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Questions and Answers on Ethanol in the context of the revision of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00)

Draft

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1. Background

Following the European Commission decision to revise the Annex of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00)[1], a multidisciplinary group of experts involving SWP (lead), QWP, PDCO, PRAC (ex PVWP), CMD(h), VWP, BWP and BPWP was created in 2011.

The objective of this group is to update the labelling of selected excipients listed in the Annex of the above mentioned EC guideline, as well as to add new excipients to the list, based on a review of their safety. The main safety aspects to be addressed were summarised in a concept paper published in March 2012[2].

Q&A documents on excipients will be progressively released for public consultation. They will include proposals for new or updated information for the labelling and package leaflet. Once a Q&A is finalised, the corresponding background report supporting its review will be also published.

When the Q&As of all the selected excipients have been finalised, they will be grouped in a single Q&A document. This information will be integrated in the updated Annex of the new revised EC guideline.

2. What is ethanol and why is it used as an excipient?

Ethanol is used as a solvent to improve drug solubility.

Ethanol can be used as an extraction solvent in herbal medicinal products (liquid extracts and tinctures). In this case, the use of ethanol is necessary for extraction of some constituents that are important for efficacy. Ethanol is also used in the production of mother tinctures for homoeopathic preparations in suitable concentration and in many liquid homeopathic medicinal products.

Ethanol has bacteriostatic, bactericidal, fungicidal and virucidal activity. In addition, ethanol also has anhidrotic, rubefacient, and astringent and haemostatic properties [1].

Of note, Ethanol is present as an endogenous substance in the blood of man, probably produced in the intestinal tract, at an average level of 1.5 mg/L [2]. According to Jones et al., endogenous ethanol reaches low concentrations of 0.39 ± 0.45 µg/mL (0.039 mg/dL) in the blood of sober people [3].

[1] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003412.pdf
[2] Concept paper on the need for revision of the 'Guideline on excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00) EMA/CHMP/SWP/888239/2011 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/03/WC500123804.pdf

3. Which medicinal products contain ethanol?

Ethanol can be found as a solvent in numerous oral liquid formulations and OTC medicines such as cough and cold medicines, iron supplements as well as homeopathic preparations with the aim to improve drug solubility. In particular, herbal medicinal products may contain significant levels of ethanol. In the EU, medicines containing ethanol include ranitidine, furosemide, mannitol, phenobarbital, trimethoprim, co-trimoxazole and paracetamol [4].

Ethanol is also an ingredient of several topical preparations used for skin disorders.

Ethanol is also employed in solutions as an antimicrobial preservative.

Of note, preparations containing 95 % ethanol are also used percutaneously as a sclerosing agent (e.g. for the treatment of some vascular disorders).

4. What are the safety concerns?

Ethanol is a central nervous system (CNS) depressant. Symptoms of mild to moderate ethanol intoxication in adults can include euphoria, ataxia, sedation, aggressive behaviour, and nausea and vomiting [5]. At high doses it can also cause respiratory depression or failure and cardiovascular toxicities such as atrial tachycardia, atrial fibrillation, arrhythmias, AV block, hypotension, congestive heart failure, and severe myocardial depression.

Alcohol metabolism varies with age but uncertainties exist about both metabolic maturation and adverse effects of low and higher amounts of ethanol in short and long term use since most literature relates to acute poisoning.

In children, signs of ethanol intoxication are hypoglycaemia, hypothermia and coma [6, 7].

Other toxicities seen after acute toxic exposure include seizures, often due to hypoglycemia in children, hypotonia, hyporeflexia, gastritis, gastrointestinal bleeding, acute hepatitis, acute pancreatitis, rhabdomyolysis, hypokalaemia, and lactic acidosis.

In the newborn, cutaneous absorption of ethanol is significant (especially under occlusion) due to the newborn's immature skin and this may lead to significant local reactions and systemic toxicity [8].

In the scientific literature, ethanol is known as a reproductive and developmental toxicant. Ethanol may cause genetic defects, which may be mediated by its metabolite, acetaldehyde. Furthermore, drinking alcoholic beverages are a known human carcinogen listed by the International Agency for Research on Cancer (IARC) [9] and the National Toxicology Program (NTP) [10].

