105年度產官學溝通會議-第3次會議

醫藥品查驗中心
Center for Drug Evaluation, Taiwan

105年05月09日 (星期一) 下午3:00-5:00

會議議程

- 報告事項
  - 近期法規資訊
  - 賦形劑相關之警語內容介紹及建議
- 綜合討論
- 臨時動議

近期法規資訊 (公告期間 105/03/01~105/04/30)

醫藥品查驗中心
Center for Drug Evaluation, Taiwan

專案管理組 張芳瑜 報告

近期法規資訊

發文日期/文號	內容
105年03月08日部授食字第1051402838號	修正105年3月1日署授食字第1051402455號公告[西藥非處方藥仿單外盒格式及規範]及實施方法之附件二
105年03月25日部授食字第1041409903D號	含testosterone類(包括methyltestosterone)成分藥品中文仿單修訂相關事宜
105年04月18日部授食字第1051403279B號	含ciprofloxacin、levofloxacin、moxifloxacin成分之口服及注射劑型藥品中文仿單修訂相關事宜
105年03月23日部授食字第1051402297號	預告「適用罕見疾病防治及藥物法之藥物品項」修正草案
105年04月11日部授食字第1051402564號	預告訂定「必要藥品短缺通報登錄及專案核准製造輸入辦法」草案
105年03月14日FDA藥字第105140051B號	105年度藥品不良品（含療效不等）及化粧品不良事件（包括不良品及不良反應）通報相關業務之委託機構
105年03月11日部授食字第1041408733號	修正「藥品安定性試驗基準」條文
105年04月06日部授食字第1051400499號	修正「藥品查驗登記審查準則」部分條文

修正105年3月1日署授食字第1051402455號公告[西藥非處方藥仿單外盒格式及規範]及實施方法之附件二

《105年03月08日部授食字第1051402838號》

一. 目的：

為強化非處方藥使用安全，鼓勵民眾在使用非處方藥前先閱讀用藥資訊，爰參考先進國家規定，考量民眾閱讀習慣及視障、銀髮等之族群需求，制訂非處方藥仿單外盒格式及相關規範，詳閱本規範之附件。

二. 適用範圍：

西藥藥品許可證分類為非處方藥者包括：**「醫師藥師藥劑生指示藥品」、「成藥」或「乙類成藥」**之外盒及仿單。

修正105年3月1日署授食字第1051402455號公告[西藥非處方藥仿單外盒格式及規範]及實施方法之附件二(續)

《105年03月08日部授食字第1051402838號》

三. 標籤仿單外盒核定、變更作業，及市售品處理原則如下：

1) 自**公告日起，新申請之非處方藥查驗登記**，或標籤仿單外盒變更申請案，業者應依上開規定，制訂其標籤仿單外盒，供本部食藥署審查。

2) 市售非處方藥應分批辦理完成標籤仿單外盒變更作業，時程如下：

- 已核准於電視及電影刊播廣告之非處方藥許可證持有者，應於**105年12月31日前**，取得標籤仿單外盒變更核備函。
- 自**106年1月1日起**，新申請於電視及電影刊播廣告之非處方藥許可證持有者，應於申請廣告前，取得標籤仿單外盒（變更）核備函。
- 市售非處方藥應於**108年12月31日前**，分年分階段完成標籤仿單外盒變更作業，其時程本部食藥署將另行公告。

3) 已至本部食藥署辦理切結不生產或輸入之藥品，暫無須依公告辦理，惟產品恢復製造或輸入時應一併完成變更作業。

4) 標仿單外盒變更核備前製造（或輸入）之產品，無須回收驗章。

含testosterone類(包括methyltestosterone)成分藥品中文仿單修訂相關事宜

《105年03月25日部授食字第1041409903D號》

一. 含testosterone類成分藥品，經本部彙整國、內外相關資料及臨床相關文獻報告進行整體性評估，其中文仿單應依下列內容修訂：

- **「適應症」**：

  與「男性更年期障礙」相關之適應症(如：男性荷爾蒙不足所引起之症狀、性腺激素缺乏症等)，**統一修訂為：「經臨床徵象及實驗室檢驗確認因睪固酮缺乏男性生殖腺功能不足症(hypogonadism)的替代治療」。**

- **「警語及注意事項」加刊**：

  1. 上市後研究發現睪固酮補充治療可能會增加嚴重心血管事件之風險，如心肌梗塞、中風或心臟衰竭，或增加靜脈栓塞事件之風險，如深層靜脈血栓形成和肺栓塞，故開立處方前後應謹慎評估患者是否具有任何心血管相關之風險因子或病史。
  2. 由於長期安全性數據資料不足，當接受睪固酮補充治療期間，應同時密切監測可能發生的嚴重心血管事件。

含testosterone類(包括methyltestosterone)成分藥品中文仿單修訂相關事宜(續)

《105年03月25日部授食字第1041409903D號》

二. 持有旨揭成分藥品許可證者，應依本公告事項修訂仿單，並於**105年06月30日前**向本部食品藥物管理署依藥品查驗登記審查準則辦理**中文仿單變更**事宜**(須以紙本送件，於期限內毋需繳交規費，逾期則須繳交規費)**。逾期未辦理者，依違反藥事法第75條相關規定處辦。

含ciprofloxacin、levofloxacin、moxifloxacin成分之口服及注射劑型藥品中文仿單修訂相關事宜

《105年04月18日部授食字第1051403279B號》

一. 有關兒童或生長期青少年使用含ciprofloxacin、levofloxacin、moxifloxacin成分之口服及注射劑型藥品之風險，經本部彙整國內外相關資料重新評估，結果認為其風險尚不明確，未達列為使用禁忌之程度，但應於「警語與注意事項」加刊相關內容，其中文仿單修訂內容如附件。

二. 持有旨揭成分藥品許可證者，應依本公告事項修訂仿單，並於**105年10月1日前**向本部食品藥物管理署依藥品查驗登記審查準則辦理**中文仿單變更**事宜**(須以紙本送件，於期限內毋需繳交規費，逾期則須繳交規費)**。逾期未辦理者，依違反藥事法第75條相關規定處辦。

含ciprofloxacin、levofloxacin、moxifloxacin成分之口服及注射劑型藥品中文仿單修訂相關事宜(續)

《105年04月18日部授食字第1051403279B號》

1) 含 ciprofloxacin 成分

- **「禁忌」：**

  刪除「對成長中之小孩、少年的安全性尚未確定，且動物實驗所顯示對未發育完全之關節軟骨造成傷害之可能尚無法完全排除，所以禁止投與」。

- **「警語及注意事項」：**

  加刊「Ciprofloxacin 已被指出會導致發育未完全動物其承受重量的關節(weight-bearing joint)產生關節病變。從使用ciprofloxacin 的病患(年齡小於 18 歲；大多數是囊腫性纖維化病患)其可取得的安全性資料分析，並無任何證據顯示與藥物有關的軟骨或關節傷害產生。」

含ciprofloxacin、levofloxacin、moxifloxacin成分之口服及注射劑型藥品中文仿單修訂相關事宜(續)

《105年04月18日部授食字第1051403279B號》

2) 含 levofloxacin 成分

- **「禁忌」：**

  刪除「兒童或生長期青少年」。

- **「警語及注意事項」：**

  加刊「觀察到使用 levofloxacin 兒童患者，比起未使用者更易發生肌肉骨骼疾病（關節痛，關節炎，肌腱和步態異常）之不良反應。動物實驗中在未成年的大鼠和幼犬，給予口服和靜脈注射之levofloxacin 皆會導致骨軟骨病(osteochondrosis) 增加，且於幼犬組織病理學檢查顯示，其承受重量的關節(weight-bearing joint)軟骨持續病變。其他氟喹諾酮類藥物亦會造成未成年動物承受重量的關節軟骨病變及關節病等不良反應。」

