* to investigate drug-drug interactions with transporters.
Clinically relevant DDI	Gives treatment precautions as a consequence of clinically relevant DDI. These precautions might be dose adjustments or certain drugs that should be avoided. The information about treatment precautions is obtained from the label, a section from the NDA.
Post marketing commitments	The post marketing commitments is a subsection concerning the phase IV commitments about DDI studies. They are an interesting side mark to the DDI in the label.

A part of the information gathered in these individual tables was comprised into one master table. The master table has the purpose to give an overview of all the examined compounds. It has several sections not mentioned above.

- The approval date was included to see if there was an evolution in the drug approval dossiers regarding transporter interaction studies.
- Therapeutic doses. Theoretically, one may expect that medicines with low therapeutic dosages probably may have a higher likelihood of being BCS class 1 or 3 than drugs with high therapeutic dosages because of difference in drug solubility and oral absorption.
- Therapeutic indication is given as extra information and to put drug approvals into their perspectives. We believe that drugs for life-threatening diseases will be more easily tolerated and approved. For example drugs for treatment of cancer will receive fewer questions on safety than antidiabetic drugs.

3.2.2 Drug classification according to BCS & BDDCS

To create an overview of the BCS and BDDCS landscape the abundance of each BCS and BDDCS class was calculated and resembled with each other. Three possible scenario's occurred. In most cases BCS & BDDCS classification were the same. Some cases had a different BCS &

BDDCS assignment. A few compounds did not receive a BCS and/ or BDDCS classification. Therefore it was also calculated how many drugs had identical and different BCS and BDDCS class.

3.2.3 Likelihood of clinically relevant DDI according to BDDCS category

In this section the data received from the Clinical Pharmacology Biopharmaceutics review was used to see if there is a link between BDDCS and DDI. For each BDDCS class the amount of drugs without relevant DDI, with dose adjustment and with drugs to avoid was calculated. These numbers were plotted per BDDCS class. An important comment should be made about the drug-drug interactions. For this plot the interactions mentioned in the label of the drugs were used. This is not the most optimal parameter. The label only mentions interactions that are clinically relevant. Whether or not an interaction is clinically relevant depends on several factors including the drug's indication and adverse effects. A better parameter could be an interaction with an AUC ratio of 200% or more in case of an inhibition.

3.2.4 Metabolism profile and likelihood of DDI

In this section the drugs were divided in two categories according to their metabolic scheme. The first category contained compounds that are metabolized by only one enzyme. The second category contained compounds that are metabolized by multiple enzymes. For all these molecules the amount of interactions was compared between the different BDDCS classes.

The assumption is that drugs that are metabolized by multiple enzymes will have fewer interactions than drugs metabolized by one enzyme.

3.2.5 Metabolic pathways other than CYP and conjugation

The BDDCS theory still has some incompletions. One of these incompletions concerns drugs that are metabolized by a pathway alternative to glucuronidation or CYP mediated oxidation. The molecules having an alternative route of metabolization were summarized and a better look was taken at their properties. The goal was to develop a valid implementation of BCS and BDDCS classification for these compounds.

3.2.6 Probes used for *in vivo* experiments

This section contains a gathering of all the probes that were used for *in vivo* interaction studies. The probes that were found were compared to the list of probes suitable for interactions published by the FDA. Any noteworthy deviation was further discussed.

4 RESULTS

4.1 SURVEY OF FDA CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS DRUG REVIEWS

4.1.1 Master table

Table 4-1 represents the master table with the 52 evaluated compounds. Each drug received an individual drug number. This makes it easier to refer to the master table in figures, tables or examples. Their ordering is in accordance with their approval date. Therapeutic doses and the BCS classification in table 4-1 were obtained directly from the Drug Review Document from each compound. None of the Drug Reviews included an assignment to a particular BDDCS class.

In this thesis, the BDDCS class was assigned according to information on the *in vivo* human mass balance studies in the reviews. The mass balance studies discuss the degree of drug metabolization, the metabolic pathways, and the excretion of unchanged drug and metabolites in urine and faeces. For (almost) all drugs, the human mass balance studies were performed after oral drug administration. No mass balance studies were initiated after intravenous drug administration. IV mass balance is more accurate as the method does not encounter unabsorbed drug and first pass metabolism. These factors can be confounders in determining the drug quantity excreted as unchanged drug in faeces.

Table 4-1: Master table of 52 drugs

Nr	Generic Name	Approval Date	Therapeutic Indication	Therapeutic Dosage	BCS From Reviews	BDDCS Assigned in Thesis
1	Ibrutinib	12/02/2014	Cancer	140 mg	2	2
2	Sofosbuvir	6/12/2013	Antiviral (hepatitis C)	400 mg	FDA:4 EMA:3	FDA:4 EMA:3
3	Simeprevir	22/11/2013	Antiviral (hepatitis C)	150 mg	4	4
4	Eslicarbazepine acetate	8/11/2013	Antiepileptica	200-800 mg	2	4
5	Macitentan	18/10/2013	Antihypertensiva	10 mg	2	2
6	Riociguat	8/10/2013	Antihypertensiva	0.5-2.5 mg	2	2
7	Conjugated Estrogens/Bazidoxifene	3/10/2013	Adverse effects menopause	0.45 mg Est and 20mg BZD	2	2
8	Vortioxetine	30/09/2013	Antidepressiva	5-20 mg	FDA:3 EMA:1	1
9	Dolutegravir	12/08/2013	HIV	50 mg	2	4
10	Afatinib	12/07/2013	Cancer	20-40 mg	1 or 3	3
11	Dabrafenib	29/06/2013	Cancer	50-75 mg	2	X[a]
12	Trametinib	29/05/2013	Cancer	0.5-2 mg	2	4
13	Canagliflozin	29/03/2013	Antidiabetica	100 mg	4	4
14	Dimethyl fumarate	27/03/2013	Multiple sclerosis	120-240 mg	FDA:1/3 EMA:1	3
15	Ospemifene	26/02/2013	Vulvar and vaginal atrophy	60 mg	2	2
16	Pomalidomide	8/02/2013	Cancer	4 mg	4	2

Table 4-1: Master table of 52 drugs part 2

17	Alogliptin benzoate		25/01/2013	Antidiabetica	25 mg	3	3
18	Apixaban		28/12/2012	Anticoagulant	2.5-5 mg	3	3
19	Bedaquiline		28/12/2012	Tuberculose	100 mg	2	2
20	Lomitapide mesylate		21/12/2012	Hypercholesterolemia	5 mg	2	2
21	Ponatinib		14/12/2012	Cancer	15-45 mg	FDA:4 EMA:2	2
22	Cabozantinib		29/11/2012	Cancer	140 mg	2 or 4	2 or 4
23	Tofacitinib		6/11/2012	Rheumatoide arthritis	5 mg	3	3
24	Perampanel		22/10/2012	Antiepileptica	2 mg	2	2
25	Bosutinib		4/09/2012	Cancer	100-500 mg	4	4
26	Enzalutamide		31/08/2012	Cancer	40 mg	2	2
27	Stribild (drug name)	Elvitegravir	27/08/2012	HIV	150 mg	2	4
		Cobicistat			150 mg	2	4
		Emtricitabine			200 mg	1	3
		Tenofovir			300 mg	3	3
28	Mirabegron		28/06/2012	Overactive bladder	25-50 mg	3	3
29	Lorcaserin		27/06/2012	Weight management	10 mg	1	1
30	Avanafil		27/04/2012	Erectile dysfunction	50-200 mg	2	2
31	Teriflunomide		12/02/2012	Multiple sclerosis	7-14 mg	2	4
32	Ivacaftor		31/01/2012	Cystic fibrosis	150 mg	2	2
33	Vismodegib		30/01/2012	Cancer	150 mg	2	4

Table 4-1: Master table of 52 drugs part 3

34	Axitinib	27/01/2012	Cancer	1-5 mg	2	2
35	Ruxolitinib	16/11/2011	Myelofibrosis	20 mg	1	1
36	Deferiprone	14/10/2011	Transfusion iron overload	25-33 mg/ kg	2 or 4	2
37	Crizotinib	26/08/2011	Cancer	200-250 mg	4	4
38	Vemurafenib	17/08/2011	Cancer	240 mg	4	4
39	Ticagrelor	20/07/2011	Platelet inhibitor	90 mg	4	4
40	Ezogabine	10/06/2011	Antiepileptica	50-400 mg	2	4
41	Telaprevir	23/05/2011	Antiviral (hepatitis C)	375 mg	2	4
42	Rilpivirine hydrochloride	20/05/2011	HIV	25 mg	4	2
43	Boceprevir	13/05/2011	Antiviral (hepatitis C)	800 mg	4	4
44	Linagliptin	2/05/2011	Antidiabetica	5 mg	3	3
45	Abiraterone acetate	28/04/2011	Cancer	250 mg	4	4
46	Vandetanib	6/04/2011	Cancer	300 mg	2	X
47	Gabapentin enacarbil	6/04/2011	Restless legs syndrome	600 mg	2	4
48	Fidaxomicin	27/03/2011	Antibioticum	200 mg	4	4
49	Roflumilast	28/02/2011	COPD	500 mg	2	2
50	Azilsartan medoxomil	25/02/2011	Antihypertensiva	40-80 mg	4	X
51	Vilazodone	21/01/2011	Antidepressiva	10-40 mg	3	3
52	Clobazam	1/01/2011	Antiepileptica	5-10 mg	2	2

[a] **Drugs with an X for BCS or BDDCS class are drugs where the BCS or BDDCS assignment was not possible**

4.1.2 Therapeutic dosage

As expected there is a correlation between the maximum therapeutic dosage and the BCS classification as depicted in figure 4-1. The average maximum therapeutic dose is lower for highly soluble than for poorly soluble compounds. These results lead to following speculations. Drugs that are poorly soluble need higher dosages to give good clinical effects. On the other hand, solubility is measured by dissolving the highest dosage in 250 ml water. As a consequence the higher the therapeutic dosage, the smaller the chances it will fully dissolve in 250 ml water.

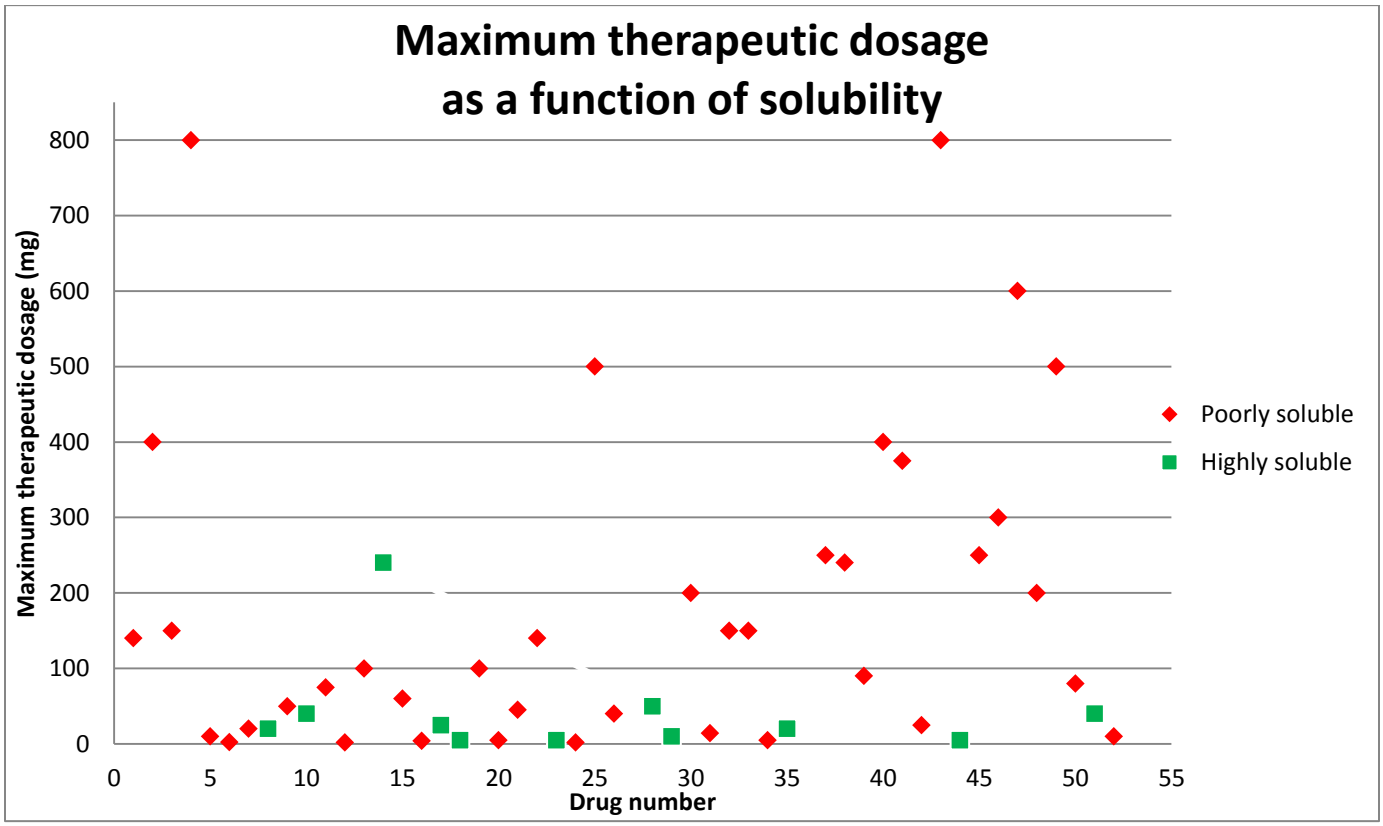

Figure 4-1: Maximum therapeutic dosage as a function of solubility

4.1.3 Evolution of investigation to transporter interactions

The last years the regulatory guidance of both EMA and FDA has spent more and more attention to transporters. It was of our interest to see if there was any evolution in the research performed to drug transporters related drug interactions.

