Drug disposition classification systems: A comparative review of BDDCS, ECCS and ECCCS

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Drug disposition classification systems

**BCS**

- **High Solubility**
  - Class 1: Metabolism
  - Class 3: Renal and/or Biliary Elimination of Unchanged Drug
- **Low Solubility**
  - Class 2: Metabolism
  - Class 4: Renal and/or Biliary Elimination of Unchanged Drug

**BDDCS**

- **High Solubility**
  - Class 1: Extensive Metabolism (Rapid Dissolution and ≤70% Metabolism for Bioavailability)
  - Class 3: High Solubility Poor Metabolism
- **Low Solubility**
  - Class 2: Low Solubility Extensive Metabolism
  - Class 4: Low Solubility Poor Metabolism

**ECCCS**

**ECCS**

- **ECC class 1**
  - Hepatic elimination primary via metabolism, Efflux transporter effects minimal
  - RENAL/PRE-10, BDDCS: Solubility, Dose10:65 MLL
- **ECC class 2**
  - Hepatic elimination via metabolism and possibly biliary secretion of unchanged drug, Influx transporter effects can occur
  - EDDS, Phe, O2, BDDCS: Metabolisation
- **ECC class 3**
  - Renal and/or biliary elimination of unchanged drug, Bilberry and renal elimination of unchanged drug, Uptake transporter effects predominant
  - EDDS: Phe, O2, BDDCS: Metabolisation
- **ECC class 4**
  - Uptake and influx transporter effects may be important
  - EDDS, Phe, O2, BDDCS: Metabolisation

**ECCS**

- **NW 5800**
  - Class 1A: Metabolism
  - Class 1B: Hepatic uptake
- **NW 4800**
  - Class 2A: Renal
  - Class 2B: Hepatic uptake or Renal
- **NW 4600**
  - Class 3A: Metabolism
  - Class 4: Renal

**References**

- Wu and Benet, 2005, Pharm Res;22:11-23
- Camenisch et al, 2015, ADMET&DMPK;1:1-14
- Camenisch, 2016, Pharm Res;33:2583-93
- Varma et al, 2015, Pharm Res;32:3785-802
Biopharmaceutics Drug Disposition Classification System (BDDCS)

Classification based on human *in vivo* metabolism (or passive permeability) and soluble dose

→ *Rather applicable in late drug development phases*

→ *Provides information about involvement of potential transport processes in absorption and elimination*

→ *Observation based classification system*
Extended Clearance Classification System (ECCS)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Permeability</th>
<th>MW</th>
<th>Process Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>$2 \times 10^{-6}$ cm/s</td>
<td>$\leq 400$ acids/ zwitts</td>
<td>Clearance determined by metabolism, Eliminated as metabolites (≥ 70%), Absorption is not permeability-limited</td>
</tr>
<tr>
<td>1B</td>
<td>$2 \times 10^{-6}$ cm/s</td>
<td>$&gt; 400$ bases/neutrals</td>
<td>Clearance determined by (active) hepatic uptake, Eliminated as metabolites (≥ 70%), Absorption is not permeability-limited</td>
</tr>
<tr>
<td>2</td>
<td>$&lt; 2 \times 10^{-6}$ cm/s</td>
<td>$\leq 400$ acids/ zwitts</td>
<td>Clearance determined by metabolism, Eliminated as metabolites (≥ 70%), Absorption is not permeability-limited</td>
</tr>
<tr>
<td>3A</td>
<td>$&lt; 2 \times 10^{-6}$ cm/s</td>
<td>$&gt; 400$ bases/neutrals</td>
<td>Clearance determined by renal, Eliminated as parent in urine (≥ 70%), Permeability-limited absorption</td>
</tr>
<tr>
<td>3B</td>
<td>$&lt; 2 \times 10^{-6}$ cm/s</td>
<td>$&gt; 400$ bases/neutrals</td>
<td>Clearance determined by hepatic uptake or renal, Eliminated as parent in bile or urine (≥ 70%), Permeability-limited absorption</td>
</tr>
<tr>
<td>4</td>
<td>$&lt; 2 \times 10^{-6}$ cm/s</td>
<td>$&gt; 400$ bases/neutrals</td>
<td>Clearance determined by renal, Eliminated as parent in urine (≥ 70%), Absorption is permeability-limited</td>
</tr>
</tbody>
</table>