含ciprofloxacin、levofloxacin、moxifloxacin成分之口服及注射劑型藥品中文仿單修訂相關事宜(續)

《105年04月18日部授食字第1051403279B號》

3) 含 moxifloxacin 成分

- **「禁忌」：**

  刪除「年齡小於 18 歲的病人」。

- **「警語及注意事項」：**

  加刊「Moxifloxacin 於兒童和小於 18 歲青少年的安全性和藥效尚未確定。動物實驗中，Moxifloxacin 會造成未成年動物關節病變。其他氟喹諾酮類藥物亦會造成未成年動物承受重量的關節(weight-bearing joint)軟骨病變及關節病等不良反應。」

預告「適用罕見疾病防治及藥物法之藥物品項」修正草案

《105年03月23日部授食字第1051402297號》

- 修正依據：

  罕見疾病防治及藥物法第三條第二項及第二十三條。

- 修正內容：

  新增認定「**Taliglucerase alfa**」（**Injection；200U/vial**）為適用罕見疾病防治及藥物法之藥物，**適應症為「第一型高雪氏症」**。

預告訂定「必要藥品短缺通報登錄及專案核准製造輸入辦法」草案

《105年04月11日部授食字第1051402564號》

■ 全文共十一條，其要點如下：

一. 訂定依據。（草案第一條）

二. 通報方式與內容之規定。（草案第二條）

三. 通報內容之登錄、揭露及專案核准製造、輸入或徵求之規定。（草案第三條）

四. 專案核准製造、輸入之申請條件、審查程序及核准基準。（草案第四條至第六條）

五. 專案核准製造、輸入藥品，其藥商應遵循事項之規定。（草案第七條及第八條）

六. 專案核准之撤銷及廢止事由之規定。(第九條)

七. 通報登錄與專案核准業務之權限委任或權限委託之規定。（草案第十條）

八. 施行日期。（草案第十一條）

105年度藥品不良品（含療效不等）及化粧品不良事件（包括不良品及不良反應）通報相關業務之委託機構

《105年03月14日FDA藥字第105140051B號》

- 為加強藥品等之品質監控，設置「全國藥品不良品通報中心」**(105年度係委託「財團法人醫藥工業技術發展中心」)**協助通報案件之處理。

  - 通報網站：「藥物食品化粧品上市後品質管理系統」
  - 網址：http://qms.fda.gov.tw
  - 專線：02-66251166轉6401
  - 業務信箱：quality@pitdc.org.tw

台灣藥物法規資訊網

(http://regulation.cde.org.tw/)

致力法規科學，守護生命健康
Regulatory Science,Service for Life

賦形劑相關之警語內容介紹

財團法人醫藥品查驗中心
藥劑科技組 化學製造管制第二小組
審查員 賴宣宏

2016.05.09

財團法人醫藥品查驗中心
Center for Drug Evaluation,Taiwan

本次演講內容僅代表查驗中心之觀點，
凡涉及政策方向及法規解釋與適用，
應依衛生主管機關之指示為準。

前言

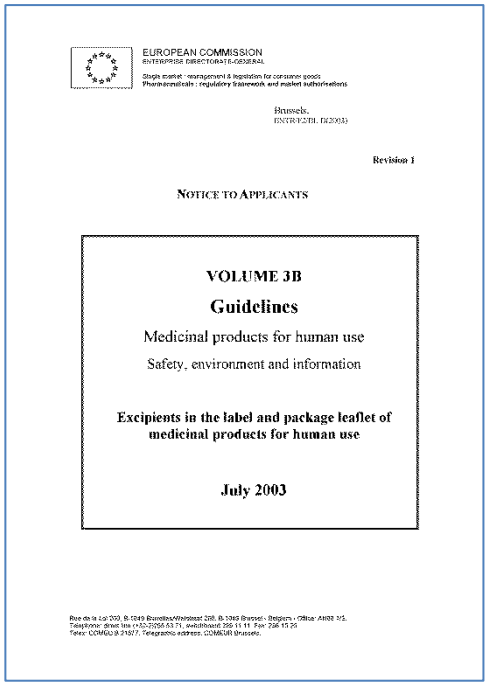
- 並非所有的賦形劑皆為惰性物質，一些已被證明為有潛在毒性物質，例如，冬青油 (methyl salicylate) 可微量使用做為調味劑，但實際上一茶匙的量即可造成相當大的毒性。曾有報導，此一賦形劑的不當使用，已造成成人及兒童死亡的意外。
- 針對賦形劑使用安全進行管理，並研擬適合我國的賦形劑管理機制，成為不可忽視的重要議題。
- 綜觀我國現行法規，目前尚無針對賦形劑警語進行通盤管理的規範。

大綱

- 一、歐盟之相關規範
- 二、美國之相關規範
- 三、我國之相關規範
- 四、歐美及我國賦形劑警語規範之比較
- 五、結語

一、歐盟之相關規範

- 歐盟於2003年發布之指引-Excipients in the label and package leaflet of medicinal products for human use
  - 標籤 (labelling)：注射劑、局部用藥*及眼用製劑須列出所有賦形劑品名；其他劑型僅須針對會產生作用或效果之賦形劑進行品名標示。
    - * 局部用藥 (topical medicinal products)：包括皮膚外用製劑、吸入性局部作用製劑、其他可藉由口服/鼻噴/直腸給藥/陰道給藥等方式產生療效的製劑。
  - 包裝單張 (package leaflet)：須列出所有賦形劑品名。



EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Single market: management & legislation for consumer goods
Pharmaceuticals: regulatory framework and market authorisations

Brussels,
ENTR/F2/BL D(2003)

Revision 1

NOTICE TO APPLICANTS

VOLUME 3B

Guidelines

Medicinal products for human use

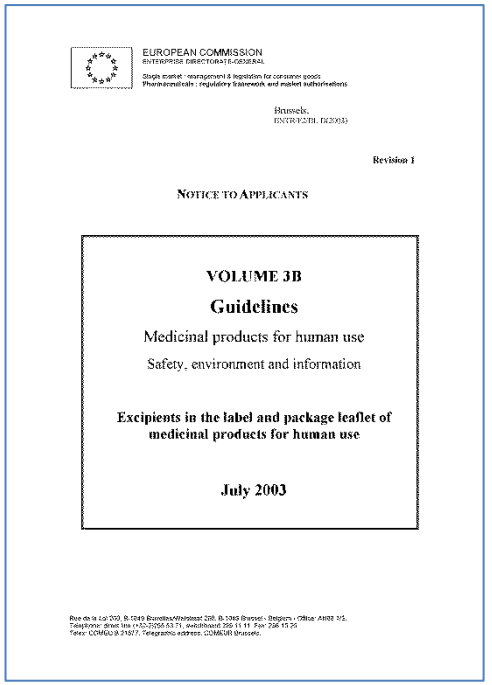
Safety, environment and information

Excipients in the label and package leaflet of medicinal products for human use

July 2003

一、歐盟之相關規範 (continued)

- 歐盟於2003年發布之指引-Excipients in the label and package leaflet of medicinal products for human use
  - 當藥品中某賦形劑之含量高於或等於指引中“閾值”欄中所列出之值時，則須於藥品仿單中加入該賦形劑之相關警語。當“閾值”欄中所列出之值為“零”，則表示無論藥品中該賦形劑之含量為何，均須於藥品仿單中加入該賦形劑之相關警語。



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歐盟2003指引中之賦形劑警語規範-以Ethanol為例

Name	Route of Administration	Threshold [1]	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 100 mg per <dose>.	This statement is to provide reassurance to parents and children concerning the low levels of alcohol in the product.
		100 mg - 3g 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.
	Oral and Parenteral	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.	

