Alcohol-induced dose dumping intentional / accidental – IPEC Working Group

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Content of the presentation

• IPEC ADD Working Group members
• Basics and facts about ADD and some drug cases
• EU- and US-Guidance
• IPEC ADD WG Position Paper (in preparation)
• Technological aspects

Scope:
No reference to tamper resistant (= abuse deterrent) formulations and is not intended to address deterrence of fraudulent behavior.
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Definition of ADD (Alcohol-induced Dose Dumping)

C. Alcohol Induced Dose Dumping

_Dose dumping_ is a term that describes the unintended, rapid release in a short period of time of the entire amount or a significant fraction of the drug contained in a modified-release dosage form. Depending on the therapeutic indication and other characteristics of the drug, dose dumping can pose a significant risk to patients, either because of safety issues or diminished efficacy or both. Generally, dose dumping is observed as a result of a compromise of the release-rate-controlling mechanism. Some modified-release oral dosage forms contain drugs and excipients that exhibit higher solubility in ethanolic solutions compared to water. Such products can be expected to exhibit a more rapid drug dissolution and release rate in the presence of ethanol. Therefore, when a modified-release product is consumed with alcohol, the modified-release mechanism could be adversely affected, which could lead to dose dumping.

Where appropriate, based on the risk of dose dumping when a modified-release drug product is consumed with alcohol, the modified-release drug product’s labeling includes warnings against the consumption of alcohol while taking the drug product. Even with significant warnings in the labeling, the consequences of concomitant alcohol use need to be considered for certain drug products because alcohol use may still be likely, and such alcohol use may lead to dose dumping, which could result in serious adverse events.

QUOTE (Docket No. FDA-2009-P-0403, FDA-CDER-Osmotica Petition)
Alcohol effects on modified release solid oral forms

Key message
ADD can cause:
- earlier drug release
- higher drug concentrations
- loss of delayed release
- risk of side effects

Minimum toxic concentration (MTC)

Regular level of API liberated from dosage form

+ alcohol: mostly no effect
   Immediate release

+ alcohol: loss of enteric protection
   pH controlled delayed release/Gastro resistance

+ alcohol: risk of toxic effects due to dumping of high drug load
   Extended release

+ alcohol: loss of timing/ targeting function
   GI Targeting

Stomach

Duodenum

Jejunum

Ileum (small intestine)

Colon (transverse)

Colon (ascending)

Colon

0.5-2h (up to 6h, depends on size and type of food)
  pH 1-1.5 (fasted), pH 2-4 (fed)

8-18h
  pH 4-6

> 10h
  pH 6-8

> 10h
  pH 6-8
EU Regulatory Case: Art. 31 Referral Procedure 2009-2010

Press release

23/07/2010

European Medicines Agency concludes review of modified-release oral opioids of the WHO level III scale for the management of pain

Benefits of most of these medicines outweigh risks; marketing authorisations of opioids using polymethacrylate-triethylcitrate controlled release systems should be suspended because of concerns over interaction with alcohol.

The European Medicines Agency has finalised a review of modified-release oral opioids of the WHO level III scale for the management of pain. The Agency’s Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of most of these medicines continue to outweigh their risks, but that the existing warnings on the interaction of these medicines with alcohol should be made consistent across the class.

However, for modified-release oral opioids that contain a polymethacrylate-triethylcitrate controlled-release system the Committee recommended suspension of the marketing authorisations, until the manufacturers have reformulated them so that they are more stable in alcohol.

Modified-release oral opioids of the WHO level III scale for the management of pain are strong painkillers used to treat pain that has not been controlled with other medicines. They release the active substance slowly, often over many hours, to reduce the number of times patients have to take the medicine every day. Included in the class are morphine and the related medicines oxycodone and hydromorphone.

Key message
- EMA is willing to remove “risky” drugs from the market.
- EMA focused for CR opioid preparations solely on the system and did not take other aspects into consideration.
In July 2005, FDA asks Purdue Pharma to withdraw PALLADONE® for safety reasons – although ADD effect was already labelled. Product is still on the market in the EU.
ADD is a multi-factorial event

- GIT (1)
- Pharmaceutical presentation (2)
- Alcohol (3)
- Food
- Active ingredient
- Gender & age
Gastro-intestinal tract effect
(stomach)

The stomach distributes different substances, nutrient matters and particles to specific areas, rather than mashing it all up to “one size of everything everywhere”.