It is important to note that the effect of long term exposure to even low levels of ethanol in medicines on the health and development of children has not been evaluated [11]. Studies and observations on FAS (foetal alcohol syndrome) and FAE (foetal alcohol effects) in children give direct evidence of the grave deleterious effects of chronic ethanol exposure, for example, on neurological and cognitive developmental processes [12, 13].

Moreover, ethanol use in adult medicines is discouraged for a number of other reasons including interactions with other medicines, diseases, effect on driving performances, issues with addiction, pregnancy and breast feeding.

5. What are the reasons for updating the information in the package leaflet?

The main reason for updating the information in the package leaflet is to adjust the thresholds in relation to the different age groups. Currently, no European guidelines proposing ethanol labelling thresholds in paediatric population are available. Indeed, the information available on ethanol acceptability for paediatric age groups is sparse and distributed over various sources.

According to a review by the French Medicines Agency [14], ethanol should not be included in medicinal products intended for children unless necessary. If used in children, the amount of ethanol should not produce blood alcohol (ethanol) concentration (BAC) greater than 0.125 g/L. In addition, the total volume of ethanol in the medicinal product should be adjusted so that a potentially lethal dose (3 g/kg) cannot be reached in the event of accidental poisoning in children involving the entire package.

The FDA also recommends not including ethanol in medicinal products intended for use in children. But if necessary, the amount of ethanol should not produce a BAC greater than 0.25 g/L and/or OTC liquid preparations should not contain more than 5% ethanol [15, 16].

The WHO proposes to limit the ethanol amount in OTC products to less than 0.5% for children less than 6 years old, less than 5% for children 6-12 years old and less than 10% for children over 12 years. However, these limits do not consider the actual dose given [17].

The current EC 'Guideline on excipients in the label and package leaflet' proposes:

99 ***Current information in the package leaflet***

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Ethanol	Oral and Parenteral	Less than 100 mg per dose	This medicinal product contains small amounts of ethanol (alcohol), less than 100mg per <dose>.	This statement is to provide reassurance to parents and children concerning the low levels of alcohol in the product.
		100 mg – 3 g per dose	This medicinal product contains ... vol % ethanol (alcohol), i.e. up to ... mg per dose, equivalent to ... mL beer, ... mL wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.	The package leaflet should give the equivalent volume of beer and wine, nominally calculated assuming 5 % vol and 12% vol ethanol respectively. Separate warning statements may be needed in different parts of the PL.
		3 g per dose	This medicinal product contains ... vol % ethanol (alcohol), i.e. up to ... mg per dose, equivalent to ... mL beer, ... mL wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease or epilepsy. The amount of alcohol in this medicinal product may alter the effects of other medicines. The amount of alcohol in this medicinal product may impair your ability to drive or use machines.	

6. Proposal for an updated information in the package leaflet

General aspects for pharmaceutical industry and healthcare professionals

[18-24]

- Ethanol should not be included in medicinal products, unless justified. The use of ethanol could be acceptable if the benefits outweigh the risks, taking into account of frequency and duration of treatment (acute and chronic), seriousness of condition treated, availability of suitable alternative treatments, ethanol exposure (BAC) and age.
- As part of the justification for the use of ethanol there should be a discussion of why other excipients cannot fulfil the functions of ethanol in the formulation.
- Where ethanol use is necessary, measures to minimise ethanol exposure should be discussed.
- Theoretical blood alcohol concentration (BAC) rise from a single dose should be estimated using a standard formula (see 'Theoretical calculation of BAC: limitations and assumptions' in Annex).
- There is little information on the health and development effects in children after long term exposure to even low levels of ethanol in medicines. Repeated short term use could induce similar effects to a chronic use. However, it seems reasonable to accept amounts which raise BAC by no greater than the endogenous BAC (1.5 mg/L). Where exposure to ethanol from a medicine is significant, consideration should be given to restricting supply to patient under the supervision of a physician (prescription-only), in order to control repeated short term use.
- The total volume of ethanol in any medicinal product should be adapted in such a way that a potentially lethal dose of 1.8 g/kg (corresponds to a predicted rise in BAC of 3 g/L) cannot be reached in the event of accidental poisoning in children involving the entire package.