Despite the extra awareness of regulatory authorities FDA and EMA on the importance of potential DDI with transporters it seems that sponsors did not do extra efforts on this subject. Figure 4-2 indicates that there is no increasing trend of *in vivo* transporter DDI studies in the NDA submissions of the last three years. Some of the studies in figure 4.2 are with inhibitors of both CYP3A4 and P-gp. However, the new guideline on investigation of drug interactions of the EMA was approved by the CHMP in 2012 and came into effect in 2013, the guideline of the FDA is still in draft. It is our opinion that the effects will emerge in the drug applications yet to be approved.

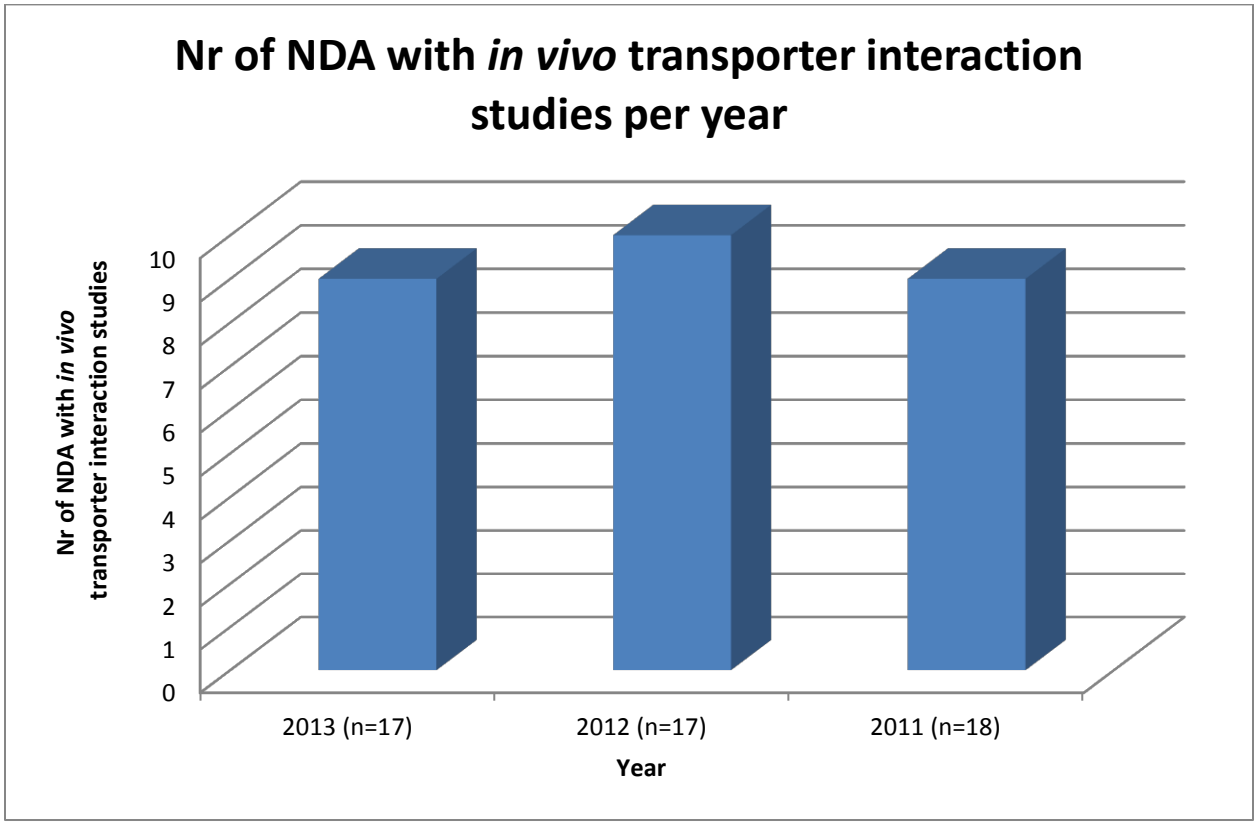

Figure 4-2: Nr of NDA with in vivo interaction studies classified per year
n= Total amount of NDA's that year

4.1.4 Impact of Post marketing studies and Accelerated approvals

Fourteen drugs of the survey received phase 4 study commitments regarding interactions from the FDA. Nine of those fourteen compounds already had DDI leading to therapy precautions. Five drugs are approved with accelerated approval requirements. Only two of them do not have therapy precautions.

Summarized, only 7 compounds without any clinically relevant DDI still have ongoing research to drug-drug interactions. This is a very limited number and we observed that these compounds are spread over the different BDDCS classes. As a conclusion we can say that our results on BDDCS classification and/ or drug-drug interactions will not be confounded due to drugs with PMS or accelerated approval requirements.

4.2 DRUG CLASSIFICATION ACCORDING TO BCS & BDDCS

Table 4-2: Distribution of the drugs in the survey according to BCS and BDDCS

BCS	Solubility: high → low	
Highly permeable ↓	**3**	**24**
Poorly permeable ↓	**6**	**12**
BDDCS	Solubility: high → low	
High metabolism	**3**	**18**
Primarily excreted unchanged In faeces and urine	**8**	**17**

Table 4-2 summarizes how many drugs each BCS and BDDCS class includes. BCS and BDDCS classification did not match for a certain amount of drugs. Respectively 33 %, 11%, 13% and 47% of all drugs with BDDCS class 1, 2, 3 and 4 had a different BCS assignment. To put this into perspective, the amount of drugs with identical BCS and BDDCS classification for those same BDDCS classes is 67%, 78%, 75% and 53% of all drugs in their respective BDDCS class. Three drugs received a BDDCS classification without having a BCS class. Similar, three other drugs received a BCS classification without receiving BDDCS classification.

10 of the 46 drugs that received a BDDCS class had a different BCS class. However the different classification can be explained and is scientifically acceptable.

- Compounds 4, 12, 31 and 47 are highly permeable and extensively metabolized but received a BDDCS class 3 or 4 assignment. Most of these drugs are metabolized by hydrolysis, esterase, et cetera. As Benet only considers compounds metabolized by CYP 450 or phase 2 enzymes as BDDCS 1&2 we had to categorize these compounds as BDDCS 3&4.
- Some compounds are conjugated as the first metabolic step but are deconjugated after biliary excretion into the intestinal tract and recovered as unchanged drug in the faeces.
- Additionally there are some borderline cases: compounds that are excreted as parent drug for just over 30%. For example, drug 33 is excreted for 31% of the total administered dose as unchanged drug. It had to be classified as BDDCS class 4, despite it is metabolized to a relative high extent.

At first glance and based upon the survey of the 52 drugs, the BDDCS classification approach of Leslie Benet seems to provide direction in many cases but some hurdle should be surmounted. A drug can be classified differently if the major pathway of metabolization is non-CYP and non-conjugation mediated. Confounding factors as deglucuronidation or unabsorbed drug should be avoided. Also there are borderline cases for which the boundaries are very strict.

4.3 LIKELIHOOD OF CLINICALLY RELEVANT DDI ACCORDING TO BDDCS CATEGORY

Figure 4-3 gives the amount and kind of DDI for compounds that are extensively or poorly metabolized. The majority of the interactions are found in the labels of BDDCS 1&2 compounds. All of them are DDI with metabolism, no DDI with transporters are reported for compounds that are extensively metabolized. BDDCS 3&4 are subject of fewer drug interactions in general and they have a higher proportion of DDI with transporters. Nevertheless, some BDDCS 3&4 compounds show DDI at the metabolic level but this will be further discussed in *5.6: Implementation of BDDCS in predicting drug-drug interactions.*

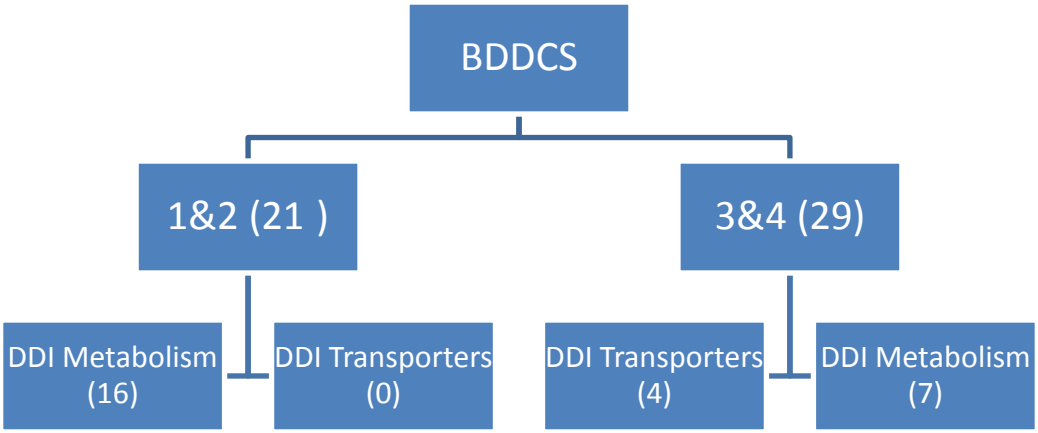

Figure 4-3: Incidence of clinically relevant drug-drug interactions

Figure 4-4 provides insight in the frequency of clinically relevant interaction per BDDCS class. The most eye-catching facts are the high frequency of DDI leading to a treatment precaution recommendation for drugs classified as BDDCS class 2 and the low frequency of treatment precautions for BDDCS class 4 drugs.

4.3.1 BDDCS 1 and 2

Fourteen of the eighteen drugs that are categorized as BDDCS class 2 had clinically relevant drug-drug interactions. As these drugs are extensively metabolized (>70%) it is more likely that they have DDI with metabolizing enzymes than class 3 and 4 drugs. An additional aspect is that BDDCS class 2 molecules are potential subject of efflux transporter interactions. As mentioned before a lot of drugs are substrate for both CYP3A4 and P-gp. Three of the fourteen drugs, that are victim of clinically relevant interactions, were subject of CYP3A4-P-gp interplay. These results are not astonishing but it gives evidence that for a certain number of drugs this interplay is present. The assumption is made that the high amount of relevant interactions is partially due to the combination effect of CYP3A4 and P-gp inhibition/induction.

Only three compounds had BDDCS class 1. Two of those three had clinically relevant DDI. This number is far too low to take any conclusions. The only thing we can learn is that the data is not inconsistent with the assumption that extensively metabolized compounds are more likely to have DDI than poorly metabolized compounds.