Results:
1. Small multi-particulate dosage forms tend to proceed faster towards the pylorus than larger monolithic dosage forms.
2. Small particles are emptied from the stomach (much) earlier than large particles (size matters!).
3. Large solid particles are ground by a forceful jet-like retropulsion through the small orifice of the terminal antral contraction.

Key message
The stomach does not act like a “bucket”, but separates materials by size and performs grinding.
Pharmaceutical presentation – example #1
ADD in vitro, but NOT in vivo

Key message
In vitro ≠ in vivo

Carvedilol Micropump®

In-vitro drug release (%) at different alcohol concentrations

Figure 1. Effect of ethanol on the in vitro dissolution of the carvedilol controlled-release capsule.

IR and CR microparticles (Flamel micropump IIa, IIc, both coated with methacrylic acid copolymers)

1. Liberation of microparticles from capsules in stomach.

2. Emptying of microparticles from stomach, once released from the capsules, happens mostly unaffected by potential alcohol induced increase of gastric retention time, because particles are sufficiently small to pass the pyloric part.

In-vivo blood levels (ng/ml) with concomitant intake of 240 ml ethanol 20%

Source: Henderson et al., J. Clin. Pharmacol. 2007; 47; 1358-1365
Opana® ER tablets (oxymorphone)

The TIMERx® drug delivery platform is based on a hydrophilic matrix, combining a mixture of xanthan and locust bean gums, in the presence of dextrose. Drug release is controlled by the rate of water penetration from the gastrointestinal tract into the TIMERx® gum matrix. It expands to form a gel, subsequently releasing the API.

It is likely that retention of this monolithic matrix in the stomach was potentially prolonged due to alcohol (40% ingested), leading to increased swelling of the matrix with subsequent release of API, maybe accompanied by increased premature damages of the swollen matrix due to increased exposure to gastric motility. No AUC change.

1. Matrix tablet swells in gastric medium.

2. Swollen tablet is prevented from being emptied during early propulsion phases, because it is too big to pass, instead it is subject to increased cumulated retropulsion forces.

In addition, Morphine was found to increase splanchnic blood flow as well by about 20% (Leaman et al., Br Heart J. 1978).40:569-571). Therefore, in vivo failure of Opana® may have been caused by several synergistic factors.

Source: David S. Craig, Pharmacy and Therapeutics, 2010 June; 35(6): 324-329, 357
Physiological aspects – gastric clearing of alcohol

After 3 min the alcohol concentration is down to 50% from the original one.

Ethanol is completely cleared from the stomach after 30-60 minutes.

Implication: Testing in vitro resistance against hydro-alcoholic gastric medium up to 2 hours is not reflecting in vivo conditions.

Key message
Alcohol is quickly absorbed in the GIT ➔ 2 h testing is of limited utility

Fig. 2. Gastric absorption and emptying when ethanol (0.15 g/kg) was administered with 380 ml of water. Shown are cumulative rates at which $^{99m}$Tc-diethylenetriamine pentaacetic acid ($^{99m}$Tc-DTPA) (△) and ethanol (●) were emptied into the duodenum, ethanol was absorbed from the stomach (○), and ethanol disappeared from the stomach, i.e., the sum of gastric emptying and gastric absorption (▲). Data are means ± SE.

1. Increased salivary flow and gastric acid secretion upon alcohol intake dilute effective alcohol concentrations in the stomach

2. High alcohol doses delay gastric emptying
   Implication: potential extension of gastric retention time of (large) monolithic modified release forms, thus increasing their exposure to gastric grinding forces.

3. Alcohol induces mucosal lesions and thus may indirectly be increasing drug absorption
   Implication: potential increase of speed and extent of drug absorption / bioavailability.