122

Name	Route of Administration	Threshold*	Information for the Package Leaflet	Comments (for health care professionals)
Ethanol	Oral and Parenteral	1 to less than 6 mg/kg/day	This medicine contains very small amount of alcohol as an ingredient necessary for the medicine to work properly.	This statement is to provide reassurance to parents and children concerning the low levels of alcohol in the medicine.
			The amount of alcohol in each <volume/unit> is xx mg.	The amount of alcohol in this range of doses is not be expected to produce a Blood Alcohol Concentration (BAC**) significantly greater than the endogenous BAC (1.5 mg/L).
			When you take your daily dose, the small amount of alcohol contained in this medicine will not have any effects.	Minute amounts of ethanol in the composition of other excipients such as flavours or colouring agents would not produce any detectable increase in BAC**.
		6 mg/Kg/day to less than 75 mg/kg/day	The amount of alcohol in each <volume/unit> is xx mg.	This statement provides a guide to the amount of alcohol consumed in understandable terms for adults and would pick up off-label use.
			The recommended dose(s) of this medicine <dose/dose range> will increase the concentration of alcohol in your body by about xx…mg/L. This is similar to an adult drinking X…mL of beer or Y…mL of wine***.	Evaluate the BAC** daily during the whole period of treatment.
			Talk to your doctor or pharmacist before giving this medicine to your child if (s)he is less than 6 years old.	The BAC** levels should not exceed 1 mg/100mL (or 1 mg/dL or 0.01 g/L or a dose of 6 mg/kg) in children less than 6 years old (equivalent statements should be considered in section 4.4 of the SmPC).

Name	Route of Administration	Threshold*	Information for the Package Leaflet	Comments (for health care professionals)
				Available acute and chronic toxicity data of ethanol in the paediatric population is limited.
			Effects of alcohol in children less than 6 years old may include drowsiness, behavioural changes, and impaired ability to concentrate and participate in school activities. Carers (e.g. school teachers) should take extra care when children undertake activities such as bike riding or other sports.	In infants (< 2 years old) and children 2-5 years old, ethanol use must be specifically justified taking into account the enzyme immaturity, potential accumulation of ethanol and lack of information on potential toxicity. The benefit of using ethanol must outweigh the potential risks.
		75 mg/kg/day and above	The amount of alcohol in each <volume/unit> is xx mg. The recommended dose(s) of this medicine <daily dose> will increase the concentration of alcohol in your body by about XX-YY mg/L. This is similar to an adult drinking X…mL of beer or Y…mL of wine***.	Evaluate the BAC** daily during the whole period of treatment. Provided BAC** levels do not exceed 12.5 mg/100mL (75 mg/kg) in patients 6 years old and above, the amount of ethanol is unlikely to produce any effects.
			Other medicines may also contain alcohol and alcohol may be consumed in food and drinks. The combined effects may lead to increased blood alcohol levels and increase the side effects of	

Name	Route of Administration	Threshold*	Information for the Package Leaflet	Comments (for health care professionals)
			alcohol.	
			Because of its amount of alcohol, this medicine should not be given in children younger than 6 years old.	
			If your child (6-11 years old) is taking this medicine, the content of alcohol could affect his/her performance, for example at school. The amount of alcohol in this medicine may affect your ability to drive or use machines and may affect your judgement and reaction times.	When possible, avoid a chronic use (more than 2 weeks). When possible, use discontinuously, and not more frequently than 4 hourly (in case of infusion).
			Talk to your doctor or pharmacist if you are pregnant or breast-feeding, if you have liver problems, if you suffer from epilepsy or if you suffer from alcoholism.	Particular precautions should be taken into account in pregnant or breast-feeding women and high-risk groups such as patients with liver disease or epilepsy (equivalent statements should be considered in sections 4.6 and 4.4 respectively of the SmPC).
			The amount of alcohol in this medicine may alter the effects of other medicines.	The interactions of ethanol should be stated and documented in the SmPC (section 4.5).
	Cutaneous	zero	This medicine contains alcohol as an ingredient necessary for the medicine to work properly.	This statement is to provide reassurance to patients concerning the presence of alcohol in the medicine.