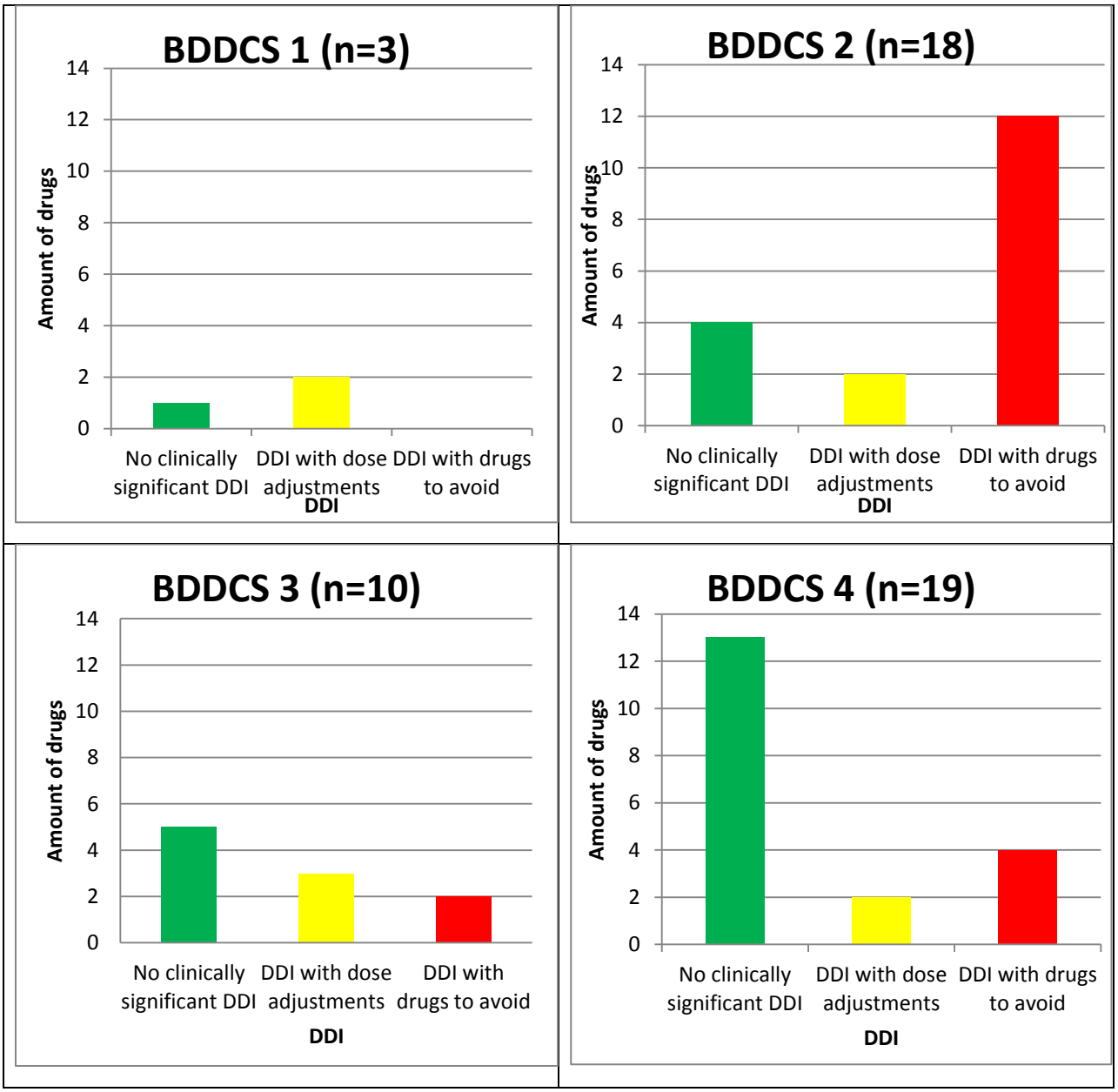

Figure 4-4: Prevalence of DDI per BDDCS class

4.3.2 BDDCS 3 and 4

The prevalence of DDI with BDDCS class 4 molecules is very low. Only six of the nineteen BDDCS class 4 compounds are submitted to clinically relevant interactions. If we take a look at all compounds that are poorly metabolized there are 29 molecules of which 18 without any clinically relevant interaction. BDDCS class 3&4 are both eliminated unchanged and influenced by transporters. Therefore it seemed better to regard all compounds with poor metabolism at the same time.

Two possible explanations could be found for the low prevalence of relevant interactions with poorly metabolized compounds (11= 38%). Companies seem to prioritize drug-drug interactions with metabolizing enzymes. As a consequence they seem to neglect interactions at transporter level. We think that the attention to transporter interactions will increase with the new guidance on drug-drug interactions. In order to find a balance in prioritizing transporter or metabolism-mediated interactions we propose that the BDDCS classification is consulted during drug development. Interaction studies with metabolizing enzymes should be focused for BDDCS 1 & 2 compounds. If the drug is a class 3 or 4 substance the focus should lie on transporter interactions.

Another explanation lies in the over appreciation of the clinical significance of drug-drug interactions at transporters. For 13 drugs *in vitro* studies predicted DDI with transporters but 9 of them had no clinically relevant *in vivo* interactions. Possibly, interactions at transporter level do occur but they do not lead to a relevant change in exposure to the drug.

These beliefs are supported by the limited number of clinical interactions at transporters. Only 4 of the 11 clinically relevant interactions with BDDCS class 3&4 compounds were transporter-mediated.

The authorities seem to think that sponsors conduct sufficient research to transport-interactions because phase 4 commitments regarding transporter-mediated interactions are very few (3 of the 14 NDA's with PMS). Class 3 and 4 contained 7 drugs with phase 4 commitments and only 2 of those concerned transporters.

4.4 METABOLISM PROFILE AND LIKELIHOOD OF DDI

Table 4-3 illustrates drugs metabolized by CYP enzymes classified by the number of enzymes and the presence of interactions. For convenience we call drugs metabolized by one enzyme type 1 drugs and drugs metabolized by multiple enzymes type 2 drugs. Type 1 drugs had, in proportion to type 2 drugs, much more drugs with interactions. In absolute numbers there are more drugs that have interactions and are type 2 drugs. However this is compensated by the high amount of type 2 drugs without relevant interactions. When multiple enzymes are capable of metabolizing the drug, other enzymes can take a part of the burden when one

enzyme is inhibited. This is not the case when only one enzyme is responsible for the metabolization of the drug.

Table 4-3: Metabolic enzymes, DDI leading to therapy precautions and BDDCS
Compounds with a brown background are BDDCS 1 & 2, compounds with a blue background are BDDCS 3&4.

Drugs that are metabolized by metabolic enzymes			
One enzyme		Multiple enzymes	
Clinically relevant interaction	No clinically relevant interaction	Clinically relevant interaction	No clinically relevant interaction
Duavee	Azilsartan medoxomil	Vortioxetine	Riociguat
Ibrutinib	Vemurafenib	Simeprevir	Canagliflozin
Bosutinib	Stribild	Macitentan	Lorcaserin
Cabozantinib		ospemifene	Mirabegron
Perampel		Dabrafenib	Rilpivirine hydrochloride
Ivacaftor		Dolutegravir	Telaprevir
Bedaquilline		Apixaban	Ezogabine
Avanafil		Lomitapide mesylate	Boceprevir
Ruxolitinib		Tofacitinib	Vilazodone
Linagliptin		Enzalutamide	Abiraterone acetate
		Ticagrelor	vismodegib
		Vandetanib	Alogliptin benzoate
		Roflumilast	
		Clobazam	
		Ponatinib tablets	
		Axitinib	
		Crizotinib	
		Afatinib	

In general BDDCS class 3 and 4 drugs have far less DDI than classes 1 and 2 in the first place. Further, when interactions occur the increase in AUC is not as high as depicted in figure 4-5. Figure 4-5 gives the increase in AUC after interaction studies with Ketoconazole, a CYP3A4 inhibitor. These phenomena are due to the minor role metabolism plays in eliminating the drug.

The expression ‘metabolized by multiple enzymes’ can be confusing. It might lead to the wrong assumption that different enzymes all contribute to plus minus the same extent. For

example, Crizotinib is metabolized for 99.4% by CYP3A4. Although CYP2C19 and CYP2D6 also play a, very small, role in the metabolization of Crizotinib it is very clear that they are of minor importance. But different criteria are hard to handle in deciding whether a drug is metabolized by one or multiple enzymes. The FDA obligates sponsors to undertake interaction studies with a certain enzyme when that enzyme represents more than 25% of metabolization. A same boundary is proposed here. A drug should be considered as having multiple metabolic enzymes when more than 1 enzyme represents a higher share than 25% of metabolism. Due to lack of information the proposed rule could not be implemented in our results. Sponsors often did not mention the contribution of each enzyme in metabolization of the compound.

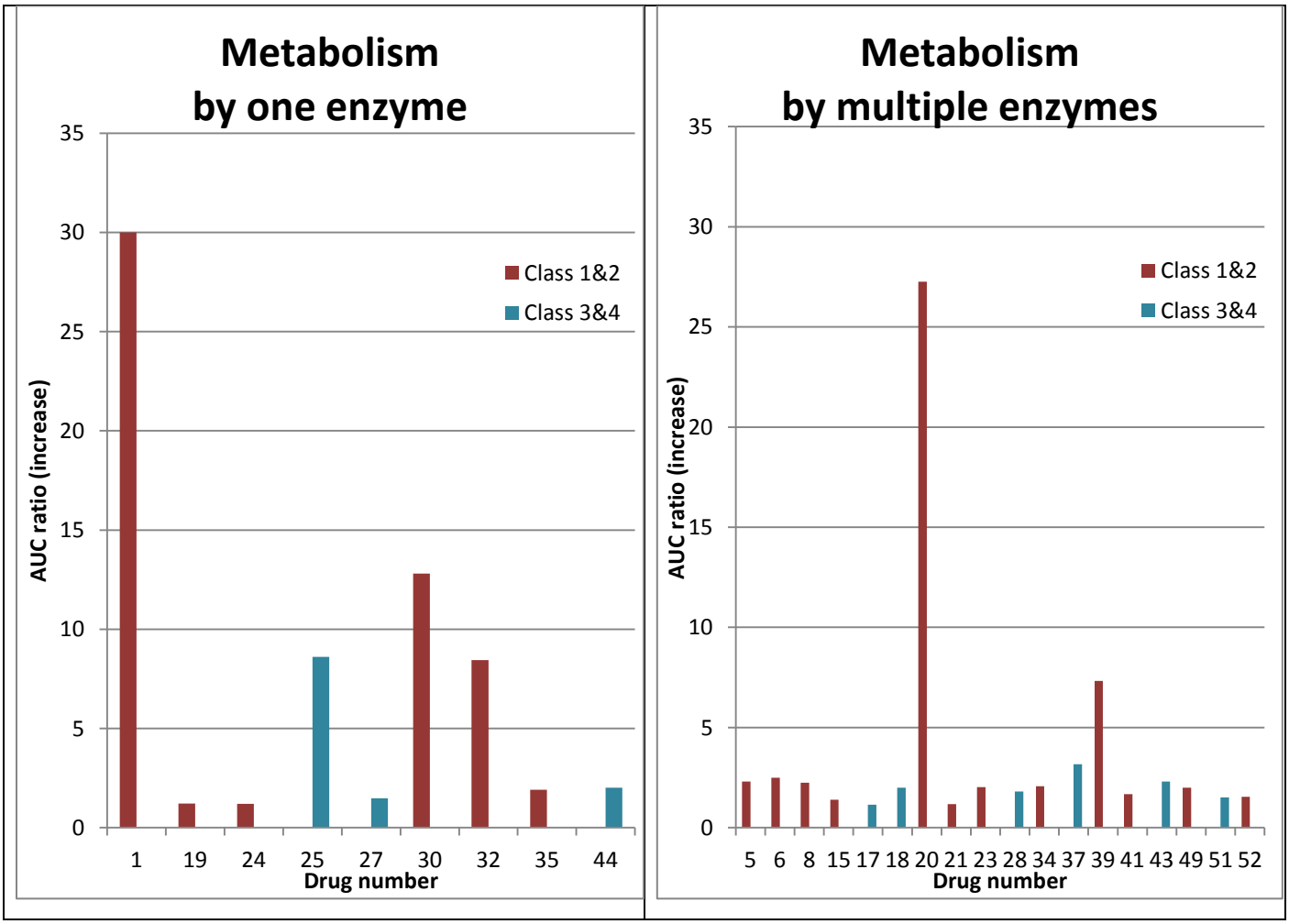

Figure 4-5: AUC increase for different BDDCS class after interaction studies with Ketoconazole, a CYP3A4 inhibitor
The AUC increase is the ratio of the substrate AUC in combination with an inhibitor over the AUC of the substrate without inhibitor.

4.5 METABOLIC PATHWAYS OTHER THAN CYP AND CONJUGATION MEDIATED

4.5.1 Current situation

Although the vast majority of drugs are metabolized via CYP or conjugation enzymes a number of exceptions with totally different metabolic pathways exist. As displayed in table 4-4 these other metabolic pathways are, for example, hydrolysis by esterase and metabolization by aldo-keto reductase (AKR).

Table 4-4: Summary of drugs with non-conventional metabolic pathways

Drug in Survey	Metabolic pathway	Drug in Survey	Metabolic pathway
4. Eslicarbazepine acetate	Hydrolysis	48. Fidaxomicin	Hydrolysis
12. Trametinib	Deacetylation (by hydrolytic esterases)	47. Gabapentin enacarbil	Hydrolysis
2. Sofosbuvir	Hydrolysis	43. Boceprevir	AKR
14. Dimethyl fumarate	Metabolized by esterases	51. Vilazodone	Carboxylesterase
31. Teriflunomide	Hydrolysis	45. Abiraterone acetate	Metabolized by esterases

Table 4-4 shows that ten of the fifty-two investigated compounds are (partially) metabolized by pathways alternative to CYP and phase 2 enzymes. The BDDCS classification, as developed by Benet *et al.*, excludes these alternative pathways from the matrix of drug metabolism. As a consequence we had to categorize them as BDDCS class 3 or 4 compounds. In the context of predicting DDI with the help of BDDCS classification, these compounds would be sensitive to transporter interactions despite that some are high permeability compounds. Eslicarbazepine acetate is a good illustration. The drug is a BCS class 2 compound and is a prodrug conversed by hydrolysis to Eslicarbazepine. Because its major metabolic pathway is hydrolysis and the compound is poorly soluble it is classified as BDDCS class 4. Following Benet's theory the substance can be subject to interactions with transporters. Since the drug is highly permeable it seems highly unlikely that transporter interactions would occur.

