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**Deliverable Report D5.1:**

**Report on the defined set of model compounds**

*Edited by*

*Mean contributors*

Work package 5

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**Maastricht University (UM)**

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## Contributions to deliverable - Internal review procedure

<b>Deliverable produced by:</b>	<b>Date:</b>
Adrian Roth - Partner Roche	September 2014
Ramona - Partner Roche	November 2014
Adrian Roth - Partner Roche	November 2014
<b>Deliverable internally reviewed by:</b>	<b>Date:</b>
Jos Kleinjans - Partner UM	November 2014

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## PUBLISHABLE SUMMARY

A balanced set of hepatotoxic, cardiotoxic and non-toxic drugs was established based on literature search, database review and guidance by consortium members.

## OBJECTIVES

Define reference compound set with known toxicological outcome to be used in in vitro models.

## INTRODUCTION

The first major task of WP5 was the selection of a set of suited reference drugs for the categories hepatotoxic, cardiotoxic and non-toxic. As drug toxicity involves a multitude of factors and in clinical situations occurs under specific - often not well defined - conditions, there is no general agreement on a given set of reference drugs. Using an approach based on FDA classifications, consortium outcomes, literature and suggestions based on clinical experience, the working group came up with a workable number of drugs to be applied to our in vitro test systems.

While toxic reference drugs could be identified, the choice of appropriate non-toxic drugs and/or non-toxic conditions were intensively discussed. While a list of separate non-toxic drugs and chemicals displaying no adverse effects was selected, it was also discussed to include a non-toxic condition for the toxic drugs. This allows for a solid benchmarking of toxic effects against both non-toxic drugs as well as non-toxic treatment of the same drug.

## RESULTS

A well-defined set of prototypical drugs has been compiled using different resources:

- 1.) For the Hepatotoxicity part, a recently published list by the FDA was used (Chen et al., Drug Discov Today. 2011 Aug; 16 (15-16):697-703.). In this publication, a systematic classification scheme using FDA-approved drug labelling was applied to assess the DILI potential of drugs, which yielded a benchmark dataset with 287 drugs representing a wide range of therapeutic categories and daily dosage amounts. To guarantee comparability of in vitro results to clinical case examples within this consortium project, an additional selection criteria was accessibility of tissue from patients. Applying these two criteria (FDA labelling & accessibility) led to the selection 31 drugs were identified with defined reporting frequency of DILI. A core set of 13 compounds (red rectangle) was derived there from as a starting set for the first round of experiments.

Compound FDA list	Therapeutic category	Label	Severity score	Reporting Frequency of DILI	Accessibility of liver tissue	Small Molecule (SM) or Biologic (B)	In Vitro Mechanism reported	Interest for HECATOS
isoniazid	Antimycobacterials	BW	8	***	*	SM	OS/Mit/Bioact	+++
methotrexate	Antineoplastic agents	BW	3	***	*	SM	Cho	+++
rifampin/rifampicin	Antimycobacterials	WP	8	***	*	SM	OS/Mit	++
diclofenac	NSAIDs	WP	7	***	*	SM	AP/Mit/Bioact	+++
erythromycin	Antibacterials	WP	5	***	*	SM	OS/AP	+++
azathioprine	Immunosuppressants	WP	3	***	*	SM	OS/Mit	+++
piroxicam	NSAIDs	WP	3	***	*	SM	Cho/Bioact	+++
valproic acid	Antiepileptics	BW	8	**	*	SM	St/OS/Bioact	+++
phenobarbital	Antiepileptics	WP	3	**	*	SM	Mit	+
phenytoin	Antiepileptics	WP	3	**	*	SM	Mit/Bioact	+++
pravastatin	Antihyperlipidemics	WP	3	**	*	SM	Mit/AP	+++
simvastatin	Antihyperlipidemics	WP	3	**	*	SM	Mit/AP	+++
tetracycline	Antibacterials	WP	2	**	*	SM	Cho/Mit	+++
cyclosporine	Immunosuppressants	WP	2	*	*	SM	OS	+++
ciprofloxacin	Antibacterials	WP	7	***	*	SM		
amoxicillin	Antibacterials	WP	3	***	*	SM		
ibuprofen	NSAIDs	WP	3	***	*	SM		
naproxen	NSAIDs	WP	3	***	*	SM		
leflunomide	Immunosuppressants	BW	8	**	*	SM		
mercaptopurine	Antineoplastic agents	WP	8	**	*	SM		
carbamazepine	Antiepileptics	WP	7	**	*	SM	Mit/Bioact	
fenofibrate	Antihyperlipidemics	WP	3	**	*	SM		
gemfibrozil	Antihyperlipidemics	WP	3	**	*	SM		
indomethacin	NSAIDs	WP	3	**	*	SM	OS/Bioact	
paroxetine	Antidepressants	AR	8	**	*	SM		
prednisolone	Corticosteroids	AR	3	**	*	SM		
ketoconazole	Antifungals	BW	8	*	*	SM		
fluconazole	Antifungals	WP	8	*	*	SM		
haloperidol	Antipsychotics	AR	5	*	*	SM		
fluoxetine	Antidepressants	AR	3	*	*	SM		
sertraline	Antidepressants	AR	3	*	*	SM		
Compound not included in the FDA list	Therapeutic category	Label	Severity score	Reporting Frequency of DILI	Accessibility of liver tissue		In Vitro reported Mechanism	Interest for HECATOS
fluorouracil	Antineoplastic agents			*	***	SM		+
irinotecan	Antineoplastic agents			*	***	SM		+
bevacizumab (Avastin)	Antineoplastic agents			*	***	B		
panitumumab (Vectibix)	Antineoplastic agents			*	**	B		
amoxicillin-clavulanate	Antibacterials			***	*	SM		+
paracetamol	Analgesic			**	*	SM	OS/AP/Bioact	+