Key message
The physiology of the stomach is highly influenced by alcoholic intake.
Physiological aspects – modified release solid oral forms

Other factors affecting the in-vivo performance of modified release drug formulations:

- Solubility of formulation (= API + excipients)
- Permeability of API
- Surface area of dosage form
- Induction / inhibition of enzymatic activities by food
- Gender and age

Key message

API properties and other factors are important ADD players
Content of the presentation

• IPEC ADD Working Group members ✓
• Basics and facts about ADD and some drug cases ✓
• EU- and US-Guidance
• IPEC ADD WG Position Paper (in preparation)
• Technological aspects
### Important EU-Guidelines + documents

<table>
<thead>
<tr>
<th>Name</th>
<th>Reference</th>
<th>Date</th>
<th>Relevance/notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms</td>
<td>EMA/CHMP/EWP/280/96 Rev1</td>
<td>2013-02-21</td>
<td>Complete Chapter on dose dumping (5.1.4.3) includes subchapter “Effects of alcohol” plus 6.9 <em>Effects of alcohol for generic oral formulations</em>. Reformulation is the recommendation.</td>
</tr>
<tr>
<td>Assessment Report for Authorized modified-release oral medicinal products of the WHO level III scale for the management of pain (intense sustained pain resistant to previous medications) (containing morphine, oxycodone, and hydromorphone)</td>
<td>EMA/355008/2011</td>
<td>2011-04-20</td>
<td>CHMP- Referral procedure for opioids. PMA-TC coating named. Risk is real for patients consuming alcohol. Reformulation is recommended.</td>
</tr>
<tr>
<td>Quality if medicines questions and answers: Part 2. Specific types of product – Need for in vitro dissolution studies with alcohol for modified release oral products including opioid drug products</td>
<td><a href="http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000072.jsp#section10">http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000072.jsp#section10</a></td>
<td>2009-04</td>
<td>Alcohol compatibility to be tested for all oral prolonged- (and delayed- and modified-) release products – not limited to opioids. In-vitro studies might be required. Alcohol testing up to 20%.</td>
</tr>
</tbody>
</table>

**Key message**

EMA provides main instruction for ADD within a superior Guideline
EU Regulatory aspects – Assessment process

EMA-Guideline EMA/CHMP/EWP/280/96 – Guideline on pharmacokinetic and clinical evaluation of modified release dosage forms

Definition of general principles for designing, conducting and evaluating for innovative and generic Modified Release Applications

Risk assess drug release mechanism and solubility of the API and excipients in alcohol

Innovator

- Low risk
- Perform in vitro dissolution testing
- Continue formulation as normal

- High risk
- Reformulate
- Perform in vitro dissolution testing
- Does dose dumping occur at low & high alcohol concentration/short period of time OR at low alcohol concentration/long period of time
- No
- Reformulate
- Yes
- Reformulate

Generics

- Perform in vitro release test in alcohol
- If dissolution results similar to the innovator: Applicant should justify lack of clinical relevance
- Yes
- Reformulate
- No
- Perform in vivo study
- Reformulate

Key message
EU: For ADD are detailed instructions available
<table>
<thead>
<tr>
<th>Name</th>
<th>Date</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANDA Submissions — Refuse-to-Receive Standards Guidance for Industry</td>
<td>Sep. 2014</td>
<td>ANDA focused. Page 17: Inadequate dissolution data are reasons to refuse-to-receive an ANDA. Page 18: Finally, other suggested types of supplemental dissolution studies include: Alcohol dose-dumping</td>
</tr>
<tr>
<td>Draft Guidance on Metoprolol Succinate (as example)</td>
<td>Recommended Jan 2008; Revised Apr 2008, Feb 2014</td>
<td>Due to concerns of dose dumping from this drug product when taken with alcohol, FDA requests to conduct additional dissolution testing using various concentrations of ethanol (0%/5%/20%/40%) in 0.1 N HCl, apparatus 2 (paddle) @ 50 rpm</td>
</tr>
</tbody>
</table>
US Regulatory aspects – Assessment process

Does test formulation release independent from ethanol concentration in media?