4.5.2 Future perspectives

Our proposal is that, for these compounds, the BCS classification is used to predict transporter DDI instead of the BDDCS classification. Compounds with poor permeability are expected to enter cells with the help of transporters. Thus BCS class 3&4 compounds are possible subjects of transporter drug-drug interactions. Highly permeable compounds have rapid access to the cell and are expected to have limited effects of transporter interactions.

For compounds that have alternative pathways of metabolization the link between BCS and BDDCS ceases to exist. As mentioned in the introduction highly permeable compounds have multiple opportunities for metabolization. As a consequence high permeability corresponds to high extent of metabolism. However the alternative pathways of metabolization often occur outside the hepatocyte so that the role of permeability is omitted as access to the hepatocyte is redundant. Therefore we want to emphasize that it cannot serve as a tool to predict metabolic drug-drug interactions.

4.5.3 Confirming examples

Sofosbuvir (compound 2) is a compound with low permeability. The solubility is a subject of disagreement between FDA and EMA. The FDA considers the drug as having low solubility because its highest dose (400 mg) cannot dissolve completely in 250 ml. The EMA however declares that the drug is highly soluble and has a pH independent solubility from pH range 1.2-7.7. The substance has a massive metabolic turnover via hydrolysis.

Due to its low permeability the drug is possibly subject to transporter interactions. *In vivo* drug interaction studies were conducted with Cyclosporine and Ritonavir boosted Darunavir. No clinically relevant DDI were observed. However a fourfold increase in AUC was seen with Cyclosporine and the increase in AUC with Ritonavir boosted Darunavir was less than 2. This underlines that the clinical significance of an interaction is determined not only by the change in exposure to the drug. The example shows that the interactions with transporters can be predicted by using the BCS classification.

Gabapentin enacarbil (compound 47) is a prodrug that is metabolized via hydrolysis. Due to its high permeability and low solubility it is a BCS class 2 compound. *In vitro* studies showed that the drug was a substrate of transporters OCT2, MCT-1 and SMVT. The sponsor conducted *in vivo* interaction studies to investigate possible transporter interactions. *In vivo* interaction studies showed an AUC increase of 39% of the prodrug with Naproxen and 124% of the drug with Cimetidine. The interaction study with Naproxen investigated the effect of MCT-1 inhibition, an uptake transporter of the prodrug in the intestine. The Cimetidine interaction study investigated the inhibition of OCT2, an uptake transporter of the drug in the kidney's. It is important to notice that only Naproxen investigates the effect of transporter interactions with high permeability compounds as only the produg is highly permeable. This example confirms the assumption that transporter interactions with highly permeable compounds are not likely to relevantly alter the pharmacokinetics of a drug.

In some cases a combination of metabolic pathways occurs. Vilazodone has 60% CYP mediated metabolization and 40% metabolization by carboxylesterases. We propose that the guideline described above is applicable for drugs where non-conventional metabolism represents more than 50% of total metabolism.

4.6 PROBES USED FOR *IN VIVO* EXPERIMENTS

Section 4.6 summarizes al the probes that were used for *in vivo* interaction studies in this survey. In accordance to all our results, the total of probes used for interaction studies with metabolizing enzymes is much larger than those for transporters. Enzyme CYP3A4 that is most common for degradation of medicines has the most probes by far.

Table 4-5: Probes for inhibition and induction of other metabolic pathways than CYP-mediated

Metabolic pathway	Inhibitor	Metabolic pathway	Inhibitor
AKR	Diflunisal	UGT	Probenecid
	Ibuprofen		Rifampin (inducer)
			Atazanavir

Table 4-6: Probes for inhibition or induction of CYP enzymes

Enzyme	Inhibitor	Enzyme	Inhibitor
INHIBITORS			
CYP3A4	Ketoconazole	CYP3A4	Erythromycin
	Itraconazole		Fluconazole
	Ritonavir		Diltiazem
	Atazanavir		Clarithromycin
CYP2C9	Fluconazole	CYP1A2	Fluvoxamine
	Gemfibrozil		
CYP2C19	Fluconazole	CYP2D6	Bupropion
	Omeprazol		
CYP2C8	Gemfibrozil		
INDUCERS			
CYP3A4	Rifampicin (Vortioxetine)	CYP3A4	Efavirenz (Simeprevir)
	Rifampin (Ibrutenib)		Phenytoin (Dabrafenib)

Table 4-7: Probes for inhibition and induction of transporters
Blue colored transporters and probes are those not found back in table 4-8, suggested probes by the FDA.

Transporter	Example substrate	Inhibitor
P-gp	Riociguat	Ketoconazole
	Afatenib	Ritonavir
	Afatenib	Rifampicin (inducer)
	Canagliflozin	Cyclosporine
	Apixaban	Naproxen
	Apixaban	Diltiazem
	Apixaban	Rifampin (inducer)
MRP2	Canagliflozin	Cyclosporine
OATP	Macitentan	Cyclosporine
MCT-1	Gabapentin enacarbil	Naproxen (substrate, competition)
OCT2	Gabapentin enacarbil	Cimetidine
	Apixaban	Famotidine
	Canagliflozin	Metformin

Tables 4-5, 4-6 and 4-7 list the inhibitor or inducer probes of the performed interaction studies in the survey. Hence they provide insight in the most commonly used probes. We compared these transporter probes with those suggested by the FDA as depicted in table 4-8. Blue colored probes or transporters are those not found in table 4-8.

Metformin, Famotidine and Naproxen were also used for *in vivo* interaction studies and are inhibitors of P-gp and OCT 2 but are not listed with the FDA. They were primarily used to evaluate the pharmacodynamic effect of interaction but in the meantime the sponsors also evaluated their pharmacokinetic effect. They are redundant in the list but are added to be as complete as possible.

Cyclosporine and Naproxen are found as inhibitors for MRP2 and MCT-1. These compounds are of interest as no probes are given by the FDA for these transporters.

Table 4-8 is almost completely copied from the guidance for industry drug interaction studies by the FDA. The column containing the specific gene that codes for the transporter was deleted and we replaced it by the organ location in the kidney, the intestine and liver. The expected effect of the probe than can be predicted with the help of table 1-1 and 1-2.

Table 4-8: FDA list of probes for transporters (Guidance for Industry Drug Interaction Studies, 2012)

Examples of *in Vivo* Inhibitors and Inducers of Selected Transporters. The location creates an idea of the effect of inhibition or induction of the transporter. The expected effect can be predicted with the help of table 1-1 and 1-2. AP= apical side of cell, BL= Basolateral side of cell

Transporter	Organ Location	Inhibitor	Inducer
P-gp	*Intestinal AP efflux* *Hepatocyte AP efflux* *Kidney AP efflux*	Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, ticagrelor, verapamil	Avasimibe, carbamazepine, phenytoin, rifampin, St John's wort, tipranavir/ritonavir
BCRP	*Intestinal AP efflux* *Hepatocyte AP efflux*	Cyclosporine, elacridar (GF120918), eltrombopag, gefitinib	Not known
OATP1B1	*Intestinal AP uptake* *Hepatocyte BL uptake*	Atazanavir, cyclosporine, eltrombopag, gemfibrozil, lopinavir, rifampin, ritonavir, saquinavir, tipranavir	Not known
OATP1B3	*Intestinal AP uptake* *Hepatocyte BL uptake*	Atazanavir, cyclosporine, lopinavir, rifampin, ritonavir, saquinavir	Not known
OCT2	*Kidney BL uptake*	Cimetidine, quinidine	Not known
OAT1	*Kidney BL uptake*	Probenecid	Not known
OAT3	*Kidney BL uptake*	Probenecid, cimetidine, diclofenac	Not known

5 DISCUSSION

5.1 INCOMPLETE DATASET

The results in this thesis are based on information that is publically available. The NDA's published by the authorities were not always complete. The authorities permit to blind some of the information given in the NDA's. As such the survey in this thesis reflects only a part of all submitted data. In the future the dataset from Janssen compounds could be used so that all information is available. A possible disadvantage could be the restriction of the amount of compounds.

5.2 THE ISSUE OF UNCHANGED DRUG IN FAECES

A number of drugs had a high amount of unchanged drug excreted in the faeces. The problem is that the origin of the unchanged compound is not always known. The high amount could be originated from unabsorbed drug after oral administration, biliary excretion of unchanged drug or deconjugation after biliary excretion of conjugated metabolites. Therefore an I.V. mass balance study could provide important information in quantifying the importance of biliary/transporter mediated efflux of orally administered drugs. Data on absolute bioavailability may also estimate the extent of elimination through these elimination routes. Thus, if a large fraction of an oral dose is recovered as unchanged drug in faeces, an I.V. mass-balance study or an absolute bioavailability study is of great value and should be considered.

5.3 COMPARISON OF REGULATORY DECISSION BETWEEN EMA AND FDA

The EMA website was consulted to gain supplementary information and to confirm the data obtained from the FDA. Authorities take efforts on trying to harmonize as much as possible. Still they seem to take different decisions on certain topics. Here we discuss the differences in assigning BCS class to 4 compounds. The four compounds of subject are Sofosbuvir, Vortioxetine, Dimethyl Fumarate and Ponatinib. These 4 drugs received a different BCS classification with the two different regulatory authorities.

Sofobusvir is believed to have low solubility at FDA and high solubility at EMA. Vortioxetine was regarded as medium permeability (BCS 3) by FDA and high permeability (BCS 1)

by EMA. The FDA bases itself on the 59% radioactivity found in urine and 75% absolute bioavailability. The EMA also bases itself on the results of the mass balance study but they added the amount of metabolites found in the faeces to the 59% in urine. The amount of metabolites is almost 26% as only negligible amounts of unchanged compound were found in the faeces. This information was enough for the EMA to consider it as being highly permeable. The sponsor's claim that Dimethyl Fumarate is a BCS 1 compound was disproved by the FDA. Jagan Parepally, reviewer from the FDA, was of the opinion that the permeability data was inconclusive and the BCS 1 claim was not legitimate. The EMA on the other hand, accepted the sponsor's BCS 1 claim. Ponatinib is highly permeable for the European authorities but the American authorities regard it as being poorly permeable. The European authorities accepted the sponsor's claim of high permeability basing itself on the data of Caco-2 cell transport studies. However, the FDA thinks that the reported permeability is moderate instead of high and was of opinion that the drug should receive a BCS class 4 classification.

These examples show that there is a difference in judgment between EMA and FDA. Conclusion is that the American authorities are stricter than the European authorities in solubility and permeability entitlements. These entitlements are critical to grant waivers for *in vivo* bioequivalence studies.

5.4 MODIFICATIONS TO BENET'S THEORY

5.4.1 Criteria for BDDCS and BCS

The criteria for permeability and solubility mentioned in the NDA's are based on the guideline for bioequivalence. These are auxiliaries to grant waivers and are maybe too strict with the eye on predicting DDI. To predict DDI it seems better to handle looser recommendations. Several drugs with medium permeability were assigned as poorly permeable. This is one of the reasons why BCS & BDDCS mismatched with some compounds. A proposal is to create a BDDCS class in correspondence to medium permeability.

Tofacitinib, compound 23, has an absolute oral bioavailability of 74%, the criteria whereupon the sponsor based itself to classify it BCS 3. However the dose recovered in urine was 80% and 13.8% was found in faeces as metabolites. With the assumption that a substance

can only be excreted as metabolite after absorption the sum of absorbed drug is 93.8% and the drug should in fact be a BCS 1 compound. *In vivo* interaction studies were done with Ketoconazole, Fluconazole, Rifampin and Cyclosporine. The following ratios of AUC were found: respectively 203.2%, 179.3%, 16.1% and 173.1%. The substance has a high metabolic clearance with 68.1% excreted as metabolite.

However, 68.1% is not enough to meet the criteria for being extensively metabolized (>70%), but as said before these criteria apply for granting biowaivers. It is too radical to say that compounds that are excreted as unchanged drug for 31.9% will primarily have transporter DDI's.

In the context of predicting drug-drug interactions this is not the most optimal situation. We propose an intermediate category. The intermediate category contains drugs excreted as unchanged drug for 30% to 50%. No predictions should be done for this intermediate category. The same measurement should be taken for drugs having an absolute bioavailability between 70% and 90%. A probe with intermediate permeability should be suggested for *in vitro* models as Caco-2 cells.

5.4.2 Metabolic interactions with BDDCS 3&4

Benet *et al.* did not exclude the possibility that interactions with metabolism could occur with BDDCS 3&4 compounds. Therefore we investigated the amount and origin of drug interactions with BDDCS 3&4 compounds. In total there are eleven BDDCS 3&4 drugs with DDI. Four drugs (10, 18, 25 and 44) have interactions with transporters. Compound 18, 25 and 44 had DDI with probes that inhibit both CYP3A4 and P-gp. We suspect that the drug-drug interactions are possibly a result of the enzyme-transporter interplay. Seven of these drugs had metabolic DDI. However for these last seven drugs, we made a difference between BDDCS 3&4 drugs with more than 50% excreted as unchanged compound and those with less than 50% excreted unchanged in urine or faeces. This 50% threshold will be used in our decision tree. Five of those 7 drugs with DDI are compounds excreted for less than 50 % as unchanged compounds, indicating that metabolic DDI cannot be excluded. Two drugs (9 & 37) with metabolic DDI were excreted for more than 50% as parent drug but there is some explanation possible. Compound

9 has 53% unchanged compound in the faeces and is primarily metabolized by conjugation. The sponsor also states that they do not know whether the parent drug in faeces is originated from unabsorbed drug or conjugated drug excreted via biliary excretion with possible deconjugation afterwards. Hence the possibility exists that in fact the drug is excreted for less than 50% as unchanged compound. Compound 37 also gives disagreement with the theory that BDDCS 3&4 do not have relevant interactions with metabolic pathways. Compound 37 is excreted 53% as unchanged in the faeces and is metabolized by CYP3A4. Here the compound is really a borderline case around the threshold of 50%. The sponsor states that the compound is extensively metabolized so that metabolic DDI's can be expected. Hence, classification of compounds according to absolute thresholds should always be done with caution.