1. It is accepted that excipients may only show an effect above a certain 'dose'. Except where otherwise stated, thresholds are expressed as Maximum Daily Doses of the excipient in question, taken as part of a medicinal product. The threshold is a value, equal to or above which it is necessary to provide the information stated. A threshold of 'zero' means that it is necessary to state the information in all cases where the excipient is present in the medicinal product.

一、歐盟之相關規範 (continued)

- 歐盟於2003年發布之指引-Excipients in the label and package leaflet of medicinal products for human use
  - 包含了藥品仿單內應刊載之47類賦形劑的警語及相關規範 (表一)：

Aprotinin	Butylated hydroxyanisole (E320)	Glucose	Mannitol E421	Soya oil (and Hydrogenated soya oil)
Arachis oil (peanut oil)	Butylated hydroxytoluene (E321)	Glycerol	Organic mercury compounds	Stearyl alcohol
Aspartame (E951)	Castor oil polyoxyl and castor oil polyoxyl hydrogenated	Heparin (as an excipient)	Parahydroxybenzoates and their esters	Sucrose
Azo colouring agents	Cetostearyl alcohol including Cetyl alcohol	Hydrogenated glucose syrup (or Maltitol liquid)	Phenylalanine	Sulphites including metabisulphites
Balsam of Peru	Chlorocresol	Invert sugar	Potassium	Wheat starch
Benzalkonium chloride	Dimethyl sulphoxide	Lactitol E966	Propylene glycol and esters	Wool fat (Lanolin)
Benzoic acid and benzoates	Ethanol	Lactose	Sesame oil	Xylitol
Benzyl alcohol	Formaldehyde	Lanolin, (see Wool fat)	Sodium	
Bergamot oil Bergapten	Fructose	Latex Natural rubber (latex)	Sorbic acid and salts	
Bronopol	Galactose	Maltitol E965 and Isomaltitol E953/Maltitol liquid	Sorbitol E420	

表一、歐盟2003指引中與賦形劑相關之藥品仿單警語及相關規範

	Name	Route of Administration	Threshold [1]	Information for the Package Leaflet	Comments
1	**Aprotinin**	Topical	Zero	May cause hypersensitivity or severe allergic reactions.	The topical route in this case refers to sites that may have access to the circulation (e.g. wounds, body cavities etc.)
2	**Arachis oil (peanut oil)**	All	Zero	(Medicinal product) contains arachis oil (peanut oil). If you are allergic to peanut or soya, do not use this medicinal product.	Purified arachis oil may contain peanut protein. The PhEur monograph does not contain a test for residual protein. SPC: contraindication
3	**Aspartame (E951)**	Oral	Zero	Contains a source of phenylalanine. May be harmful for people with phenylketonuria.	
4	**Azo colouring agents: for example: E102, tartrazine E110, sunset yellow FCF E122, azorubine, carmoisine E123, amaranth E124, ponceau 4R red, cochineal red A E151, brilliant black BN, black PN**	Oral	Zero	May cause allergic reactions.	
5	**Balsam of Peru**	Topical	Zero	May cause skin reactions.	
6	**Benzalkonium chloride**	Ocular	Zero	May cause eye irritation. Avoid contact with soft contact lenses. Remove contact lenses prior to application and wait at least 15 minutes before reinsertion. Known to discolour soft contact lenses.	
		Topical		Irritant, may cause skin reactions.	
		Respiratory	10 micrograms/ delivered dose	May cause bronchospasm.	

表一、歐盟2003指引中與賦形劑相關之藥品仿單警語及相關規範 (continued)

	Name	Route of Administration	Threshold [1]	Information for the Package Leaflet	Comments
7	**Benzoic acid and benzoates: for example: E210 benzoic acid E211 sodium benzoate E212 potassium benzoate**	Topical	Zero	Mildly irritant to the skin, eyes and mucous membranes.	
		Parenteral	Zero	May increase the risk of jaundice in newborn babies.	
8	**Benzyl alcohol**	Parenteral	Exposures less than 90 mg/kg/day	Must not be given to premature babies or neonates. May cause toxic reactions and allergic reactions in infants and children up to 3 years old.	SPC: 'allergic' should be expressed as 'anaphylactoid' The amount of benzyl alcohol in mg per <volume> should be stated in the package leaflet and SPC.
			90 mg/kg/day	Must not be given to premature babies or neonates. Due to the risk of fatal toxic reactions arising from exposure to benzyl alcohol in excess of 90 mg/kg/day, this product should not be used in infants and children up to 3 years old.	The amount of benzyl alcohol per <volume> should be stated in the package leaflet and SPC.
9	**Bergamot oil Bergapten**	Topical	Zero	May increase sensitivity to UV light (natural and artificial sunlight).	Does not apply when bergapten is shown to be absent from the oil
10	**Bronopol**	Topical	Zero	May cause local skin reactions (e.g. contact dermatitis).	
11	**Butylated hydroxyanisole (E320)**	Topical	Zero	May cause local skin reactions (e.g.contact dermatitis), or irritation to the eyes and mucous membranes.	
12	**Butylated hydroxytoluene (E321)**	Topical	Zero	May cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.	
13	**Castor oil polyoxyl and castor oil polyoxyl hydrogenated**	Parenteral	Zero	May cause severe allergic reactions.	
		Oral	Zero	May cause stomach upset and diarrhoea.	
		Topical	Zero	May cause skin reactions.	
14	**Cetostearyl alcohol including Cetyl alcohol**	Topical	Zero	May cause local skin reactions (e.g. contact dermatitis).	

表一、歐盟2003指引中與賦形劑相關之藥品仿單警語及相關規範 (continued)

	Name	Route of Administration	Threshold [1]	Information for the Package Leaflet	Comments
15	**Chlorocresol**	Topical, parenteral	Zero	May cause allergic reactions.	
16	**Dimethyl sulphoxide**	Topical	Zero	May be irritant to the skin.	
17	**Ethanol**	Oral and Parenteral	Less than 100 mg per dose	This medicinal product contains small amounts of ethanol (alcohol), less than 100 mg per <dose>.	This statement is to provide reassurance to parents and children concerning the low levels of alcohol in the product.
			100 mg - 3g 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.
		Oral and Parenteral	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.	

表一、歐盟2003指引中與賦形劑相關之藥品仿單警語及相關規範 (continued)

	Name	Route of Administration	Threshold [1]	Information for the Package Leaflet	Comments
18	**Formaldehyde**	Topical	Zero	May cause local skin reactions (e.g. contact dermatitis).	
		Oral	Zero	May cause stomach upset and diarrhoea.	
19	**Fructose**	Oral, parenteral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SPC proposal: Patients with rare hereditary problems of fructose intolerance should not take this medicine.
			5 g	Contains x g fructose per dose. This should be taken into account in patients with diabetes mellitus.	
		Oral liquids, lozenges and chewable tablets	Zero	May be harmful to the teeth.	Information to be included only when the medicinal product may be intended for chronic use, e.g. for two weeks or more
20	**Galactose**	Parenteral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SPC proposal: Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia should not take this medicine.
		Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars contact your doctor before taking this medicinal product.	SPC proposal: Patients with rare hereditary problems of galactose intolerance e.g. galacotosaemia, or glucose-galactose malabsorption should not take this medicine.
		Oral, parenteral	5 g	Contains x g galactose per dose. This should be taken into account in patients with diabetes mellitus.	