- 2.) For the cardiotoxic reference drugs, 3 recent publications were used where cardiac liabilities in clinic and in vitro were well-described (Guo et al., TOXICOLOGICAL SCIENCES 123(1), 281–289 (2011); Guo et al., Toxicol Sci. 2013 Dec;136(2):581-94.; Pointon et al., toxicological sciences 132(2), 317–326 2013). Merging that list and - as for the hepatotoxic reference drugs – crosschecking with availability of clinical case examples yielded a set of 12 drugs with defined cardiac liability as a starting set.

Drug Name	Target/Indication	Label/FDA class
Amiodarone HCl	Antiarrhythmic	Arrhythmia, heart block, sinus bradycardia, CHF, ventricular fibrillation
Daunorubicin	Antineoplastic	Myocardial toxicity manifested in its most severe form by potentially fatal congestive heart failure may occur either during therapy or months to years after termination of therapy. The incidence of myocardial toxicity increases after a total cumulative dose exceeding 400 to 550 mg/m <sup>2</sup> in adults, 300 mg/m <sup>2</sup> in children more than 2 years of age, or 10 mg/kg in children less than 2 years of age.
Taxane (Taxol/Paclitaxel).		Bradycardia, abnormal ECG: Sinus bradycardia, atrial and ventricular arrhythmias, MI, supraventricular tachycardia, AV or left bundle branch block
Docetaxel		
Epirubicin		fatal congestive heart failure (CHF), may occur either during therapy with Epirubicin Hydrochloride Injection or months to years after termination of therapy
Cyclophosphamide	Antineoplastic	Acute cardiac toxicity, CHF, myocarditis, myocardial necrosis
Doxorubicin HCl	Antineoplastic	CHF, decreased LVEF, sinus tachycardia, myocarditis, cardiomyopathy
Fluorouracil	Antineoplastic	HF, MI, ventricular dysfunction, cardiac fibrillation, arrhythmia
Idarubicin HCl	Antineoplastic	CHF, arrhythmia, cardiomyopathy, decreased LVEF
Mitoxantrone diHCl	Antineoplastic	CHF, decreased LVEF, tachycardia, arrhythmia
celecoxib		
lapatinib		

- 3.) As non-toxic controls, a published list of the top 200 prescribed drugs was used (Stepan et al., Chem. Res. Toxicol. 2011, 24, 1345–1410). Out of this list, a set of 11 compounds was selected which does not bear hepatotoxic liability based on FDA classification in Chen et al 2011 and where no reports on cardiac side effects exist based on Pharmapendium records.

Drug	Heptox	cardiotox	FDA	Cardiotox Level based on US Label
penicillin G	low	low	Drug of no concern for DILI	
aspirin	low	low	Drug of no concern for DILI	no CV warnings
kanamycin	low	low		
Sibrafiban	low	low	Discont. In Phase III due to lack of efficacy	Discont. In Phase III due to lack of efficacy = never registered
Acyclovir	low	low		no Cardiotox warnings
Saquinavir	low	low		no Cardiotox warnings
Ambrisentan	low	low		Note: warning on HF associated with fluid retention
Aliskiren	low	low	No ALT increase reported	no Cardiotox warnings
Tiotropium	low	low		no Cardiotox warnings
Carisoprodol	low	low	No clear association	no Cardiotox warnings
Promethazine	low	low	No clear association	no Cardiotox warnings

## DIFFICULTIES

Selection of reference drugs is generally a challenge as there is no such thing as “a toxic drug” or “a non-toxic drug”. A balanced selection after intense consideration of literature and other data sources was thus necessary. In order not to limit ourselves too much we decided to look into low dose treatments as well as non-toxic/inert substances to serve as controls. Data will tell which might be the better option.

## REFERENCES

- Chen et al., Drug Discov Today. 2011 Aug;16 (15-16):697-703.
- Guo et al., TOXICOLOGICAL SCIENCES 123(1), 281–289 (2011).
- Guo et al., Toxicol Sci. 2013 Dec;136(2):581-94.
- Pointon et al., toxicological sciences 132(2), 317–326 2013.
- Stepan et al., Chem. Res. Toxicol. 2011, 24, 1345–1410.