5.4.3 Benet and Non-CYP, Non-Conjugation related metabolism

Metabolization as subject of BDDCS is limited to CYP and conjugation enzymes. Other metabolic pathways like hydrolysis are not included. Benet and coworkers do not cover these compounds in their papers. It is not clear how these compounds should be classified. In this thesis we classified these compounds as BDDCS 3 and 4. As said in 4.5 we suggest that for compounds with other metabolic pathways the BCS classification is used to predict transporter drug-drug interactions.

5.5 IMPLEMENTATIONT OF BDDCS IN PREDICTING DRUG-DRUG INTERACTIONS

The overall outcome of the survey is that neither BDDCS nor BCS is currently used by pharmaceutical companies or regulatory authorities to predict metabolic and/ or transporter DDI's. The analysis, however, on the drug reviews of the 52 approved drugs in the period 2011-2013 indicate that BDDCS has value as a roadmap to guide, to prioritize and understand the type of drug-drug interaction. As in the past, CYP mediated drug-drug interactions for BCS/BDDCS 2 drugs require most attention as most cases of the clinically relevant drug interactions and dose adjustments occurred in that class. Far less clinically relevant interactions are seen with BCS/ BDDCS 3&4 compounds.

Our recommendation is that the focus of attention with BDDCS 1 and 2 compounds lies on interaction at the level of metabolism. Interactions with transporters rarely lead to

treatment precautions especially with drugs that have high extent of metabolism. Only 4 drugs in our dataset had a clinically relevant interaction with a transporter (all of them with P-gp). All four were drugs with BDDCS class 3 or 4, most likely because the low drug concentrations of poorly permeable compounds do not saturate the efflux transporters. Drugs that are BDDCS 3 and 4 should receive attention with regard to interactions with transporters, especially P-gp.

A general decision tree that we propose as roadmap is given in figure 5-1 and is being further discussed below. It gives four possible scenarios that can be followed. It is important to use the decision tree in combination with the regulatory guidance concerning interactions. Where possible it should be further fine-tuned when more data becomes available.

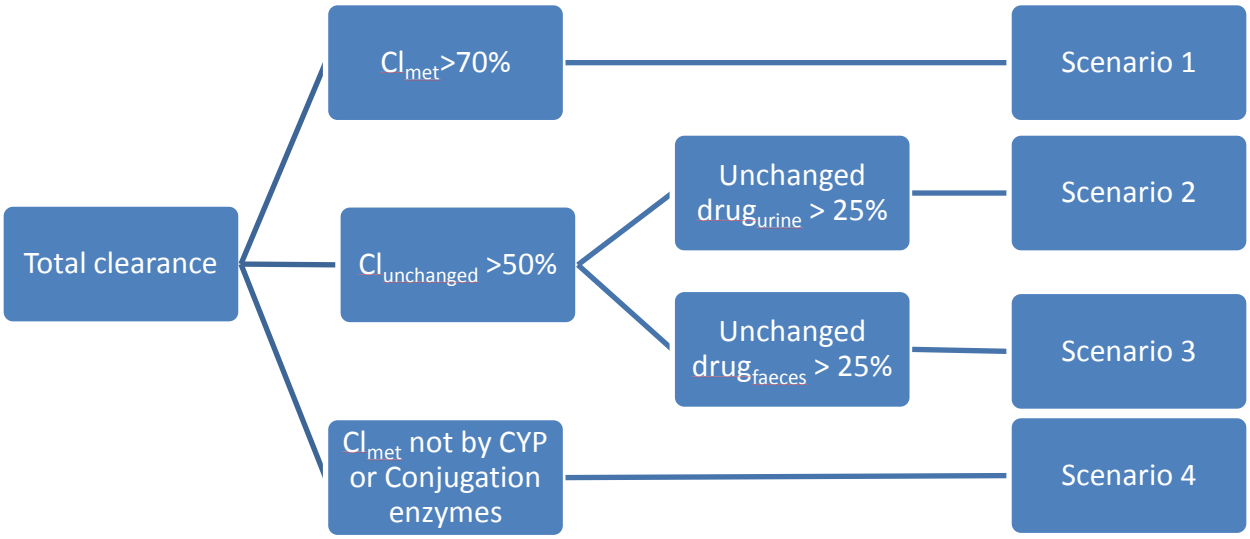

Figure 5-1: Proposed decision tree to predict type and degree of DDI

5.5.1 Scenario 1: Clearance by metabolization is 70% or more

When more than 70% of the drug is metabolized, relevant interactions with transporters are expected to be absent. Therefore interaction studies should concentrate on metabolism. As showed in section 4.3 interactions are bigger the lesser number of involved metabolic enzymatic pathways. The extent of the interaction is the biggest when a compound is cleared by one metabolic enzyme for more than 70%.

Ibrutinib (compound 1) is excreted for 99.2 % as metabolite, has only one metabolizing enzyme (CYP3A4) and undergoes extensive first pass metabolism. In accordance to the expectations the

increase in AUC of ibrutinib was large (more than 30 fold) when combined with Ketoconazole (a CYP3A4 inhibitor).

5.5.2 Scenario 2: Amount of unchanged drug in urine >25%

In situation 2 & 3 the drug is excreted for more than 50% as unchanged compound. For situation 2 the drug is excreted for more than 25 percent in the urine as unchanged compound. Either the drug is excreted in urine by glomerular filtration which is passive or by active secretion. The first step is to determine whether or not there are transporters involved. The glomerular filtration rate multiplied with the free fraction of the drug gives an indication of involvement of drug transporters. If the renal clearance of the compound is larger than the glomerular filtration rate, than efflux transporters might be involved, if the renal clearance is smaller, reuptake transporters are possibly involved. If there is a participation of transporters in the elimination of the molecule, interaction studies should be conducted to evaluate the effect of inhibition or induction.

Alogliptin benzoate, drug 17, is such a compound that is primarily excreted in urine. It is a real BCS and BDDCS class 3 compound with 76% found in urine with only traces of metabolites. *In vivo* interaction studies were conducted with Fluconazole, Ketoconazole, Gemfibrozil, Cyclosporin and Metformin. They give the following ratios (in percentage) in AUC: 99.14, 115.39, 112.88, 110.29 and 118.9%, respectively.

Another example of a drug with BDDCS 3 and high renal excretion of unchanged drug is Apixaban (compound 18). 42% of oral administration is excreted as unchanged drug in the urine. The drug underwent several interaction studies also investigating transporter interactions. Interaction trials with Ketoconazole, Naproxen and Rifampin were done giving AUC ratios of 200%, 150% and 50%, respectively.

5.5.3 Scenario 3: Amount of unchanged drug in faeces >25%

For situation 2&3 more than 50% is excreted as unchanged. When the drug is well absorbed and when more than 25% is found as parent compound in the faeces, the drug is probably actively secreted in the bile with the help of transporters. Possible DDI with the transporter in question should be investigated. However, there is a risk for potential

misclassification of the compound. Misclassification can occur due to high amount of unabsorbed drug after oral administration or deconjugation after biliary excretion of conjugation metabolites. An I.V. mass balance study or biliary secretion study can rule out the misperception that low absorption creates.

Substance 9 (Dolutegravir) is a good example to discuss about regarding the subject above. It is BDDCS class 4 despite of its BCS 2 classification. The cause of this mismatch is the high abundance of unchanged drug in the faeces (53%). The origin of the unchanged drug is not yet cleared out. It is unknown whether this is due to unabsorbed drug, excretion of unchanged drug or deconjugation after excretion of metabolites. Several factors lead to the assumption that the drug is in fact BDDCS class 2 and is highly conjugated. The first lead is that UGT1A1 is the major pathway of metabolization. Second, UGT inhibitors (Atazanavir) lead to a relevant increase in AUC of the compound. The last argument is the fact that metabolites represent the highest part in plasma.

Substance 13 (Cangliflozin) is another example. BCS and BDDCS are both class 4 but there are beliefs that both are wrong. The drug has an intermediate permeability and is classified as BCS 4 in accordance to bioequivalence guidelines. The drug is mainly excreted in the faeces as unchanged drug (40%). Again the sponsor was not quite sure regarding the origin of parent drug presence in faeces. Glucuronidation represents the major pathway of metabolization. UGT inducers (rifampin, probenecid as inhibitor) lead to a relevant decrease in the AUC of the drug. The absolute bioavailability seems reasonable (65%) so the high amount unchanged drug in faeces is probably not caused by unabsorbed drug.

5.5.4 Scenario 4: Metabolic clearance is not by CYP or conjugation enzymes

Drugs where CYP or conjugation related metabolization represents less than 50% of total metabolization belong to this section. For these compounds the BCS classification should be used to predict transporter interactions. BCS 1&2 compounds are not expected to have interactions with transporters whereas BCS 3&4 compounds are possible subject for transporter interactions. BCS classification for these compounds should not be used to predict metabolism related interactions.

6 CONCLUSION

Our first objective was to explore the BDDCS classification system and its value as a roadmap for a smart prioritization of pharmacokinetic drug interaction studies on candidate drugs as a substrate for DDI's. We saw that compounds with a high extent of metabolism have by far the most DDI. The interactions were exclusively metabolism related. Poorly permeable compounds have much less interactions. In addition, for drugs excreted unchanged >50%, DDI were primarily transporter related. Neither BCS nor BDDCS classification were momentarily mentioned in the surveyed Clinical Pharmacology and Biopharmaceutics Reviews as a guide to direct DDI programs and to predict DDI. An assignment to a BDDCS class was not available in the regulatory review of the approved compounds. Based upon this thesis, it can be implemented after instituting some additions. BCS instead of BDDCS classification should be used as a roadmap for drugs that have non-CYP, non-conjugation related metabolism. The BDDCS roadmap is not suitable for compounds that are excreted as unchanged compound for 30%-50% or have intermediate permeability.

Second objective, what efforts have pharmaceutical companies done during drug development? We see that the main focus of companies is on metabolic drug-drug interactions. Research to drug-drug interactions with transporters was not a priority so far and the number of transport related DDI studies did not increase over the last three years. Although, since the new guidance of the authorities ask more efforts on this subject, we think that more interaction studies will be done. Possibly more clinically relevant interactions with transporters will be discovered in this way. The probes that were used for *in vivo* transporter interaction studies are summarized in table 4-7, and provide Janssen with a direction for such drug interaction studies and programs.

The third and last objective was to summarize the lessons learned and to find a way to implement them in a roadmap for Janssen. Figure 5-1 gives the roadmap as a decision tree. Drugs that are mainly metabolized should receive attention on DDI in line with their metabolism. Drugs that are mainly excreted as unchanged compound should be investigated for the possibility of transporter interactions. For drugs that are metabolized via non-CYP and,

non-conjugation pathways the BCS instead of BDDCS classification should be used. Drugs having high permeability are not expected to have different exposures as consequence of transporter interactions. Drugs with poor permeability are probably subject of transporters and could be subject of clinically relevant interactions with transporters.

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8 ADDENDUM

8.1 SURVEY OF NEW DRUG APPROVALS 2011-2013

New drug approvals 2013

1) **Imbruvica (Ibrutinib) accelerated approval regulations**
   EMA: Categorized as rare disease designation.

