

# Comments Concerning Revised Texts Published in Supplement 7.3

Here follows information concerning technical modifications to revised texts adopted by the European Pharmacopoeia Commission at the November 2010 session. This information completes the modifications indicated by lines in the margin. Therefore, the information below is not necessarily exhaustive.

## GENERAL TEXTS

### 2.2.35. Osmolality

*Method:* volume of sample modified to take into consideration various equipment currently available.

### 2.7.15. Assay of hepatitis B vaccine (rDNA)

*In vitro assay:* the BRPs previously mentioned in the assay were developed for use in a product- and method-specific context. The methods (A and B) referred to are no longer used by manufacturers, resulting in the disappearance of the specific commercial kits associated with those methods. The

BRPs are therefore no longer relevant and the reference to them has been deleted.

### 2.9.3. Dissolution test for solid dosage forms

Further to the revision of the harmonised chapter by the PDG, the wire diameter specification set for the basket component of the stirring element (apparatus 1) was modified; the diameter stated in the previous version of the chapter did not reflect the diameter used in commercialised equipment.

## GENERAL MONOGRAPHS

### Allergen products (1063)

*Protein content:* it is specified that, when the final product contains proteinaceous excipients, the test is carried out as late as possible during production before addition of the proteinaceous excipient.

### Herbal drugs (1433)

*Microbial contamination:* the introduction of chapter 5.1.8 *Microbiological quality of herbal medicinal products for oral use* in the Ph. Eur. has necessitated reference to this chapter under Microbial contamination in the Tests section. Whilst making this modification, the opportunity has been taken to reword the text to make it more specific with regard to the inclusion of herbal drugs, as such, in medicinal products/pharmaceutical preparations. The test has been moved to below the sentence 'Where necessary herbal drugs comply with other tests, such as the following, for example' as these recommendations are intended only for routine application where herbal drugs are used, as such, in medicinal products/pharmaceutical preparations.

### Monoclonal antibodies for human use (2031)

#### Visible particles

As for all solutions for injection or infusion, monoclonal antibody (mAb) products should not contain extraneous visible particles. This is because the occurrence of adverse events in recipients has, at least in some cases, been associated with batches of products containing such particles. Such particles can originate from the environment (e.g. personnel involved in production), reagents or materials used for production (e.g. column- or filter-derived substances), lines or piping forming part of the production plant, or containers and closures used for the product. They may consist of glass, plastic, metals, rubber, hair, fibrous materials, etc.

The Ph. Eur. monograph *Parenteral preparations (0520)* states, in the relevant definition sections, that such preparations should be 'practically free from particles' when examined under suitable conditions of visibility. The Ph. Eur. also describes a method for assessing contamination with extraneous visible particles in final containers of liquid products (2.9.20. *Particulate contamination: visible particles*).

Manufacturers are expected to test every bottle/vial/ampoule of each batch of product for such particles and reject any contaminated units.

The term 'practically free from particles' has been the subject of considerable discussion and debate and has been interpreted in different ways. The intention of this wording in the monograph *Parenteral preparations (0520)* is to indicate that the relevant parenteral products should be free from such particles, but due to the impossibility of guaranteeing that testing will be 100 per cent accurate and that 100 per cent of particles will be detected, the qualifying term 'practically' has been inserted.

This situation is made more complex for high-molecular-mass protein-based products (like mAbs) as these can often contain non-extraneous, product-related, visible particles (sometimes called coacervates to distinguish them from insoluble extraneous particles), which can be detected by the method described in the Ph. Eur. (2.9.20. *Particulate contamination: visible particles*) as well as other procedures.