Yes

- Test formulation is rugged
- No additional testing needed

No

1. Compare test and reference drug release rates in various ethanol concentrations
2. Are test formulation drug release rates comparable to or lower than those of reference?

Yes

No

Options:
- OGD requests clinical result
- Applicant conducts in vivo study
- Applicant reformulates

Key message
US: For ADD are instructions available
## Regulatory aspects – US vs. EU requirements

<table>
<thead>
<tr>
<th>Topic</th>
<th>US</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methodological requirements</td>
<td><strong>Medium</strong>: 0.1 N HCl</td>
<td><strong>Medium</strong>: same as that proposed for routine testing</td>
</tr>
<tr>
<td></td>
<td>Alcohol: 0%, 5%, 20% and 40%</td>
<td>Alcohol: 5%, 10% and 20%</td>
</tr>
<tr>
<td></td>
<td><strong>Time</strong>: every 15 minutes till 2 h</td>
<td><strong>Time</strong>: not defined</td>
</tr>
<tr>
<td>Products to be tested</td>
<td>At least all (generic) versions for modified-release opioid drug products.</td>
<td>All oral modified release applications.</td>
</tr>
<tr>
<td></td>
<td>More preferably for (all) modified-release drug products with risk of alcohol-induced dose dumping.</td>
<td><strong>Key message Recommendations in EU and the US are not fully harmonized</strong></td>
</tr>
<tr>
<td>Acceptance criterion</td>
<td>1. Generics should show rugged performance in alcohol. *</td>
<td>1. If in-vitro alcohol incompatibility of the drug product is demonstrated, product should be reformulated.</td>
</tr>
<tr>
<td></td>
<td>2. If generic releases more rapidly in alcohol, rate should be comparable to that of reference product. *</td>
<td>2. If alcohol effect cannot be avoided and is present also in the reference product, applicant should justify / demonstrate that it lacks clinical relevance.</td>
</tr>
</tbody>
</table>

* Source: Hanan Kakish, Medical Research Scientist FDA, 2009, Bioequivalence Data Submission Requirements
Ethanol is diluted in gastric medium.

Implication: Setting resistance against (240ml) 40% ethanol as regulatory worst case in vivo / in vitro test condition requirement is physiologically not relevant.

**Key message**
40% ethanol concentration can hardly be reached in the stomach

In other words:

In order to reach 40% ethanol concentration in the stomach, assuming the same volumes as above, the ethanol concentration in the drink would have to be 240 ml of a beverage with 56% alcohol concentration.

[* Ethanol concentration and volume according to Lennernas, Molec. Pharma. 6(5), 1429-1440, 2009]
Content of the presentation

• IPEC ADD Working Group members ✓
• Basics and facts about ADD and discuss some drug cases ✓
• EU- and US-Guidance ✓
• IPEC ADD WG Position Paper (in preparation)
• Technological aspects
Purpose of the IPEC ADD Working Group´s Position Paper:

- Foster discussion about ADD issue
- Address lack of harmonisation between e.g. EU and US
- Address issues of guidance, e.g. 40% testing
- Focus on therapeutically useful formulations
- Provide practical hints to avoid ADD issues during development

Scope
This IPEC position paper comments on the currently available EMA and FDA regulations on ADD and aims at practical improvements. In addition, the position paper provides IPEC´s insights to ADD best practices needed during drug product development.

Please note that this paper does not refer to tamper resistant (= abuse deterrent) formulations and is not intended to touch deterrence of fraudulent behavior. Consequently, it does not focus on formulations with abuse potential (e.g. opioids), but on modified release formulations, which require an appropriate, robust formulation in order to assure patient safety (e.g. due to a small therapeutic window).
Critical aspects of formulation development

Lack of clarity might limit formulation flexibility:

• Misleading to use more expensive manufacturing technology with higher prices for the users.

• Inconsistent and incomplete guidelines mean that some therapeutically useful formulations could be excluded simply because they show some solubility in alcohol.

• This will lead to a restriction in the types of dosage forms that are available or considered suitable and could drive up the cost of medicines.

• This incomplete picture could also impact the likelihood that newer excipients or more novel approaches are evaluated consistently as there is no set methodology set out in the EU (but there is in the US), which is perhaps too stringent and not based on all the evidence.