表一、歐盟2003指引中與賦形劑相關之藥品仿單警語及相關規範 (continued)

	Name	Route of Administration	Threshold [1]	Information for the Package Leaflet	Comments
21	**Glucose**	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SPC proposal: Patients with rare glucose-galactose malabsorption should not take this medicine.
		Oral, parenteral	5 g	Contains x g glucose per dose. This should be taken into account in patients with diabetes mellitus.	
		Oral liquids, lozenges and chewable tablets	Zero	May be harmful to the teeth.	Information to be included only when the medicinal product may be intended for chronic use, e.g. for two weeks or more.
22	**Glycerol**	Oral	10 g/dose	May cause headache, stomach upset and diarrhoea.	
		Rectal	1 g	May have a mild laxative effect	
23	**Heparin (as an excipient)**	Parenteral	Zero	May cause allergic reactions and reduced blood cell counts which may affect the blood clotting system. Patients with a history of heparin-induced allergic reactions should avoid the use of heparin-containing medicines.	
24	**Hydrogenated glucose syrup (or Maltitol liquid)**	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SPC proposal: Patients with rare hereditary problems of fructose intolerance should not take this medicine.
			10 g	May have a mild laxative effect Calorific value 2.3 kcal/g of hydrogenated glucose syrup.	

表一、歐盟2003指引中與賦形劑相關之藥品仿單警語及相關規範 (continued)

	Name	Route of Administration	Threshold [1]	Information for the Package Leaflet	Comments
25	**Invert sugar**	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SPC proposal: Patients with rare hereditary problems of fructose intolerance or glucose-galactose malabsorption should not take this medicine.
			5 g	Contains x g of a mixture of fructose and glucose per dose. This should be taken into account in patients with diabetes mellitus.	
		Oral liquids, lozenges and chewable tablets	Zero	May be harmful to the teeth.	Information to be included only when the medicinal product may be intended for chronic use, e.g. for two weeks or more.
26	**Lactitol, E966**	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars contact your doctor before taking this medicinal product.	SPC proposal: Patients with rare hereditary problems of fructose intolerance, galactose intolerance, galactosaemia or glucose-galactose malabsorption should not take this medicine.
			10 g	May have a mild laxative effect Calorific value 2.1 kcal/g lactitol.	
27	**Lactose**	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SPC proposal: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
			5 g	Contains x g lactose (x/2 g glucose and x/2 g galactose) per dose. This should be taken into account in patients with diabetes mellitus.	
28	**Lanolin (see Wool fat)**	Topical	Zero	May cause local skin reactions (e.g. contact dermatitis).	

表一、歐盟2003指引中與賦形劑相關之藥品仿單警語及相關規範 (continued)

	Name	Route of Administration	Threshold [1]	Information for the Package Leaflet	Comments
29	**Latex Natural rubber (latex)**	All	Zero	The container of this medicinal product contains latex rubber. May cause severe allergic reactions.	Not a typical excipient, but a warning is considered necessary.
30	**Maltitol E965 and Isomaltitol E953, Maltitol liquid (see Hydrogenated glucose syrup)**	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SPC proposal: Patients with rare hereditary problems of fructose intolerance should not take this medicine.
			10 g	May have a mild laxative effect Calorific value 2.3 kcal/g maltitol (or isomaltitol).	
31	**Mannitol, E421**	Oral	10 g	May have a mild laxative effect.	
32	**Organic mercury compounds: for example: Thiomersal Phenylmercuric nitrate, acetate, borate**	Ocular	Zero	May cause allergic reactions.	See EMEA Public Statement, 8 July 1999, Ref. EMEA/20962/99.
		Topical	Zero	May cause local skin reactions (e.g. contact dermatitis) and discolouration.	
		Parenteral	Zero	This medicinal product contains (thiomersal) as a preservative and it is possible that <you/your child> may experience an allergic reaction. Tell your doctor if <you/your child> have/has any known allergies.	See EMEA Public Statement, 8 July 1999, Ref. EMEA/20962/99.
				Tell your doctor if you/your child have/has experienced any health problems after previous administration of a vaccine.	Additional statement to be mentioned for vaccines.

表一、歐盟2003指引中與賦形劑相關之藥品仿單警語及相關規範 (continued)

	Name	Route of Administration	Threshold [1]	Information for the Package Leaflet	Comments
33	**Parahydroxybenzoates and their esters for example: E214, ethyl hydroxybenzoate E216, propylhydroxybenzoate E217, sodium propylhydroxybenzoate E218, methylhydroxybenzoate E219, sodium methylhydroxybenzoate**	Oral, ocular, topical	Zero	May cause allergic reactions (possibly delayed).	
		Parenteral, respiratory	Zero	May cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.	
34	**Phenylalanine**	All	Zero	This medicine contains phenylalanine. May be harmful for people with phenylketonuria.	
35	**Potassium**	Parenteral	Less than 1 mmol per <dose>	This medicine contains potassium, less than 1 mmol (39 mg) per <dose>, i.e. essentially 'potassium- free'.	Information relates to a threshold based on the total amount of K+ in the medicinal product It is especially relevant to products used in paediatric doses, to provide information to prescribers and reassurance to parents concerning the low level of K+ in the product.
		Parenteral, oral	1 mmol per <dose>	This medicine contains x mmol (or y mg) potassium per <dose>. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.	
		Parenteral-intravenous	30 mmol/l	May cause pain at the site of injection.	

表一、歐盟2003指引中與賦形劑相關之藥品仿單警語及相關規範 (continued)

	Name	Route of Administration	Threshold [1]	Information for the Package Leaflet	Comments
36	**Propylene glycol and esters**	Topical	Zero	May cause skin irritation.	
		Oral, parenteral	400 mg/kg adults 200 mg/kg children	May cause alcohol-like symptoms.	
37	**Sesame oil**	All	Zero	May rarely cause severe allergic reactions.	
38	**Sodium**	Parenteral	Less than 1 mmol per <dose>	This medicinal product contains less than 1 mmol sodium (23 mg) per <dose>, i.e. essentially 'sodium- free'.	Information relates to a threshold based on the total amount of Na+ in the medicinal product It is especially relevant to products used in paediatric doses, to provide information to prescribers and reassurance to parents concerning the low level of Na+ in the product.
		Oral, parenteral	1 mmol per <dose>	This medicinal product contains x mmol (or y mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.	
39	**Sorbic acid and salts**	Topical	Zero	May cause local skin reactions, (e.g. contact dermatitis).	
40	**Sorbitol E420**	Oral Parenteral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SPC proposal: Patients with rare hereditary problems of fructose intolerance should not take this medicine.
		Oral	10 g	May have a mild laxative effect Calorific value 2.6 kcal/g sorbitol.	
41	**Soya oil (and Hydrogenated soya oil)**	All	Zero	(Medicinal product) contains soya oil. If you are allergic to peanut or soya, do not use this medicinal product.	In line with Arachis oil. SPC: contraindication.
42	**Stearyl alcohol**	Topical	Zero	May cause local skin reactions (e.g. contact dermatitis)	

表一、歐盟2003指引中與賦形劑相關之藥品仿單警語及相關規範 (continued)