Thus, some mAb final products, like many other biological/biotechnological products, may contain proteinaceous visible particles that are intrinsic to the product. The particles may be in equilibrium with non-particulate product and can reform from such product if removed, e.g. by filtration. In such cases, it is appropriate and necessary for a manufacturer to make every effort to develop a formulation that minimises the presence of such particles. However,

for some products it will be difficult, if not impossible, to ensure that no such particles are present at release, or form over the product's shelf-life. As such, these visible particles are considered to be an inherent quality attribute of the drug product, which will have been characterised and tested for appropriate safety and efficacy during non-clinical and clinical studies. Assuming that the results of non-clinical and clinical studies are supportive, such intrinsic proteinaceous visible particles, when controlled within characterised limits (specifications), should not present a quality or safety concern. In view of the above, the present monograph has been revised to take account of this characteristic of some mAb products. It is hoped that this modification to the monograph will clarify the situation regarding particles in mAb products, be consistent with the current situation with such products and continue to promote the safety of mAbs approved for *in vivo* clinical use.

### Summary of changes made to the monograph

**Definition:** introduction of a requirement for preparations to be practically free from particles when examined under suitable conditions of visibility, in line with *Parenteral preparations (0520)*. It is to be noted that 'practically free' is often misinterpreted; due to human error, it is not possible to guarantee the absence of particles even if a 100 per cent visual inspection by trained operators is carried out; in addition, it is clarified that conjugated antibodies are covered by the monograph.

**Cell line producing the monoclonal antibody:** evaluation of cell line suitability using level of expression and level of glycosylation reworded to be more general; in line with ICH Q5D, introduction of the possibility to use nucleic acid testing or product analysis to demonstrate the consistency of the coding sequence of the expression construct.

**Cell banks:** concept of 'sterility' reworded to 'absence of bacterial, fungal and mycoplasmal contamination', since 'sterility' is misleading when used in the context of living organisms/cells.

**Culture and harvest:** introduction of possibility to harvest at a fixed harvest time for production at finite passage level.

**Purification:** in line with industry practice, harvests or intermediate pools may be pooled before further processing.

**Active substance:** in line with commonly used terminology, 'purified monoclonal antibody' replaced by 'active substance' and new Active substance section added; tests for product- and process-related impurities including tests for host cell-derived proteins and host cell- and vector-derived DNA moved from Final bulk to the new section and tests for appearance, identity, product-related substances and protein content added to reflect the production process. When the active substance is a conjugated or transformed antibody, appropriate testing must be performed before and after conjugation/modification.

**Final bulk:** the final bulk is the formulated active substance and may be produced from one or more batches of active substance; it is not necessarily kept as an intermediate that is subject to testing before release for further processing; it is not sterile since it is not yet sterile-filtered; the tests for bacterial endotoxins and sterility have therefore been deleted. However, the final bulk must be stored under validated conditions with respect to bioburden and stability.

**Final lot:** introduction of a requirement to sterile-filter the final bulk and of the possibility to freeze-dry the final lot, for clarification; introduction of a paragraph explaining that containers containing visible particles should be eliminated and that it should be demonstrated during development either that the process does not generate proteinaceous particles or that the process reduces the proteinaceous particle content to a low level as justified and authorised. It is stated that visual inspection is not a quality control test, even though performed at the end of the production.

**Characters:** section not to be interpreted in a strict sense as the statements are not requirements; guidance regarding visible particles deleted to avoid confusion; description of colour for both liquid preparations and freeze-dried products broadened to 'slightly coloured'.

**Appearance:** degree of opalescence (2.2.1) and degree of coloration (2.2.2) comply with limits approved for the particular products. Requirement to have preparations 'without visible particles' intentionally kept to give clear guidance to producers of mAbs that the presence of visible particles is unwanted and that appropriate formulation studies should be performed during development to find an optimal formulation; introduction of an escape clause 'unless otherwise justified and authorised' for products in cases where producers can demonstrate that it is not possible to remove all visible particles; it is to be noted that 'practically free' cannot be a pass/fail criteria in a test.

**Solubility:** section modified to conform with requirements of Appearance section.

**Osmolality:** introduction of an escape clause to give, for example, the possibility to accept lower values if the product is diluted in an isotonic solution for infusion before use.

**Purity:** techniques given as examples deleted; introduction of the possibility to omit the tests for process-related impurities if they have been carried out with satisfactory results on the active substance or on the final bulk.