BCS-class	2
BDDCS-class	2
Major route of elimination	Primarily excreted in faeces (80.6%, 0.77% of total unchanged). Renal route has a minor contribution (7.8%). Renal clearance of unchanged drug is negligible.
DDI metabolism (substrate)	CYP3A4
Probes used	Inhibitor: ketoconazole Inducer: rifampin
DDI transporters (substrate)	X
Probes used	X
Clinically relevant DDI	Avoid CYP3A4 inducers/inhibitors
Post marketing commitments	Assess the effect of rifampin on the PK in healthy subjects

2) **Sovaldi (Sofosbuvir)**

BCS-class	FDA: 4; EMA: 3
BDDCS-class	FDA: 4; EMA: 3
Major route of elimination	Hepatic, primarily in urine as active metabolite. Recovery: urine 80% (3.5 % unchanged), faeces 14% and respired 2.5%.
DDI metabolism (substrate)	Hydrolase cleavage.
Probes used	X
DDI transporters (substrate)	P-gp and BCRP
Probes used	Cyclosporine A (potent P-gp and BCRP inhibitor), RTV-boosted DRV (less potent P-gp inhibitor)
Clinically relevant DDI	X
Post marketing commitments	X

3) Olysio (Simeprevir) (EMA approval May 2014)

BCS-class	4
BDDCS-class	4
Major route of elimination	Recovery in faeces (91.2%) and urine (0.039%) In faeces: Phase 1 metabolites: 25.9%, unmetabolized:31.0%
DDI metabolism (substrate)	CYP3A4 (33.67%), CYP2C8 (5.86%), CYP2C19 (0.6%)
Probes used	Inducer: rifampin (strong) , efavirenz (moderate) Inhibitor: erythromycin (moderate), ritonavir (moderate,)
DDI transporters (substrate)	P-gp, MRP2, PCRP, OATP1B1/3, OATP2B1
Probes used	X
Clinically relevant DDI	Dose adjustments with CYP3A4 inducers
Post marketing commitments	X

4) Aptiom (Eslicarbazepine Acetate)

BCS-class	2
BDDCS-class	4
Major route of elimination	Prodrug: rapidly and extensively metabolized to major active metabolite by hydrolytic first-pass metabolism Drug: renal excretion 67% unchanged, 33% after conjugation
DDI metabolism (substrate)	Prodrug; not a substrate of any CYP isoenzyme
Probes used	X
DDI transporters (substrate)	X
Probes used	X
Clinically relevant DDI	X
Post marketing commitments	X

5) Opsumit (Macitentan)

BCS-class	2
BDDCS-class	2
Major route of elimination	Excretion in the urine (49.7%) (0% unchanged). Excretion in the faeces amounts for 23.9% of dose. 4% of dose was found unchanged in faeces.
DDI metabolism (substrate)	CYP3A4 (99%), CYP2C19 (little contribution)
Probes used	Cyclosporine-A (OATP1B1/1B3 and CYP3A inducer), Ketoconazole (strong CYP3A inhibitor) and rifampin (Strong CYP3A inducer).
DDI transporters (substrate)	The influence of transporters on the uptake of macitentan is absent.
Probes used	X
Clinically relevant DDI	Co-administration of macitentan and CYP3A4 inducers/ inhibitors should be avoided.
Post marketing commitments	X

6) Adempas (Riociguat) (EMA: still pending)

BCS-class	2
BDDCS-class	2
Major route of elimination	Metabolization followed by excretion in urine (40%) and faeces (53%). Respectively 6% and 15% of the administered dose was recovered as unchanged in urine and faeces.
DDI metabolism (substrate)	**CYP1A1**,CYP3A4/5, CYP2C8,CYP2J2 (percentages not found)
Probes used	Ketoconazole (multi-CYP/transporter inhibitor), Clarithromycin (CYP3A4 inhibitor) No specific tests are listed for the interactions with CYP1A1 or other metabolizing enzymes except CYP3A4.
DDI transporters (substrate)	P-gp, BCRP
Probes used	X
Clinically relevant DDI	X
Post marketing commitments	X

7) Duavee (Conjugated Estrogens/ Bazedoxifene)

BCS-class	Bazedoxifene: 2
BDDCS-class	Bazedoxifene : 2
Major route of elimination	Mainly in bile/faeces, extensively metabolized (glucuronidation is major pathway) BZA: Partial hydrolysis (20-40%) of BZA glucuronides to BZA occurred in spiked fecal samples. Biliary clearance for the phenyl glucuronide may be higher than that for the indole glucuronide.
DDI metabolism (substrate)	Oestrogens: CYP3A4 Bazedoxifene: UGT
Probes used	X
DDI transporters (substrate)	X
Probes used	X
Clinically relevant DDI	CYP3A4 inducers/inhibitors Adequate diagnostic measures with UGT inducers
Post marketing commitments	X

8) Brintellix Tablets (Vortioxetine)

BCS-class	FDA:3, EMA:1
BDDCS-class	1
Major route of elimination	Metabolism, metabolites (60% urine, 20% faeces) only negligible amounts of unchanged vortioxetine was excreted. No detectable unchanged vortioxetine was identified in the 59% of the radioactivity recovered in the urine
DDI metabolism (substrate)	CYP2D6,CYP2C8/9/19,CYP3A4/5, CYP2A6, CYP2B6 (percentages were not mentioned)
Probes used	Bupropion (CYP2D inhibitor), Rifampicin (CYP inducer), fluconazole (inhibition CYP2C9, CYP2C19, CYP3A4), Ketoconazole (CYP3A4/5 and P-gp inhibitor)
DDI transporters (substrate)	Poor P-gp substrate
Probes used	X
Clinically relevant DDI	Dose decrease (x1/2) if combined with potent CYP2D6 inhibitor. Dose should be increased (x3) when combination with strong inducers

	occurs. Otherwise no dose adjustments are required.
Post marketing commitments	X

9) Tivicay (Dolutegravir)

BCS-class	2
BDDCS-class	4
Major route of elimination	Hepatic elimination, primarily via UGT1A1, less via CYP3A4. Urine 31% (<1% unchanged). 64% in faeces, 53% excreted as unchanged in the faeces
DDI metabolism (substrate)	UGT1A1, CYP3A4 (minor pathway, 10 % in mass balance)
Probes used	Etravirine (CYP3A4 inducer) Efavirenz (CYP3A and UGT1A inducer) Fosamprenavir (CYP3A inducer)/ ritonavir Tipranavir (CYP3A inducer)/ ritonavir (UGT inducer) Rifampin (CYP3A and UGT1A inducer) Atazanavir (UGT1A1 inhibitor)
DDI transporters (substrate)	X
Probes used	X
Clinically relevant DDI	Dose adjustments with CYP3A4 inducers.
Post marketing commitments	X

10) Gilotrif (Afatinib)

BCS-class	1/3
BDDCS-class	3
Major route of elimination	Fecal elimination (85.4%), urine (4%). Low metabolic impact (64.1% unchanged in urine and faeces)
DDI metabolism (substrate)	CYP3A4 (9%), FMO3 (48%)
Probes used	X
DDI transporters (substrate)	P-gp, BCRP
Probes used in vitro	Cyclosporine A, verapamil, zosuquidar (inhibitors), fumitremorgin (in vitro)
Probes used	Ritonavir (inhibitor), rifampicin (inducer)
Clinically relevant DDI	Dose adjustments when co-administered with P-gp inducers/inhibitors
Post marketing commitments	X

11) Tafinlar (dabrafenib)

BCS-class	2
BDDCS-class	X
Major route of elimination	Fecal excretion: 71.1%, Urinary excretion:22.7%
DDI metabolism (substrate)	CYP3A4, CYP2C8 (no percentages given, mass balance is not clear)
Probes used	Ketoconazole (CYP3A4 inhibitor), phenytoin (CYP3A4 inducer)
DDI transporters (substrate)	P-gp, BCRP1 (in vitro)
Probes used	X
Clinically relevant DDI	Strong inducers/inhibitors CYP3A4/2C8 are to be substituted if possible. If last mentioned is not possible it is necessary to monitor the patient.
Post marketing commitments	What are the effects of strong CYP3A4/ CYP2C8 inducers/inhibitors

12) Mekinist (Trametinib) (Still under evaluation with EMA)

BCS-class	2
BDDCS-class	4
Major route of elimination	Dose excreted in faeces >80% (39.2% of oral dose), indicating hepatic elimination is the major elimination pathway. <20% (9% of oral dose) was recovered from the urine. Less than 0.1 % unchanged in urine. 27.4%-45% was excreted as unchanged in faeces.
DDI metabolism (substrate)	Non-CYP450 mediated metabolism. Major route of metabolism is deacetylation (hydrolytic esterases) in some cases followed by hydroxylation
Probes used	X
DDI transporters (substrate)	X
Clinically relevant DDI	X
Post marketing commitments	X

13) Invokana (Canagliflozin)

BCS-class	4
BDDCS-class	4
Major route of elimination	Excretion in faeces is 60.4% (40% unchanged) suggesting biliary excretion as major elimination pathway. Excretion in urine (32.5%) (1% unchanged).
DDI metabolism (substrate)	O-glucuronidation (by UGT2B4 and UGT1A9) Minor pathway of CYP3A4 (7%) and CYP2D6
Probes used	Rifampin (UGT inducer), Probenecid (UGT inhibitor)
DDI transporters (substrate)	P-gp (MDR1), MRP2
Probes used	Verapamil (P-gp inhibitor) (in vitro), cyclosporine (P-gp inhibitor and MPR2)), Metformin (hOCT1 & 2 inhibitor)
Clinically relevant DDI	Dose adjustment when combined with UGT inducers.
Post marketing commitments	X

14) Tecfidera (Dimethyl fumarate)

BCS-class	FDA : 1/3 ,EMA : 1
BDDCS-class	3
Major route of elimination	Exhalation as CO_2 (60%), renal (15.5%) (Most abundant as conjugates cysteine and N-acylcysteine), Fecal (1%). Metabolized by esterases.
DDI metabolism (substrate)	X
Probes used	X
DDI transporters (substrate)	X
Probes used	X
Clinically relevant DDI	X
Post marketing commitments	X

15) Osphena (Ospemifene) (Still under evaluation by EMA)

BCS-class	2
BDDCS-class	2
Major route of elimination	The compound is extensively metabolized. 75% was recovered in the faeces, 7% was recovered in the urine.
DDI metabolism (substrate)	CYP3A4 (40-50%), CYP2C9 (25%)/19(25%)
Probes used	Ketoconazole (strong CYP3A4 inhibitor), Rifampicin (strong CYP3A4 inducer), Fluconazole (CYP2C9/19, CYP3A4 inhibitor), omeprazole (CYP2C19 inhibitor)
DDI transporters (substrate)	X
Probes used	X
Clinically relevant DDI	Fluconazole should not be used in co-administration. A decreased systemic exposure might be observed when Ospemifene is administered in combination with Rifampin. The risk at adverse effects may increase when used in combination with ketoconazole.
Post marketing commitments	X

16) Pomalyst (Pomalidomide) (Accelerated approval regulations, EMA: categorized as rare disease designation.)

BCS-class	4
BDDCS-class	2
Major route of elimination	72.8% (2.2%unchanged) recovery in the urine, 15.5% (7.7% unchanged) recovery in faeces.
DDI metabolism (substrate)	**CYP3A4 (30%), CYP1A2 (54%)**, CYP2C19 (11%), CYP2D6 (4%)
Probes used	Carbamazepine (strong CYP3A4/5 inducer) Fluvoxamine (CYP1A2 inhibitor)
DDI transporters (substrate)	P-gp
Probes used	Ketoconazole, verapamil (P-gp inhibitors) (in vitro)
Clinically relevant DDI	X
Post marketing commitments	X

17) Nesina (Alogliptin benzoate)

BCS-class	3
BDDCS-class	3
Major route of elimination	Fecal excretion: 13%. Urinal excretion (76%), mainly unchanged. The two metabolized compounds M1 and M2 represented respectively <1% and < 4%.
DDI metabolism (substrate)	Primarily dealkylation (by CYP2D6) and N-acetylation, CYP3A4
Probes used	Fluconazole, ketoconazole, gemfibrozil**,** **cyclosporine**, pioglitazone,…)
DDI transporters (substrate)	Cimetidine (OCT1, OCT2, MATE1 and MATE 2 inhibitor)
Clinically relevant DDI	X
Post marketing commitments	X

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18) Eliquis (Apixaban)

BCS-class	3
BDDCS-class	3
Major route of elimination	Urine (50%) (as unchanged drug 42%), in faeces (31%) (as unchanged drug 9%)
DDI metabolism (substrate)	CYP3A4/5 (80%) SULT1A1
Probes used	Ketoconazole (CYP3A4 and P-gp inhibitor) Diltiazem (less potent CYP3A4 and P-gp inhibitor) Rifampin (strong CYP and P-gp inducer)
DDI transporters (substrate)	P-gp and BCRP
Probes used	Ketoconazole (CYP3A4 and P-gp inhibitor) Diltiazem (less potent CYP3A4 and P-gp inhibitor) Naproxen (P-gp inhibitor) Rifampin (strong CYP and P-gp inducer) Famotidine (OCT inhibitor)
Clinically relevant DDI	Avoid co-administration with dual P-gp and CYP3A4 inhibitors/inducers.
Post marketing commitments	X

19) Sirturo (bedaquiline) (Accelerated approval requirements) (EMA: pending approval decision)

BCS-class	2
BDDCS-class	2
Major route of elimination	Fecal
DDI metabolism (substrate)	CYP3A4
Probes used	Rifampin (CYP3A4 inducer), Ketoconazole (CYP3A4 inhibitor)
DDI transporters (substrate)	X
Probes used	X
Clinically relevant DDI	Systematic combination with strong CYP3A4 inducers should be avoided. Combined use with strong/moderate CYP3A4 inhibitors should not last longer than 14 days.
Post marketing commitments	In vivo study to conduct potential as substrate of OATP1B1 and OATP1B3 transporters

20) Juxtapid (Lomitapide mesylate)