Classification based on \textit{in vitro} permeability and physicochemical properties (MW, charge)

→ \textbf{Applicable in early drug development phases}

→ \textbf{Allows to identify the rate-limiting clearance processes (absorption, distribution and elimination model)}

→ \textbf{Observation based classification system (based on the extended clearance concept)}
**Extended Clearance Concept Classification System (ECCCS = EC3S)**

\[
\text{CL}_{\text{h,int}} = \frac{\text{PS}_{\text{inf,act}} + \text{PS}_{\text{inf,pas}}}{\text{PS}_{\text{eff,act}} + \text{PS}_{\text{eff,pas}} + \text{CL}_{\text{int}}} \times \text{CL}_{\text{int}}
\]

**in vitro input parameters**

- **PS\textsubscript{inf,pas}**: Hepatic uptake / MDCK permeability
- **PS\textsubscript{inf,act}**: Hepatic uptake
- **CL\textsubscript{int,met}**: Liver microsomes / Hepatocytes / S9
- **CL\textsubscript{int,sec}**: Sandwich-cultured hepatocytes
- **PS\textsubscript{eff,act} = PS\textsubscript{inf,pas}**

Extended Clearance Concept Classification System (ECCCS = EC3S)

Classification based on *in vitro* permeability and *in vitro* metabolic and biliary clearance data

→ **Allows to identify the rate-limiting clearance processes (absorption, distribution and elimination model)**

→ **Rate-limiting step of hepatic elimination**

→ **Model-based drug absorption, distribution and elimination drug classification system**
EC3S – Elimination mechanisms

CYP, non-CYP

Class 2cd

Class 1,2ab

Predominantly CYP

Class 3,4ab

Metabolic, renal, biliary possible
EC3S – Elimination mechanisms

• Metabolic elimination generally well predicted (MDCK-LE $P_{\text{app}} > 5 \cdot 10^{-6}$ cm/s)
• EC3S provides information for CYP (Class 1,2ab) vs non-CYP (class 3,4ab)

→ Prediction of major elimination mechanisms in early development phase
**EC3S – Hepatic clearance IVIVE**

*Rate-determining process*

**Hypothesis:** knowing the rate-limiting process of hepatic elimination will facilitate selection of the most predictive clearance prediction tool
## EC3S – Hepatic clearance IVIVE

### Mechanism:

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>In vitro assay</th>
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<tbody>
<tr>
<td>sinusoidal influx/efflux</td>
<td>suspended hepatocytes (SHH)</td>
</tr>
<tr>
<td>metabolism</td>
<td>liver microsomes (HLM), hepatocytes (HH)</td>
</tr>
<tr>
<td>biliary secretion</td>
<td>sandwich-cultured hepatocytes (SCH)</td>
</tr>
<tr>
<td>Extended Clearance Model (ECM)</td>
<td>HLM, SHH, SCH</td>
</tr>
<tr>
<td>plasma protein binding</td>
<td>ultrafiltration, ultracentrifugation or or equilibrium-dialysis</td>
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</tbody>
</table>

\[
CL_{\text{int,all}} = CL_{\text{met,u}}
\]

**HH, HLM**

\[
CL_h = Q_h \cdot E_h = \frac{Q_h \cdot f_{u,b} \cdot CL_{\text{int,all}}}{Q_h + f_{u,b} \cdot CL_{\text{int,all}}}
\]

\[
CL_{\text{int,all}} = PS_{\text{inf}}
\]

**SHH**

\[
CL_{\text{int,all}} = \frac{PS_{\text{inf}} \times (CL_{\text{sec,u}} + CL_{\text{met,u}})}{PS_{\text{inf,pas}} + (CL_{\text{sec,u}} + CL_{\text{met,u}})}
\]

**ECM**

\[
CL_{\text{int,all}} = \frac{PS_{\text{inf}} \times CL_{\text{met,u}}}{PS_{\text{inf,pas}} + CL_{\text{met,u}}}
\]

**ECM (-)**

→ **Expectation:** different outcomes depending on rate-limiting clearance mechanism (EC3S class-dependent)

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PK Sciences

EC3S – Hepatic clearance IVIVE

HLM:

\[ CL_{int,all} = CL_{met} \]

→ Class 2 generally well predicted
→ Often under-predictive for class 4
→ Tendency for being over-predictive for class 1 and class 3