	Name	Route of Administration	Threshold [1]	Information for the Package Leaflet	Comments
43	**Sucrose**	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product	SPC proposal: Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
			5 g	Contains x g of sucrose per dose. This should be taken into account in patients with diabetes mellitus.	
		Oral liquids, lozenges and chewable tablets	Zero	May be harmful to the teeth.	Information to be included only when the medicinal product may be intended for chronic use, e.g. for two weeks or more.
44	**Sulphites including metabisulphites for example: E220, sulphur dioxide E221, sodium sulphite E222, sodium bisulphite E223, sodium metabisulphite E224, potassium metabisulphite E228, potassium bisulphite**	Oral Parenteral Respiratory	Zero	May rarely cause severe hypersensitivity reactions and bronchospasm	

表一、歐盟2003指引中與賦形劑相關之藥品仿單警語及相關規範 (continued)

	Name	Route of Administration	Threshold [1]	Information for the Package Leaflet	Comments
45	**Wheat starch**	Oral	Zero	Suitable for people with coeliac disease. Patients with wheat allergy (different from coeliac disease) should not take this medicine.	Wheat starch may contain gluten, but only in trace amounts, and is therefore considered safe for people with coeliac disease. (Gluten in wheat starch is limited by the test for total protein described in the PhEur monograph.)
46	**Wool fat (Lanolin)**	Topical	Zero	May cause local skin reactions (e.g. contact dermatitis).	
47	**Xylitol**	Oral	10 g	May have a laxative effect. Calorific value 2.4 kcal/g xylitol.	

1. It is accepted that excipients may only show an effect above a certain 'dose'. Except where otherwise stated, thresholds are expressed as Maximum Daily Doses of the excipient in question, taken as part of a medicinal product. The threshold is a value, equal to or above which it is necessary to provide the information stated. A threshold of 'zero' means that it is necessary to state the information in all cases where the excipient is present in the medicinal product.

一、歐盟之相關規範 (continued)

- 賦形劑之藥品仿單警語草案或修正草案
  - 仿單警語修正草案(6項)
    - **benzalkonium chloride**: EMA/495737/2013, 22 May 2014.
    - **benzoic acid and benzoates**: EMA/CHMP/508189/2013, 23 January 2014.
    - **benzyl alcohol**: EMA/CHMP/508188/2013), EMA, 23 January 2014.
    - **ethanol**: EMA/CHMP/507988/2013, 23 January 2014.
    - **propylene glycol and esters**: EMA/CHMP/704195/2013, 20 November 2014.
    - **wheat starch containing gluten**: EMA/CHMP/704219/2013, 24 July 2014.
  - 仿單警語草案(3項)
    - **boric acid**: EMA/CHMP/619104/2013, 23 July 2015.
    - **cyclodextrins**: EMA/CHMP/495747/2013, 20 November 2014.
    - **sodium laurilsulfate**: EMA/CHMP/606830/2014, 23 July 2015.
- 歐盟2003年指引加上上述草案，已發布警語的賦形劑總計五十項。

二、美國之相關規範

- 美國關於藥品仿單中賦形劑警語相關規定，主要收錄於美國聯邦法規21 CFR Part 201 Labeling條文中。
  - 包含10類賦形劑之藥品仿單警語 (表二~表九)
    - (1) FD+C Yellow No. 5 (tartrazine)
    - (2) FD+C Yellow No. 6 (sunset yellow FCF)
    - (3) phenylalanine as a component of aspartame
    - (4) sulfites
    - (5) sodium
    - (6) potassium
    - (7) calcium
    - (8) magnesium
    - (9) mineral oil
    - (10) methyl salicylate (wintergreen oil)

表二、美國法規中與FD+C Yellow No. 5 (tartrazine)相關之警語及規範

Title21 Part. Section	Condition	Threshold	Statements or Warning statements
201.20(a)	For **over-the-counter and prescription drug products** intended for human use administered orally, nasally, rectally, or vaginally, or for use in the area of the eye, containing FD+C Yellow No. 5 as a color additive using the names FD+C Yellow No. 5 and tartrazine[1]	N/A	The labeling shall bear a statement such as "Contains FD+C Yellow No. 5 (tartrazine) as a color additive" or "Contains color additives including FD+C Yellow No. 5 (tartrazine)".
201.20(b)	For **prescription drugs** for human use containing FD+C Yellow No. 5 that are administered orally, nasally, vaginally, or rectally, or for use in the area of the eye	N/A	The labeling shall bear the warning statement "This product contains FD+C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD+C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity."

1. The labels of certain drug products subject to this labeling requirement that are also cosmetics, such as antibacterial mouthwashes and fluoride toothpastes, need not comply with this requirement provided they comply with the requirements of 701.3 of this chapter.

表三、美國法規中與FD+C Yellow No. 6 (sunset yellow FCF)相關之警語及規範

Title21 Part. Section	Condition	Threshold	Statements or Warning statements
201.20(c)	For **over-the-counter drug** products intended for human use administered orally, nasally, rectally, or vaginally containing FD+C Yellow No. 6[1]	N/A	The label shall specifically declare the presence of FD+C Yellow No. 6 by listing the color additive using the name FD+C Yellow No. 6.
	For **over-the-counter and prescription drug products** containing FD+C Yellow No. 6[1]	N/A	The labeling shall declare the presence of FD+C Yellow No. 6.

1. The labels of certain drug products subject to this labeling requirement that are also cosmetics, such as antibacterial mouthwashes and fluoride toothpastes, need not comply with this requirement provided they comply with the requirements of 701.3 of this chapter.

表四、美國法規中與Phenylalanine as a component of aspartame 相關之警語及規範

Title21 Part. Section	Condition	Threshold	Statements or Warning statements
201.21(b)	For **over-the-counter** human drug products containing aspartame as an inactive ingredient	N/A	The label and labeling shall bear a statement to the following effect: Phenylketonurics: Contains Phenylalanine (_)mg Per (Dosage Unit)
201.21(c)	For **prescription drugs** for human use containing aspartame as an inactive ingredient	N/A	The package labeling and other labeling providing professional use information shall bear a statement to the following effect under the “Precautions” section of the labeling, as required in 201.57(f)(2): Phenylketonurics: Contains Phenylalanine (_)mg Per (Dosage Unit)

表五、美國法規中與Sulfites (e.g. sodium or potassium sulfites)相關之警語及規範

Title21 Part. Section	Condition	Threshold	Statements or Warning statements
201.22(b)	For **prescription drugs** for human use containing a sulfite, except epinephrine for injection when intended for use in allergic or other emergency situations	N/A	The labeling shall bear the warning statement "Contains (insert the name of the sulfite, e.g., sodium metabisulfite), a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people."
201.22(c)	For **sulfite-containing epinephrine for injection** for use in allergic emergency situations	N/A	The labeling shall bear the warning statement "Epinephrine is the preferred treatment for serious allergic or other emergency situations even though this product contains (insert the name of the sulfite, e.g., sodium metabisulfite), a sulfite that may in other products cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. The alternatives to using epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite(s) in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations."

表六、美國法規中與Sodium及Potassium相關之警語及規範

Title21 Part. Section	Inactive ingredient	Condition	Threshold	Statements or Warning statements
201.64(c)	Sodium	For **over-the-counter (OTC) drug products** intended for oral ingestion	140 mg (the amount of sodium present in the labeled maximum daily dose of the product)	The labeling shall contain the following statement under the heading “Warning”: “Ask a doctor before use if you have [in bold type] [bullet] a sodium-restricted diet.”
201.72(c)	Potassium	For **OTC drug products** intended for oral ingestion	975 mg (the amount of potassium present in the labeled maximum daily dose of the product)	The labeling shall contain the following statement under the heading “Warning”: “Ask a doctor before use if you have [in bold type] [bullet] kidney disease [bullet] a potassium-restricted diet.”