BCS-class	2
BDDCS-class	2
Major route of elimination	Extensive metabolization 59.5% urine (0% unchanged) and 33.4% faeces (5% unchanged).
DDI metabolism (substrate)	CYP3A4, (CYP1A2, CYP2B6, CYP2C8, CYP2C19) (no percentages found)
Probes used	Ketoconazole Ethinyl estradiol (weak CYP3A4 inhibitor)
DDI transporters (substrate)	X
Probes used	X
Clinically relevant DDI	Avoid moderate and strong CYP3A4 inhibitors. Dose adjustments with weak CYP3A4 inhibitors.
Post marketing commitments	X

21) Iclusig (Ponatinib tablets)

BCS-class	FDA:4, EMA:2
BDDCS-class	2
Major route of elimination	Mainly via faeces (86.6%, 23.7 % unchanged)). Hepatic elimination is major route of elimination. Excretion via urine 5% (<1% unchanged).
DDI metabolism (substrate)	CYP3A4 (52%), (CYP2C8 (28.4%), CYP2D6 (9%), CYP3A5 (2.6%)
Probes used	Ketoconazole (CYP3A4 inhibitor)
DDI transporters (substrate)	Weak substrate of P-gp and BCRP
Probes used	X
Clinically relevant DDI	Dose reduction when co-administrations with strong CYP3A4 inhibitors occur. Avoid simultaneous use with CYP3A4 inducers.
Post marketing commitments	Investigate the effect of rifampin on the PK of the drug

22) Cometriq (Cabozantinib) (EMA: pending approval decision)

BCS-class	2/4
BDDCS-class	2/4
Major route of elimination	Faeces accounts for 53.8% recovery, 27.3% was recovered in urine. Percentages of unchanged drug have not been found.
DDI metabolism (substrate)	CYP3A4
Probes used	Rifampin (strong CYP3A4 inducer), Ketoconazole (strong CYP3A4 inhibitor)
DDI transporters (substrate)	X
Probes used	X
Clinically relevant DDI	Avoid chronic use of strong CYP3A4 inducers/ inhibitors.
Post marketing commitments	X

23) Xeljanz (Tofacitinib)

BCS-class	3
BDDCS-class	3
Major route of elimination	Hepatic elimination. In urine (80.1%)but primarily metabolized (29% unchanged). In faeces (13.8 %) 1% unchanged.
DDI metabolism (substrate)	**CYP3A4**, CYP2C19, (CYP1A1,CYP1A2,CYP2A6,CYP2B6, CYP2C8,CYP2C9,CYP2C18,CYP2D6, CYP2E1,CYP3A5)
Probes used	Ketoconazole (CYP3A4 and P-gp inhibitor), Fluconazole (moderate inhibitor of CYP3A4 and potent inhibitor of CYP2C19), Rifampin (potent P-gp and CYP3A4 inducer)
DDI transporters (substrate)	P-gp
Probes used	Cyclosporine, Ketoconazole (CYP3A4 and P-gp inhibitor), Rifampin (potent P-gp and CYP3A4 inducer)
Clinically relevant DDI	Dose adjustment with CYP3A4 inhibitors.
Post marketing commitments	X

24) Fycompa (Perampanel)

BCS-class	2
BDDCS-class	2
Major route of elimination	Hepatic metabolism is the major route. 48% (<9.4% unchanged) in faeces and 22% in urine (0.2% unchanged).
DDI metabolism (substrate)	CYP3A4
Probes used	Ketoconazole (strong CYP3A4 inhibitor), Carbamazepine (Strong inducer of CYP3A4).
DDI transporters (substrate)	X
Probes used	X
Clinically relevant DDI	Avoid strong CYP3A inducers
Post marketing commitments	In vitro studies to determine the contributions of major CYP isoenzymes and non-CYP enzymes to the metabolism

25) Bosulif (Bosutinib)

BCS-class	4
BDDCS-class	4
Major route of elimination	91.3% (40% unchanged) recovered in faeces and 3.29% (72% unchanged) recovered in urine.
DDI metabolism (substrate)	CYP3A4
Probes used	Ketoconazole (CYP3A4 inhibitor), rifampin (CYP3A4 inducer)
DDI transporters (substrate)	P-gp
Probes used	X
Clinically relevant DDI	Avoid strong and moderate CYP3A4 inhibitors/inducers and P-gp inhibitors.
Post marketing commitments	PMR will be issued to determine the needs of clinical trial with moderate CYP3A4 inhibitors/inducers.

26) Xtandi (Enzalutamide)

BCS-class	2
BDDCS-class	2
Major route of elimination	Hepatic metabolism. Urine accounts for 71.0% (unchanged amount: 0.0%). Faeces accounts for 13.6% (0.39% unchanged).
DDI metabolism (substrate)	**CYP2C8**, CYP3A4/5
Probes used	Gemfibrozil (strong CYP2C8 inhibitor), itraconazole (CYP3A4 inhibitor), Itraconazole (CYP3A4 inhibitor)
DDI transporters (substrate)	X
Probes used	X
Clinically relevant DDI	Co-administration with strong CYP2C8 inhibitors should be avoided. Concomitant medication without CYP3A4 induction is preferred.
Post marketing commitments	Conduct a clinical trial to evaluate the effect of rifampin. PMR: CYP2C8/CYP3A4 inducers.

27) Stribild (Elvitegravir/Cobicistat/Emtricitabine/Tenofovir)

BCS-class	Elvitegravir: 2 Cobicistat:2 Emtricitabine:1 Tenofovir DF:3
BDDCS-class	Elvitegravir: 4 Cobicistat:4 Emtricitabine:3 Tenofovir DF:3
Major route of elimination	EVG:Fecal 94.8% (30.8% unchanged), Urine 5.6% (0% unchanged) Cobi: Fecal 86.2% (27% unchanged), Urine 8.2% (6.3% unchanged) FTC and TDF primarily eliminated unchanged by combination of glomerular filtration and active tubular secretion. FTC and TDF are not relevantly metabolized.
DDI metabolism (substrate)	EVG:CYP3A and UGT1A1 Cobi:CYP3A4 and CYP2D6
Probes used	Ketoconazole (CYP3A4 inhibitor)
DDI transporters (substrate)	EVG:P-gp substrate Cobi: P-gp and BCRP substrate
Probes used	X
Clinically relevant DDI	X
Post marketing commitments	Elvitegravir and Cobicistat: Evaluate transport by hepatic transporters OATP1B1, OATP1B3 and OCT1. Evaluate transport by P-gp and BCRP. Emtricitabine and Tenofovir: Evaluate transport by renal transporters OCT2, OAT1, OAT3 and MRP2. Evaluate transport by P-gp and BCRP.

28) Myrbetriq (Mirabegron)

BCS-class	3
BDDCS-class	3
Major route of elimination	Primary renal 55% (via active tubular secretion and glomerular filtration) (25%unchanged) secondary biliary (34% faeces).
DDI metabolism (substrate)	**CYP3A4**, (CYP2D6)

Probes used	Ketoconazole (CYP3A4 and P-gp inhibitor), Rifampin (CYP3A4 and P-gp inducer)
DDI transporters (substrate)	P-gp
Probes used	Ketoconazole (CYP3A4 and P-gp inhibitor), Rifampin (CYP3A4 and P-gp inducer) Metformin (OCT substrate)
Clinically relevant DDI	X
Post marketing commitments	X

29) Belviq (Lorcaserin) (Dossier withdrawn in Europe)

BCS-class	1
BDDCS-class	1
Major route of elimination	92.3% recovery in urine (Lorcaserin was extensively metabolized). 2.2% recovery in faeces <1.5% excreted as unchanged
DDI metabolism (substrate)	CYP P450 (1A1/2/6, 2B6,2C19,2D6,2E1,3A4) UGT (1A9,2B7,2B15,2B17) SULT(1A1,1A2,2A1,1E1) (no percentages were found and mass balance was not clear)
Probes used	X
DDI transporters (substrate)	X
Probes used	X
Clinically relevant DDI	X
Post marketing commitments	X

30) Stendra (Avanafil)

BCS-class	2
BDDCS-class	2
Major route of elimination	61% (6%unchanged) fecal recovery and 21% urinal recovery (no unchanged drug)
DDI metabolism (substrate)	CYP3A4
Probes used	Ketoconazole and Ritonavir (CYP3A4 inhibitors), Erythromycin (moderate CYP3A4 inhibitor)
DDI transporters (substrate)	X
Probes used	X
Clinically relevant DDI	Avoid co-administration with strong CYP3A4 inhibitors.
Post marketing commitments	X

31) Aubagio (Teriflunomide)

BCS-class	2
BDDCS-class	4
Major route of elimination	Excretion in faeces: 37.2% (35.7% unchanged) 22.6 % excreted in urine (0.147% unchanged).
DDI metabolism (substrate)	Not a substrate of any CYPs or FMOs. Hydrolysis
Probes used	X
DDI transporters (substrate)	BCRP
Probes used	Rifampin (CYP and P-gp inducer)
Clinically relevant DDI	X
Post marketing commitments	X

32) Kalydeco (Ivacaftor)

BCS-class	2
BDDCS-class	2
Major route of elimination	Hepatic metabolism is the major route of elimination. 87.8% fecal (2.52% unchanged drug) and 6.6% renal (0.002% unchanged).
DDI metabolism (substrate)	CYP3A4/5 (no percentages found)
Probes used	Ketoconazol (CYP3A4 inhibitor), Fluconazole (moderate CYP3A4 inhibitor), Rifampin (strong CYP3A4 inducer)
DDI transporters (substrate)	P-gp
Probes used	X
Clinically relevant DDI	Strong CYP3A4 inhibitors: dose reduction Moderate CYP3A4 inhibitors: dose reduction Strong CYP3A inducers are contraindicated
Post marketing commitments	X

33) Erivedge (Vismodegib)

BCS-class	2
BDDCS-class	4
Major route of elimination	Faeces (82.2%), Urine (4.4%) (parent drug as major component and minor metabolism)
DDI metabolism (substrate)	CYP2C9, (CYP3A4/5,CYP2C18,CYP2C19,CYP2D6) (no % given)
Probes used	X
DDI transporters (substrate)	P-gp
Probes used	X
Clinically relevant DDI	X
Post marketing commitments	X

34) Inlyta (Axitinib)

BCS-class	2
BDDCS-class	2
Major route of elimination	Faeces: 40.6% (12% of dose unchanged), urine 22.7%. (0% unchanged)
DDI metabolism (substrate)	CYP P450: CYP3A4, (CYP1A2,CYP2C19,CYP3A5) UGT (no percentages found)
Probes used	Ketoconazole (CYP3A4 inhibitor), Rifampine (CYP3A4 inducer)
DDI transporters (substrate)	P-gp,BCRP
Probes used	X
Clinically relevant DDI	Concomitant use of strong CYP3A4/5 inducers/inhibitors should be avoided.
Post marketing commitments	X

35) Jakafi (Ruxolitinib)

BCS-class	1
BDDCS-class	1
Major route of elimination	Urine: 73.61% and faeces: 21.92%. Less than 1% excreted as unchanged drug in urine and faeces.
DDI metabolism (substrate)	CYP3A4
Probes used	Ketoconazole (CYP3A4 inhibitor), Erythromycin (moderate CYP3A4 inhibitor), rifampin (CYP3A4 inducer)
DDI transporters (substrate)	X
Probes used	X
Clinically relevant DDI	Dose adjustments when combined with strong CYP3A4 inhibitor. Patients should be closely monitored and the dose titrated when usage of strong CYP3A4 inducers occurs.
Post marketing commitments	X

36) Ferriprox (Deferiprone) (accelerated approval requirements)

BCS-class	2/4
BDDCS-class	2
Major route of elimination	Renal: 75%-90% (95% metabolized)
DDI metabolism (substrate)	3-O glucuronidation (UGT1A6)
Probes used	X
DDI transporters (substrate)	X
Probes used	X
Clinically relevant DDI	X
Post marketing commitments	Conduct in vitro studies to determine the effect of moderate to strong UDP glucuronosyltransferase (UGT) inhibition and moderate to strong UGT induction on the metabolism of deferiprone. The results of the in vitro evaluations will determine the need for additional in vivo drug interaction trials.

37) Xalkori (Crizotinib) Accelerated approval requirements

BCS-class	4
BDDCS-class	4
Major route of elimination	63.1% (53% unchanged) recovery in faeces, 22.2 % (1.3% unchanged) in urine. Extensive hepatic metabolism.
DDI metabolism (substrate)	CYP3A4(99.4%) /5, CYP2C19(0.5%), CYP2D6(0.1%)
Probes used	Ketoconazole (CYP3A4 inhibitor), rifampin (CYP3A4 inducer)
DDI transporters (substrate)	P-gp
Probes used	X
Clinically relevant DDI	Avoid strong CYP3A4 inducers
Post marketing commitments	Study if dose adjustment is necessary when using CYP3A4 inducer/inhibitor.