ECM (-):

\[ CL_{int,all} = PS_{inf} \]

→ Class 1 and class 3 generally well predicted
→ Over-predictive for some class 2 and class 4 cpds

\[ CL_{int,all} = \frac{PS_{inf} \times CL_{met}}{PS_{inf,pas} + CL_{met}} \]

→ Class 1, class 3 and class 2 generally well predicted
→ Under-predictive for some class 4 cpds
**EC3S – Hepatic clearance IVIVE**

\[ CL_{\text{int,all}} = \frac{PS_{\text{inf}} \times (CL_{\text{sec}} + CL_{\text{met}})}{PS_{\text{eff}} + (CL_{\text{sec}} + CL_{\text{met}})} \]

→ Predictive for all EC3S classes

**IVIVE recommendations:**

- **HH** is the method of choice for IVIVE of EC3S **class 1** cpds
- **HLM** or **HH** is the method of choice for IVIVE of EC3S **class 2** cpds
- **SHH** is recommended for EC3S **class 3** cpds (**HH** is the best alternative)
- **ECM** is needed for EC3S **class 4** cpds (no real alternative available)
EC3S – Total Clearance IVIVE

Estimation of fractional hepatic elimination

Total drug clearance ($CL_{tot}$)

$$CL_{tot} = CL_h + CL_{ren}$$

→ Is it possible to estimate relative contributions of hepatic ($fn_h$) and non-hepatic elimination pathways?

$$CL_{tot} = \frac{CL_h}{fn_h}$$

Extended Clearance Model

no appropriate renal \textit{in vitro} model available
**EC3S – Total Clearance IVIVE**

*Estimation of fractional hepatic elimination*

**Observation:** hepatic uptake permeability correlates with elimination pathway

\[
1 = f_{n_{\text{ren}}} + f_{n_{\text{sec}}} + f_{n_{\text{met}}} + f_{n_h}
\]

\[
f_{n_h} = 1 - \exp^{-0.01741 \cdot PS_{\text{inf}}}
\]

\[
r^2 = 0.82
\]

Camenisch et al, 2015, ADMET&DMPK; 3:1-14
**EC3S – Total Clearance IVIVE**

*Estimation of fractional hepatic elimination*

ECCCS class 1/2:

**hepatic** drug elimination

\[
CL_{\text{tot}} = \frac{CL_h}{fn_h}
\]

ECCCS class 3/4:

**hepatic** and **renal** drug elimination

→ Accurate prediction of total drug clearance independent of elimination pathways

**EC3S – Total Clearance IVIVE**

*Estimation of fractional hepatic elimination*

**Prediction of total human clearance**

1) \( f_{n,h} \) estimated from \( PS_{inf,pas} \)

2) \( CL_{tot} \) calculated with:

\[
CL_{tot,\text{pred}} = \frac{CL_{h,\text{pred}}}{f_{n,h,\text{pred}}}
\]

(assuming absence of other elimination routes)

Applications for drug classification

Guidance for the drug development process

- What is the recommendation with regards to metabolism investigations (in vivo or in vitro)?
- What is the most appropriate clearance prediction tool for IVIVE?
- Are there opportunities to waive any animal studies (e.g. bile-duct cannulation studies)?
- What is the potential leverage with regards to in silico PK work?
- Is it recommended to synthesize a radiolabel in an early development phase?
- Which DDI follow-up studies (cpd as perpetrator vs victim) are recommended?
## Applications for drug classification

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<td>− Camenisch and Umehara, Biopharm Drug Dispo (2012)</td>
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<td><strong>Kp uu</strong></td>
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<td>− Riede et al, Drug Metab Dispos (2017)</td>
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<td><strong>Food effect</strong></td>
<td>− Custodio et al, Adv Drug Deliv Rev (2008)</td>
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Summary

• All compound classification systems provide information on drug disposition and the interplay between metabolic enzymes and transporters.

• ECCs and EC3S use *in vitro* data only. BDDCS requires information of a clinical dose and may therefore be positioned at a later stage in the drug development process.

• EC3S provides directly enables quantitative estimates of hepatic clearance and disposition processes given the required *in vitro* parameters are generated.

• All three classification systems may facilitate the compound class-dependent drug development process by guiding the selection of the most appropriate *in vitro* and *in vivo* studies.
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