表七、美國法規中與Calcium及Magnesium相關之警語及規範

Title21 Part. Section	Inactive ingredient	Condition	Threshold	Statements or Warning statements
201.70(c)	Calcium	For **OTC drug products** intended for oral ingestion	3.2 g (the amount of calcium present in the labeled maximum daily dose of the product)	The labeling shall contain the following statement under the heading “Warning”: “Ask a doctor before use if you have [in bold type] [bullet] kidney stones [bullet] a calcium-restricted diet.”
201.71(c)	Magnesium	For **OTC drug products** intended for oral ingestion	600 mg (the amount of magnesium present in the labeled maximum daily dose of the product)	The labeling shall contain the following statement under the heading “Warning”: “Ask a doctor before use if you have [in bold type] [bullet] kidney disease [bullet] a magnesium-restricted diet.”

表八、美國法規中與Mineral oil相關之警語及規範

Title21 Part. Section	Condition	Threshold	Statements or Warning statements
201.302(d)	A drug for oral administration consisting in whole or in part of mineral oil	N/A	The following form of warning is suggested: "Caution: To be taken only at bedtime. Do not use at any other time or administer to infants, except upon the advice of a physician."

表九、美國法規中與Methyl salicylate (wintergreen oil)相關之警語及規範

Title21 Part. Section	Condition	Threshold	Statements or Warning statements
201.314(g)(1)	Any drug	5%	The label should bear a conspicuous warning such as: "Do not use otherwise than as directed." These drug products must also include the "Keep out of reach of children" warning and the accidental ingestion warning as required in 330.1(g)[1] of this chapter.
201.314(g)(2)	If the preparation is a **counterirritant or rubefacient**	N/A	The label should also bear a caution such as, "Caution: Discontinue use if excessive irritation of the skin develops. Avoid getting into the eyes or on mucous membranes."

1. 330.1(g): The labeling for all drugs contains the general warning: "Keep out of reach of children." [highlighted in bold type]. The labeling of drugs shall also state as follows: For drugs used by oral administration, "In case of overdose, get medical help or contact a Poison Control Center right away"; for drugs used topically, rectally, or vaginally and not intended for oral ingestion, "If swallowed, get medical help or contact a Poison Control Center right away"; and for drugs used topically and intended for oral use, "If more than used for" (insert intended use, e.g., pain) "is accidentally swallowed, get medical help or contact a Poison Control Center right away."

三、我國之相關規範

- 我國針對特定賦形劑警語之相關規範，並未如歐美般集結於單一指引或法規，而是散見於各項公告或審查基準之中。
- 經搜尋共有五起相關公告 (表十)。

表十、我國已公告之賦形劑警語相關規範

公告	適用之藥品類別	適用時機/對象	警語內容
99年11月25日署授食字第0991413901號函	含阿斯巴甜 (Aspartame) 成分藥品	苯酮尿症患者	本品含阿斯巴甜 (Aspartame) 賦形劑，苯酮尿症患者 (Phenylketonurics) 不宜使用。
86年05月20日衛署藥字第85063092號公告	含0.5% w/v酒精濃度以上營養內服液製劑之仿單及包裝	限成人使用	1. 主要成分含量：標示該製劑之酒精及其含量。惟屬「口服液」製劑者，若其酒精含量在5% w/v以下，得不標示。 2. 注意事項：須置於小孩接觸不到之處。
94年01月05日衛署藥字第0940301733號公告	含酒精之內服液劑(包括Amino Acid 類及多種維他命類營養劑)及中藥酒劑外包裝	N/A	本藥品含酒，服用過量，有害健康。成人每次服用〇〇～〇〇cc，一日〇次。
96年11月14日衛署藥字第0960337455號公告	含0.5% w/v酒精濃度以上內服液劑(含Amino Acid類及多種維他命類營養劑)及中藥酒劑外包裝	N/A	本藥品含酒(〇% v/v 或 〇度)，服用過量，有害健康。成人每次服用〇〇～〇〇cc，一日〇次。
103年07月22日FDA藥字第1031407346號函 (Docetaxel 成分藥品安全資訊風險溝通表)	衛生福利部核准含docetaxel 成分藥品製劑許可證共12 張	含docetaxel 成分藥品製劑	食品藥物管理署說明： 1. 我國核准docetaxel成分藥品原廠(賽諾菲股份有限公司)仿單已刊載相關內容，包含：「對於患有酒精中毒的患者有害」、「應審慎評估對懷孕或哺乳婦女，兒童和高危險患者如肝臟疾病患者或癲癇患者的影響」、「本品酒精含量可能會影響其他藥品的效果」及「本品酒精含量可能會影響患者駕駛或使用機器的能力」等內容。 2. 針對本次美國FDA 將增修該藥品仿單內容，原廠說明將待其英文仿單核定後，儘速向本署申請中文仿單變更事宜。

三、我國之相關規範

- **指示藥品審查基準**中關於賦形劑警語之規範：
  - 眼用製劑基準中關於**防腐劑**之警語：
    - 對本藥之主要成分、防腐劑或其他賦形劑過敏者，不建議使用
    - 佩帶隱形眼鏡時，請勿點用含防腐劑及含懸浮液之眼藥水。
  - 眼用製劑含有**汞化合物**當防腐劑時加列下述警語：
    - 本藥含有汞化合物【成分名稱】當防腐劑，若對含汞化合物(或汞本身)過敏者，或使用數通後產生接觸性眼瞼炎或角結膜炎，則不要使用本藥。
  - 胃腸製劑如含制酸、止瀉或消化酵素成分且賦形劑中含有**乳糖**，且每日最大建議劑量乳糖超過5g者，增列下述警語：
    - 本藥每日最大建議劑量之乳糖含量超過 5g，對於牛奶或乳製品耐受度低者應小心服用或請諮詢醫師藥師藥劑生。

四、歐美及我國賦形劑警語規範之比較

- 比對歐美及我國所公告之賦形劑規範，可發現在歐(表一)美(表二~九)法規及我國的公告(表十)中皆已列入之賦形劑為：
  - aspartame
    - 歐盟2003指引中所用的賦形劑名稱為aspartame (E951)
    - 美國聯邦法規中所用的賦形劑名稱為phenylalanine as a component of aspartame
    - 我國公告中所用的賦形劑名稱為阿斯巴甜

表十一、歐美與我國Aspartame警語相關規範之比對

歐盟指引相關規範 (Excipient names: Aspartame (E951))			美國CFR Title 21法規相關規範 (Excipient names: Phenylalanine as a component of aspartame)			
Route of Administration	**Threshold**	**Information for the Package Leaflet**	**Title21 Part. Section**	**Condition**	**Threshold**	**Statements or Warning statements**
Oral	Zero	Contains a source of phenylalanine. May be harmful for people with phenylketonuria.	201.21(b)	For **over-the-counter** human drug products containing aspartame as an inactive ingredient	N/A	The label and labeling shall bear a statement to the following effect: Phenylketonurics: Contains Phenylalanine (_)mg Per (Dosage Unit)
			201.21(c)	For **prescription drugs** for human use containing aspartame as an inactive ingredient	N/A	The package labeling and other labeling providing professional use information shall bear a statement to the following effect under the “Precautions” section of the labeling, as required in 201.57(f)(2): Phenylketonurics: Contains Phenylalanine (_)mg Per (Dosage Unit)

我國Aspartame警語相關規範			
公告	適用之藥品類別	適用時機/對象	警語內容
99年11月25日署授食字第0991413901號函 [13]	含阿斯巴甜 (Aspartame) 成份藥品	苯酮尿症患者	本品含阿斯巴甜 (Aspartame) 賦形劑，苯酮尿症患者 (Phenylketonurics) 不宜使用。