Name	Route of Administration	Threshold*	Information for the Package Leaflet	Comments (for health care professionals)
			The amount of alcohol in each <volume/unit> is xx mg.	
			May be irritant to the skin.	
			Cutaneous and general effects of alcohol are enhanced in neonates and infants (less than 2 years old) compared to older children and adults due to a higher absorption through the skin. Speak to your doctor or pharmacist before giving this medicine to your baby.	Alcohol is an agent that poses a risk of percutaneous toxicity, particularly in the neonates (pre-term and term newborn infants). Exposure of immature skin (especially under occlusion) may lead to significant local reactions and systemic toxicity.

Notes:
* This threshold will trigger the inclusion in the package leaflet of the corresponding safety statements (provided in the column “information for the Package Leaflet”).
** see Annex.
*** The package leaflet should give the equivalent volume of beer and wine, nominally calculated assuming 5% vol and 12% vol ethanol respectively.

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Annex

Theoretical calculation of BAC: limitations and assumptions

It is important to note the limitation of blood ethanol (alcohol) estimates from mathematical modelling. The formula presented below makes many assumptions but may be used in the approximate estimation of blood alcohol concentration (BAC) rise. For example the equation below assumes complete and instantaneous absorption of ethanol orally ingested ethanol.

$$\text{BAC (g/L)} \approx \text{Blood ethanol (mg/100mL or mg/dL)} = \frac{\text{Ingested Ethanol in a single dose (g)}}{\text{Volume of distribution (L/kg) x Weight (kg)}}$$

BAC = Blood Alcohol Concentration (g/L) is a common way of expressing ethanol (alcohol) concentrations that avoids the use of decimal points and should therefore be encouraged. Alternatively g/L can be used. As there are many ways of expressing BAC it is sometimes advisable to express the amount in both mg/100mL and g/L to achieve clarity.

An example displaying the predicted rise in BAC assuming volume of distribution is presented below:

Exposure to ethanol in mg/kg and predicted rise in BAC

Ethanol intake in g/kg and mg/kg	**Predicted rise in BAC** **Assuming Volume of distribution** **(Vd) 0.6L/kg**		**Recommendations**
0.006 g/kg 6 mg/kg	1mg/100mL	0.01 g/L	Suggested limit in medicines for patients 2-6 years old
0.075 g/kg 75 mg/kg	12.5mg/100mL	0.125 g/L	Suggested limit in medicines patients 6 years old and over
0.3 g/kg 300 mg/kg	50mg/100mL	0.5 g/L	Limit for driving in many EU countries
0.6 g/kg 600 mg/kg	100mg/100mL	1 g/L	With BAC of 1 g/L increases in mortality has been seen in children
1.8 g/kg 1,800 mg/kg	300mg/100mL	3 g/L	Life-threatening BAC usually reported to be approximately 3 g/L in adults.

Ingested Ethanol (g) may be calculated from the concentration of ethanol (alcohol) and the volume of a single dose. The specific gravity of ethanol (alcohol) is 0.789 i.e. 1 mL weighs 0.789 g (0.8 may be used as an approximation). In calculating ingested ethanol (alcohol) it may be necessary to first convert the percentage v/v into percentage w/v. For example an ethanol (alcohol) concentration of 12.5%v/v corresponds to 10%w/v (12.5mL /100mL x 0.8= 10g/100mL).

A 5-mL spoon would contain 0.5 g ethanol (alcohol) (10g/100mL, is equivalent to 1g/10mL or 0.5g/5mL).

Volume of distribution (L/kg) should be assumed to be 0.6. This is a simplification which may serve to overestimate the BAC in children as precautionary measure.

Alcohol is contained in the water compartment of the body. The volume of distribution (Vd) of ethanol is dependent on the water compartment of the body. Neonates and children may have a larger water compartment than adults and the Vd might be higher (0.7-0.9).

Equations for estimating blood ethanol rises are based on the Widmark equation. Widmark recognised from experimental work that the Vd varied between individuals and adult males and females that have different Vds. Widmark assigned a Vd for males as 0.68 ±0.085 and for females as 0.55 ±0.055. The difference is thought to be related to the water compartment of the body and is thought to explain differences in the ethanol toleration by the genders.

In conclusion, it should be recognised that the above equation provides an estimate of blood ethanol (alcohol) rise and that many assumptions are made. Values obtained will be limited with regard to accuracy.