38) Zelboraf (Vemurafenib)

BCS-class	4
BDDCS-class	4
Major route of elimination	Faeces (94.1%) (37% unchanged), urine (0.97%)
DDI metabolism (substrate)	CYP3A4
Probes used	X
DDI transporters (substrate)	P-gp
Probes used	X
Clinically relevant DDI	X
Post marketing commitments	Effects of strong CYP3A4 inducer/inhibitor

39) Brilinta (Ticagrelor)

BCS-class	4
BDDCS-class	4
Major route of elimination	Extensively metabolized, 57.8% (27% unchanged) faeces, 26.5% urine (<1% unchanged)
DDI metabolism (substrate)	CYP3A, CYP2C9, CYP1A2
Probes used	Ketoconazole (CYP3A inhibitor), Rifampin (CYP3A4 inducer), Diltiazem (moderate CYP3A4 inhibitor) (omeprazole (CYP2C9 inhibitor), furafylline (CYP1A2 inhibitor) in vitro)
DDI transporters (substrate)	P-gp
Probes used	X
Clinically relevant DDI	Avoid concomitant use with strong CYP3A inducers/ inhibitors.
Post marketing commitments	X

40) Potiga (Ezogabine) EMA not found

BCS-class	2
BDDCS-class	4
Major route of elimination	84% recovery in urine (36% unchanged), 13.5% in faeces (3% unchanged).
DDI metabolism (substrate)	NAT2, UGT1A4, UGT1A1, UGT1A3,UGT1A9
Probes used	X
DDI transporters (substrate)	X
Probes used	X
Clinically relevant DDI	X
Post marketing commitments	X

41) Incivek (Telaprevir)

BCS-class	2
BDDCS-class	4
Major route of elimination	Faeces 81.6% (31.8% unchanged) Urine: 1.00% (0.11% unchanged) Expired air: 8.15%
DDI metabolism (substrate)	**CYP3A4**, CYP1A2,CYP2C9/19, CYP2D6, CYP2E1
Probes used	Ketoconazole (CYP3A4 inhibitor)
DDI transporters (substrate)	P-gp
Probes used	Cyclosporine A (P-gp inhibitor), ritonavir (P-gp inducer)
Clinically relevant DDI	X
Post marketing commitments	X

42) Edurant (Rilpivirine hydrochloride)

BCS-class	4
BDDCS-class	2
Major route of elimination	Faeces: 85% (25% unchanged), Urine 6.1% (<1% unchanged)
DDI metabolism (substrate)	CYP3A4 (>50%), CYP2C19
Probes used	X
DDI transporters (substrate)	X
Probes used	X
Clinically relevant DDI	X
Post marketing commitments	X

43) Victrelis (Boceprevir)

BCS-class	4
BDDCS-class	4
Major route of elimination	Faeces 78.9%, 7.89% in faeces was unchanged. 9.3% in urine (2.97% unchanged).
DDI metabolism (substrate)	CYP3A4**, AKR1C2, AKR1C3 (both for 69%)**
Probes used	Ketoconazole (CYP3A4 inhibitor), diflunisal (AKR inhibitor), efavirenz (CYP3A4 inducer)
DDI transporters (substrate)	P-gp
Probes used	X
Clinically relevant DDI	X
Post marketing commitments	X

44) Tradjenta (Linagliptin) (No dossier at EMA for Linagliptin but dossier for combination of linagliptin/ metformin hydrochloride)

BCS-class	3
BDDCS-class	3
Major route of elimination	Faeces (80%), Urine (5.4%) 90% excreted as unchanged in urine and faeces
DDI metabolism (substrate)	CYP3A4
Probes used	X
DDI transporters (substrate)	P-gp, linagliptin was a substrate for OATP8-, OCT2-, OAT4-, OCTN1- and OCTN2, suggesting a possible OATP8-mediated hepatic uptake, OCT2-mediated renal uptake and OAT4-, OCTN1- and OCTN2-mediated renal secretion and reabsorption of linagliptin in vivo
Probes used	Ritonavir & rifampicin (potent CYP3A4 and P-gp inducers)
Clinically relevant DDI	Avoid P-gp and CYP3A4 inducers.
Post marketing commitments	X

45) Zytiga (Abiraterone acetate)

BCS-class	4
BDDCS-class	4
Major route of elimination	88% faeces (55% unchanged) 5 % urine (no percentages found of unchanged drug in urine)
DDI metabolism (substrate)	CYP3A4, SULT2A1, UGT1A4. Conversion to abiraterone is a esterase activity
Probes used	X
DDI transporters (substrate)	X
Probes used	X
Clinically relevant DDI	X
Post marketing commitments	Conduct DDI trial to investigate effect of strong CYP3A4 inducer/inhibitor

46) Caprelsa (Vandetanib)

BCS-class	2
BDDCS-class	X
Major route of elimination	Both urinary(25.2%, 5% unchanged) and fecal (44.1%) excretion (no percentages found for unchanged drug in faeces)
DDI metabolism (substrate)	CYP3A4 FMO1 and FMO3
Probes used	Itraconazole (CYP3A4 inhibitor), rifampicin (CYP3A4 induction)
DDI transporters (substrate)	X
Probes used	X
Clinically relevant DDI	The use of strong CYP3A4 inducers should be avoided.
Post marketing commitments	X

47) Horizant (Gabapentin enacarbil) (No dossier found at EMA)

BCS-class	2
BDDCS-class	4
Major route of elimination	Urine 94% Faeces: 5%
DDI metabolism (substrate)	Hydrolysis
Probes used	X
DDI transporters (substrate)	OCT2, MCT-1, SMVT
Probes used	Cimetidine (OCT-2 inhibitor), Naproxen (MCT1 substrate)
Clinically relevant DDI	X
Post marketing commitments	X

48) Dificid (Fidaxomicin)

BCS-class	4
BDDCS-class	4
Major route of elimination	Faeces: (92.6%), as metabolite (66.2% metabolite, 26.4% unchanged). No unchanged drug was found in the urine.
DDI metabolism (substrate)	Hydrolysis
Probes used	X
DDI transporters (substrate)	P-gp
Probes used	Cyclosporin (P-gp inhibitor)
Clinically relevant DDI	X

Post marketing commitments	X

49) Daliresp (Roflumilast)

BCS-class	2
BDDCS-class	2
Major route of elimination	Urine: 70.1% (0% unchanged) , Faeces: 20.2% (no percentages found for unchanged drug in faeces)
DDI metabolism (substrate)	CYP1A2 and CYP3A4
Probes used	Erythromycin (moderate CYP3A4 inhibitor) Ketoconazole (Strong CYP3A4 inhibitor) Rifampicin (Strong CYP3A4 inducer)
DDI transporters (substrate)	X
Probes used	X
Clinically relevant DDI	Strong CYP450 inducers are not recommended. CYP3A4 and CYP1A2 inhibitors may result in increased incidence of adverse reactions
Post marketing commitments	X

50) Edarbi (Azilsartan medoxomil)

BCS-class	4
BDDCS-class	X
Major route of elimination	Excreted in urine 72% (15% unchanged) as inactive metabolites. Faeces:22%
DDI metabolism (substrate)	CYP2C9
Probes used	Fluconazole (CYP2C9 inhibitor)
DDI transporters (substrate)	x
Probes used	x
Clinically relevant DDI	X
Post marketing commitments	X

51) Viibryd (Vilazodone) (No dossier found at EMA)

BCS-class	3
BDDCS-class	3
Major route of elimination	Faeces 65% (2% unchanged), urine 20% (1% unchanged)
DDI metabolism (substrate)	**CYP3A4**, CYP2C19, CYP2D6 (60% CYP-mediated), non-CYP mediated (40%) (Possibly by carboxylesterase).
Probes used	Ketoconazole (CYP3A4 inhibitor)
DDI transporters (substrate)	X
Probes used	X
Clinically relevant DDI	Dose adjustments with strong CYP3A4 inhibitors.
Post marketing commitments	Investigate need for dose adjustment when administration with CYP3A4 inducer occurs. Is it a P-gp substrate?

52) Onfi (Clobazam)

BCS-class	2
BDDCS-class	2
Major route of elimination	Urine: 82% (2% unchanged) Faeces: 11% (1% unchanged)
DDI metabolism (substrate)	CYP3A4, CYP2C19, CYP2B6
Probes used	Ketoconazole (CYP3A4 inhibitor), CYP3A4 inducers (phenobarbital, phenytoin, and carbamazepine), CYP2C9 inducers (valproic acid, phenobarbital, phenytoin, and carbamazepine), and CYP2C9 inhibitors (felbamate and oxcarbazepine)
DDI transporters (substrate)	P-gp
Probes used	X
Clinically relevant DDI	Dose adjustments might be necessary when co-administered with strong or moderate CYP2C19 inhibitors.
Post marketing commitments	X

8.2 LECTURES OF PROFESSOR CROMMELIN

Impact of the pharmaceutical sciences over the past 50 years and … Quo Vadis?

Past performance? Impact of the Pharmaceutical sciences

In the period before 1964 the medicinal world had to help itself with very limited tools. Over the past 50 years the pharmaceutical sciences really developed itself and took huge steps forward. Especially in the seventies and eighties a huge amount of small molecule blockbusters came to the market. Since then the discovery of new small molecule drugs is stuttering.

Did we lose something? Do we never learn?

Not only had the rate of discovery of new drugs diminished. It seems to be a trend in the whole pharmaceutical field. Another example is the discovery of new methods of drug application. Inventions in the field of drug application had a peak in the seventies and eighties and are reduced since then. Professor Crommelin blames the precautionary principle as one of the big causes. Briefly this means that pharmaceutical companies have to proof that their product is safe or it can't be authorized. The professor thinks that this principle makes it really hard to have a high return in drug development. I know he is intentionally oversimplifying it but still I do not agree with his opinion. Sure this really slows down the research and prevents regulation of a few interesting drugs. But it is of crucial importance and warrants the health of global population. The past has several examples and in fact we really do learn. The hunger of target groups to new and better therapies and of companies to more money sometimes makes us forget that. My opinion is that the easy targets already are discovered and that we have to work much harder now to keep on improving our health care. New methods for drug development are not yet perfected but we have to grant it some time.

Future scenarios: Emerging areas/ Blurring borderlines

Technology becomes so sophisticated that the borderlines between different fields are vanishing. A good example is the difference between diagnosis, drugs and devices. Nowadays there are devices that comprise the drug and diagnosis that are part of the intervention. This makes it really hard to distinguish the separate fields.

Scenarios for the future of the pharmaceutical sciences and implications

Scenario analysis is a great tool used to arm against changes in the future. Instead of forecasting the future it thinks of possible scenarios that could happen. This makes it easier to anticipate. The first step is demarcating the field that is going to be analyzed. In this case the field is pharmaceutical sciences. The core consists of discovery, development, manufacturing, distribution & prescribing support and last but not least medication support. In addition to these aspects there is the operational window, legal and regulatory framework and competencies foundation, education and training. The second step is identifying the aspects that will be the most determining in the future. My opinion is that molecular biology, biomarkers and genomics will be the most important factor. Secondly there is the financial system that will be very determining. Thirdly you have demographics, longevity and chronic diseases. The last step in scenario analysis is predicting what will happen and what is wanted to happen with those key aspects.

Innovation strategies and public private partnerships

Innovation is one of the most dangerous things to do as a company and ironically one of the most important things to survive. Our country is at the top of scientific knowledge and scientific performances. It is necessary to increase our efforts to maintain our supremacy. A public private partnership is an initiative between a private organization and a public organization. A great example is the collaboration between the university and a company. It serves the benefit of both the company as the community.

The changing role of the pharmacist in an international perspective

There are still plenty of shortcomings in our healthcare system that needs to be fixed and where pharmacists can play a role. For example pharmacists can play a role in preventing drug interactions and compliance failure. In addition to this are internet pharmacy, automated dispensing machines, e-healthcare and education about medicines in high school. There are upcoming fields where pharmacists could possibly engage. He could check the patient's genetic profile before administering medication or manufacture small batches for stratified patient groups. A last possible field is ensuring the quality of advanced therapies.

Biotech takes over and we better be prepared

Biotech products represent a continuous increasing amount of the approved marketing authorization applications. These biotech products exist out of endogen en exogenous products. Examples for endogen structures are monoclonal antibodies, cytokines, hormones, growth factors et cetera. Examples of exogenous structures are vaccines and antigens. How do biopharmaceuticals differ from small molecules? They cost much more, have a very high molecular weight and have a much more complex structure. Furthermore they are less stable, are more immunogenetic, can't be administered orally and are species specific. Last but not least, they are very hard to characterize. Intravenous administration of Biopharmaceutics has many side-effects and a lot of alternatives have been investigated without result so far. Side-effects are needle phobia which occurs with at least 10% of the population. Another side-effect is blood born infection. When administration is not fully sterile a risk for infection occurs. Investigated possibilities are pulmonary application, microneedles, needle-free injections et cetera.

Biosimilars and non-biological complex drugs

Biosimilars are the equivalent for generic drugs in the field of biopharmaceutics. Because it is a biological product it is impossible to produce a product identical to the originator. As a consequence sponsors must perform more work so that their product gets approved. The amount of approved biosimilars is still low but the end of several patents opens a door for a steep increase in biosimilars. Next to complex biologics there are complex non-biologics. These are molecules with high molecular weight and that are not produced by biological systems. As with biologics they are hard to characterize.