四、歐美及我國賦形劑警語規範之比較

- 比對**歐盟及美國**皆已公告之賦形劑規範，共發現六類賦形劑在歐盟指引(表一)及美國聯邦法規(表十一)中皆列出：
  - aspartame (美國聯邦法規中所用的賦形劑名稱為phenylalanine as a component of aspartame)
  - tartrazine (美國聯邦法規中所用的賦形劑名稱為FD+C Yellow No. 5)
  - sunset yellow FCF (美國聯邦法規中所用的賦形劑名稱為FD+C Yellow No. 6)
  - potassium (鉀，此指鉀離子)
  - sodium (鈉，此指鈉離子)
  - sulphites (美國聯邦法規中所用的賦形劑名稱為sulfites)

表十二、歐美Tartrazine警語相關規範之比對

歐盟指引相關規範 (Excipient names: Tartrazine (E102))			美國CFR Title 21法規相關規範 (Excipient names: FD+C Yellow No. 5)			
Route of Administration	**Threshold**	**Information for the Package Leaflet**	**Title21 Part. Section**	**Condition**	**Threshold**	**Statements or Warning statements**
Oral	Zero	May cause allergic reactions.	201.20(a)	For **over-the-counter and prescription drug products** intended for human use administered orally, nasally, rectally, or vaginally, or for use in the area of the eye, containing FD+C Yellow No. 5 as a color additive using the names FD+C Yellow No. 5 and tartrazine	N/A	The labeling shall bear a statement such as "Contains FD+C Yellow No. 5 (tartrazine) as a color additive" or "Contains color additives including FD+C Yellow No. 5 (tartrazine)".
			201.20(b)	For **prescription drugs** for human use containing FD+C Yellow No. 5 that are administered orally, nasally, vaginally, or rectally, or for use in the area of the eye	N/A	The labeling shall bear the warning statement "This product contains FD+C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD+C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity."

表十三、歐美Sunset yellow FC警語相關規範之比對

歐盟指引相關規範 (Excipient names: Sunset yellow FCF (E110))			美國CFR Title 21法規相關規範 (Excipient names: FD+C Yellow No. 6)			
Route of Administration	**Threshold**	**Information for the Package Leaflet**	**Title21 Part. Section**	**Condition**	**Threshold**	**Statements or Warning statements**
Oral	Zero	May cause allergic reactions.	201.20(c)	For **over-the-counter drug products** intended for human use administered orally, nasally, rectally, or vaginally containing FD+C Yellow No. 6	N/A	The label shall specifically declare the presence of FD+C Yellow No. 6 by listing the color additive using the name FD+C Yellow No. 6.
				For **over-the-counter and prescription drug products** containing FD+C Yellow No. 6	N/A	The labeling shall declare the presence of FD+C Yellow No. 6.

表十四、歐美Potassium (K^+)警語相關規範之比對

歐盟指引相關規範			美國CFR Title 21法規相關規範			
Route of Administration	**Threshold [1]**	**Information for the Package Leaflet**	**Title21 Part. Section**	**Condition**	**Threshold**	**Statements or Warning statements**
Parenteral	Less than 1 mmol per <dose>	This medicine contains potassium, less than 1 mmol (39 mg) per <dose>, i.e. essentially 'potassium- free'.				
Parenteral, oral	1 mmol per <dose>	This medicine contains x mmol (or y mg) potassium per <dose>. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.	201.72(c)	For OTC drug products intended for oral ingestion	975 mg (the amount of potassium present in the labeled maximum daily dose of the product)	The labeling shall contain the following statement under the heading "Warning": "Ask a doctor before use if you have [in bold type] [bullet] kidney disease [bullet] a potassium-restricted diet."
Parenteral–intravenous	30 mmol/l	May cause pain at the site of injection.				

1. Information relates to a threshold based on the total amount of K+ in the medicinal product It is especially relevant to products used in paediatric doses, to provide information to prescribers and reassurance to parents concerning the low level of K+ in the product.

表十五、歐美Sodium (Na^+)警語相關規範之比對

歐盟指引相關規範			美國CFR Title 21法規相關規範			
Route of Administration	**Threshold [1]**	**Information for the Package Leaflet**	**Title21 Part. Section**	**Condition**	**Threshold**	**Statements or Warning statements**
Parenteral	Less than 1 mmol per <dose>	This medicinal product contains less than 1 mmol sodium (23 mg) per <dose>, i.e. essentially 'sodium- free'.				
Oral, parenteral	1 mmol per <dose>	This medicinal product contains x mmol (or y mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.	201.64(c)	For over-the-counter (OTC) drug products intended for oral ingestion	140 mg (the amount of sodium present in the labeled maximum daily dose of the product)	The labeling shall contain the following statement under the heading "Warning": "Ask a doctor before use if you have [in bold type] [bullet] a sodium-restricted diet."

1. Information relates to a threshold based on the total amount of Na+ in the medicinal product It is especially relevant to products used in paediatric doses, to provide information to prescribers and reassurance to parents concerning the low level of Na+ in the product.

表十六、歐美Sulfites警語相關規範之比對

歐盟指引相關規範[1]			美國CFR Title 21法規相關規範[2]			
Route of Administration	**Threshold**	**Information for the Package Leaflet**	**Title21 Part. Section**	**Condition**	**Threshold**	**Statements or Warning statements**
Oral Parenteral Respiratory	Zero	May rarely cause severe hypersensitivity reactions and bronchospasm	201.22 (b)	For **prescription drugs** for human use containing a sulfite, except epinephrine for injection when intended for use in allergic or other emergency situations	N/A	The labeling shall bear the warning statement "Contains (insert the name of the sulfite, e.g., sodium metabisulfite), a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people."
			201.22 (c)	For **sulfite-containing epinephrine for injection** for use in allergic emergency situations	N/A	The labeling shall bear the warning statement "Epinephrine is the preferred treatment for serious allergic or other emergency situations even though this product contains (insert the name of the sulfite, e.g., sodium metabisulfite), a sulfite that may in other products cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. The alternatives to using epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite(s) in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations."

1. Sulphites including metabisulphites, for example: sulphur dioxide (E220), sodium sulphite (E221), sodium bisulphite (E222), sodium metabisulphite (E223),potassium metabisulphite (E224),potassium bisulphite (E228)
2. Sulfites includes, e.g., sodium bisulfite, sodium metabisulfite, sodium sulfite, potassium bisulfite, and potassium metabisulfite.

四、歐美及我國賦形劑警語規範之比較

- 比對**美國及我國**所公告之賦形劑規範，除aspartame外無共同之賦形劑類別。
- 比對**歐盟及我國**所公告之賦形劑規範，除aspartame外，在歐盟指引(表一)及我國的公告或審查基準中之共同賦形劑類別：
  - 乙醇 (ethanol)
  - 乳糖 (lactose)

歐盟指引及我國的公告中皆列出之共同賦形劑類別-乙醇 (ethanol)

- 乙醇被廣泛用於各種藥物製劑、主要做為溶劑之用，亦可做為消毒劑 (disinfectant) 以及溶液劑型中作為抗菌防腐劑 (antimicrobial preservative) 之用，亦用於化妝品及消費酒精飲料。
- 許多藥品含有乙醇作為賦形劑，如果攝取足夠大的數量時，可能會引起中毒的不良症狀。
- 關於酒精成分的警語目前國內有衛生福利部的公告(參見表十九)，乃是關於藥酒劑警語的規範。
- 衛生福利部公告之docetaxel成分藥品安全資訊風險溝通表中亦提到使用docetaxel 成分藥品含有乙醇(酒精)，可能有造成病人酒精中毒的風險，已公告要求含docetaxel成分藥品製劑許可證共12張(均為注射劑型)須依原廠仿單刊載乙醇成分相關警語
  - 此內容與歐盟於2003發布之指引中之乙醇成分警語相同，但國內尚未有針對所有含乙醇製劑一般性的仿單警語規範。

表十七、歐盟與我國乙醇 (ethanol)警語相關規範之比對

歐盟指引相關規範		
Route of Administration	**Threshold**	**Information for the Package Leaflet**
Oral and Parenteral	Less than 100 mg per dose	This medicinal product contains small amounts of ethanol (alcohol), less than 100 mg per <dose>. [1]
	100 mg - 3g per dose	This medicinal product contains ... vol % ethanol (alcohol), i.e. up to ... mg per dose, equivalent to ... ml beer, ... ml wine per dose. [2] 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.
Oral and Parenteral	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.