• All of these factors cause hurdles for formulators.
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- IPEC ADD Working Group members
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Problem statement:

• The *Assessment Report for Authorised modified-release oral medicinal products of the WHO level III scale for the management of pain (London, 20 April 2011 Doc.Ref: EMA/355008/2011)* implies that the risk of ADD is limited to polymethacrylate formulations.

**BUT:**

• These suspect formulations contained triethylcitrate, which is highly soluble in ethanol
• Other enteric polymers can also be inherently vulnerable to ethanol, e.g. HPMC acetate succinate, HPMC phthalate
Vulnerability of standard delayed release coatings (1/2)

Typical enteric coatings are not resistant to ethanol *in vitro*

**HPMC acetate succinate**

**Methacrylic Acid Copolymer Dispersion NF (e.g. EUDRAGIT® L 30 D-55)**

[Cymbalta® (Duloxetine) 60 mg DR capsule]

[Caffeine pellets]

*Test conditions: 2 hours acidic state followed by buffer pH 6.8*

Key message
ADD is an issue pertaining to many excipients
Vulnerability of standard delayed release coatings (2/2)

Commercial OTC Omeprazole DR pellet capsules formulated with HPMC phthalate

Due to coating vulnerability, complete drug degradation occurred in alcoholic media in vitro.

Key message
Missing ADD resistance can even lead to extensive API degradations

Omeprazole standard at retention time of 3.983

After 2 hrs in 40% alcoholic HCl, no omeprazole peak is observed at retention time 3.9
Alcohol Resistant Formulation Solutions – Example (1/2)

Methacrylic Acid Copolymer Dispersion NF + Alginate Bilayer Technology:

- Top coat of Methacrylic Acid Copolymer Dispersion NF or similar *
- Sodium alginate layer
- Core pellets (prepared by drug layering or extrusion spheronization)

3 step process:
- Prepare coating suspensions
- Apply sodium alginate layer and
- Apply Methacrylic Acid Copolymer Dispersion layer

No additional equipment needed!

Key message
Apparently ADD critical excipients can still be ADD resistant by using the right technology

* e.g. EUDRAGIT® L 30 D-55 or EUDRAGIT® NE 30 D
Alcohol Resistant Formulation Solutions – Example (1/2)

Alcohol resistant enteric release formulation obtained using EAMMCD* + sodium alginate (metoprolol succinate pellets)

EAMMCD = Ethyl acrylate and Methyl Methacrylate Copolymer Dispersion – NF, e.g. EUDRAGIT® NE 30 D

Key message
The right technology supports here 40% ethanol conc. for pellets
Alcohol Resistant Formulation Solutions – Example (2/2)

Matrix formulations can be resistant to ADD

Key message
The right technology supports here 40% ethanol conc. for matrix tablets

WELLBUTRIN® SR (Bupropion HCl)
150 mg matrix tablets
SR polymer: HMPC

Bupropion HCl matrix tablets
SR polymer: EUDRAGIT® NM 30 D
Excipients maybe seen as critical in the past, can still be a solution option when used with the right technology.

In this sense, poly(meth)acrylate polymers are not part of the problem, but can be part of the solution!

**Key message**
Excipients seen in the past as inappropriate can still be an option for ADD resistant formulations
Critical parameters to be considered for alcohol resistant formulations

Key message
For ADD resistance, consider all pertinent aspects

- **Dosage form properties**
  (e.g. dimension, size, release-controlling mechanism)

- **GIT physiology**
  (e.g. gastric motility, retention times)

- **Solubility in hydro-alcoholic medium**
  (API, release-controlling polymer, excipients)
ADD: key take aways

• ADD is a multi-factorial event
• ADD cannot simply reduced to a non-conformance of the constituent excipients in alcoholic solution
• Knowledge about all pertinent factors can facilitate the pharmaceutical development of ADD-resistant drugs
• Regulatory Guidance and harmonisation still needs some improvement to better support the development of drugs
• The Excipient Industry is able to provide technological solutions
Thanks for your attention
Any questions?