1. This statement is to provide reassurance to parents and children concerning the low levels of alcohol in the product.
2. 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.

公告	適用之藥品類別	適用時機/對象	警語內容
103年07月22日FDA藥字第1031407346號函 (Docetaxel 成分藥品安全資訊風險溝通表)	衛生福利部核准含docetaxel 成分藥品製劑許可證共12 張	含docetaxel 成分藥品製劑	對於患有酒精中毒的患者有害。 應審慎評估對懷孕或哺乳婦女，兒童和高危險患者如肝臟疾病患者或癲癇患者的影響。 本品酒精含量可能會影響其他藥品的效果。 本品酒精含量可能會影響患者駕駛或使用機器的能力。

乳糖 (lactose)賦形劑之相關警語規範

- 已被廣泛用於藥物口服製劑如錠劑和膠囊中作為稀釋劑、填料或黏合劑等用途、亦可能用於靜脈注射。
- 該賦形劑類別在我國「指示藥品審查基準胃腸製劑」中已有規範，且歐盟於2003發布之指引中已包含了此賦形劑之警語，目前已有為數不少含乳糖成分之已上市的口服製劑的仿單中包含相關警語。
- 此一賦形劑被列入警語規範的主要原因為半乳糖不耐症(galactose intolerance)、Lapp乳糖酶缺乏 (Lapp lactase deficiency)或葡萄糖-半乳糖吸收不良 (glucose-galactose malabsorption)等罕見遺傳性疾病。

表十七、歐盟與我國乳糖 (lactose)警語相關規範之比對

歐盟指引相關規範			
Route of Administration	Threshold	Information for the Package Leaflet	Comments
Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SPC proposal: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
	5 g	Contains x g lactose (x/2 g glucose and x/2 g galactose) per dose. This should be taken into account in patients with diabetes mellitus.	

相關規範	適用之藥品類別	適用時機/對象	警語內容
100年02月25日署授食字第1001400521號公告「指示藥品審查基準胃腸製劑」	符合「指示藥品審查基準胃腸製劑」之胃腸製劑	胃腸製劑如含制酸、止瀉或消化酵素成分且賦形劑中含有乳糖，且**每日最大建議劑量乳糖超過5g**者	**本藥每日最大建議劑量之乳糖含量超過5g**，對於牛奶或乳製品耐受度低者應小心服用或請諮詢醫師藥師藥劑生。

結語

- 國際上賦形劑警語標示的相關規範目前以歐盟的規範最為完備，已發布之賦形劑警語規範(含草案)有五十類。
- 美國於其聯邦法規21 CFR Part 201 Labeling 條文中規定須標示警語之賦形劑亦有十類。
- 相較之下，我國賦形劑警語標示規定多為通則性規範(例如，指示藥品審查基準眼用製劑中關於防腐劑賦形劑警語之規範僅提及類別，未特定至防腐劑個別品項)，較少針對特定賦形劑品項。

結語 (Continued)

- 處方藥使用之賦形劑目前並未見有明確的警語標示規定。
- 如欲進一步健全賦形劑警語相關規範，或可考量由以下的賦形劑警語相關規範著手：
  - 藥品中使用頻率較高，國內外的藥品仿單中已廣泛標示相關警語之賦形劑，例如乳糖及乙醇，可考慮參考歐盟指引，將相關警語規範擴及所有使用該賦形劑的藥品種類。
  - 第二階段，將歐美等國際主要法規單位皆已要求標示賦形劑警語規範之賦形劑，納入要求；例如 tartrazine、含鉀離子、含鈉離子及sulfites等賦形劑。
  - 已有明確的風險，並有安全性資料支持之賦形劑。

已有明確安全性資料支持之賦形劑

- 歐盟的指引草案或修正草案(投影片第36頁)，除針對賦形劑特定的使用途徑或劑型，明訂其特定用量下的警語及使用注意事項外，亦提供相關的賦形劑安全性資料以支持該賦形劑於仿單的警語及使用注意事項。
- 例如以benzalkonium chloride為例，使用此賦形劑以眼用劑型最多，基於使用風險的考量，可針對含此賦形劑的眼用劑型處方藥進行規範。

benzalkonium chloride成分仿單警語擬定之範例

Route of Administration	Threshold [1]	Information for the Package Leaflet	Comments
Ocular	Zero	May cause eye irritation. Avoid contact with soft contact lenses. Remove contact lenses prior to application and wait at least 15 minutes before reinsertion. Known to discolour soft contact lenses.	
Topical		Irritant, may cause skin reactions.	
Respiratory	10 micrograms/ delivered dose	May cause bronchospasm.	

使用途徑	閾值*	警語內容	參考文獻
眼用	零	已有報告指出benzalkonium chloride會造成眼睛刺激。 使用之前，應先將隱形眼鏡摘除，在投藥後至少15分鐘才可重新配戴。 其可能被軟式隱形眼鏡吸收，亦可能使軟式隱形眼鏡變色。	1. 歐盟指引已有相關規範。 2. 歐盟發布的修正草案(EMA/495737/2013, 22 May 2014)揭示相關之安全性資訊如下： (1) 於醫藥品(例如：多劑量之鼻用、眼用、耳用製劑)中，benzalkonium chloride可為防腐劑，自1950年，已於眼藥水中做為防腐劑(濃度約0.01%至0.02%)使用。 (2) 根據調查，在歐盟，約有74%眼用製劑、超過200種鼻用製劑、約10種吸入劑，使用benzalkonium chloride為防腐劑。較少使用於其他途徑(例如：皮膚、口服、口腔黏膜、直腸、陰道及腸道外給藥)。 (3) 大量文獻指出benzalkonium chloride可能損傷眼睛。 (4) Benzalkonium chloride於臨床中當眼藥水使用時，已有報告指出會造成點狀角膜病變與/或毒性角膜潰瘍。此外，benzalkonium chloride可能刺激眼睛，且亦會使軟式隱形眼鏡變色。 3. 仿單中包含此賦形劑相關警語內容之國內上市藥品： (1) 愛爾康比利時廠愛舒壓點眼懸液劑(衛署藥輸字第022934號) (2) “愛力根”露明目點眼液劑 0.03% (衛署藥輸字第023491號)

* 當藥品中該賦形劑之含量高於或等於“閾值”欄中所列出之值時，則須於藥品仿單中加入該賦形劑之相關警語。當“閾值”欄中所列出之值為“零”，則表示無論藥品中該賦形劑之含量為何，均須於藥品仿單中加入該賦形劑之相關警語。

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綜合討論

臨時動議

謝謝聆聽
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