**Assay:** text clarified to indicate that a suitable assay is usually a biological assay.

### Vaccines for human use (0153)

**Thermal stability:** a paragraph concerning this test has been added to this general monograph to clarify the situation regarding thermal stability testing for live attenuated vaccines, as questions from Ph. Eur. users regarding this test were frequently received. The position of the responsible Group of Experts regarding the rationale behind the thermal stability test, the test conditions and the applicability of the test is explained below.

#### Scope of the thermal stability test

The thermal stability test is required in Ph. Eur. monographs for a majority of live attenuated vaccines and is recommended for virus vectors used for gene transfer medicinal products for human use.

Thermal stability as a lot release test is a measurement of the stability of a vaccine after exposure to a temperature higher than that recommended for storage for a specified period of time. It is expressed in terms of loss in potency in comparison to the unheated vaccine.

Thermal stability should be considered as a vaccine characteristic that provides an indicator of consistency

of production in the context of lot release. The thermal stability test is not part of the real-time stability testing programme, which is designed to recommend storage conditions and to establish the shelf-life and/or the release specifications. It is also not part of the accelerated stability programme, which is aimed at determining the rate of change of vaccine properties over time as a consequence of exposure to temperatures higher than those recommended for storage.

The prerequisite for an efficient immune response to be triggered after administration of live attenuated vaccines is to have infectious/viable particles. A live attenuated vaccine is not a homogeneous product but a complex mixture of infectious/viable particles more or less weakened and non-infectious/non-viable particles. The composition of this mixture will depend on virus propagation/bacterial growth conditions and loss of infectivity/viability during the subsequent stages of the vaccine manufacturing process, such as concentration, purification, formulation and freeze-drying, when applicable. The potency assay will estimate the number of infectious/viable particles (more or less weakened) in the final product. The thermal stability test requires an additional step of incubation of the live

attenuated vaccine batch at a suitable temperature prior to the performance of the potency assay. In this context, the thermal stability test allows the quantification of the heat-sensitive weakened viral/bacterial particles. It is considered as an important tool to monitor the consistency of the manufacturing process since it may reveal unverifiable deviations during production.

#### Test conditions

The parameters selected for the thermal stability are the temperature (e.g. 37 °C) and the incubation time, depending on the particles' sensitivity to changes in temperature. The nature of the virus/bacteria, the stabilising properties of the formulation and data obtained from accelerated stability studies are taken into account to define the appropriate temperature and incubation time. Suitable conditions are indicated in individual monographs.

#### Applicability

When the thermal stability test is prescribed in a monograph for a live attenuated vaccine, it is included in the Production section under Final lot. It is not considered as a shelf-life requirement and will therefore usually not be part of the Tests section.

## DOSAGE FORMS

### Preparations for inhalation (0671)

The monograph has been revised to take account of:

- the newly elaborated general chapter 2.9.44. *Preparations for nebulisation: characterisation* (published in Supplement 7.3);

- the existence of non-pressurised metered-dose preparations for inhalation, previously and incorrectly called metered-dose nebulisers.

Requirements for the microbiological quality of preparations for nebulisation have been introduced (see also chapter 5.1.4); a number of editorial changes have been made to facilitate the interpretation of the text and improve its clarity.

## VACCINES FOR HUMAN USE

### BCG vaccine, freeze-dried (0163)

**Thermal stability:** following the revision of the general monograph *Vaccines for human use (0153)*, published in Supplement 7.3, this test has been moved to the Final lot section to monitor the lot-to-lot consistency in heat-sensitivity of bacterial particles in the product; the wording has been harmonised with that in other live attenuated vaccine monographs.

### Measles, mumps, rubella and varicella vaccine (live) (2442)

**Thermal stability:** the escape clause has been deleted since it is covered by the revised general monograph *Vaccines for human use (0153)*, published in Supplement 7.3.

### Poliomyelitis vaccine (oral) (0215)

**Thermal stability:** following the revision of the general monograph *Vaccines for human use (0153)*, published in Supplement 7.3, this test has been moved to the Final lot section to monitor the lot-to-lot consistency in heat-sensitivity of viral particles in the product; the wording has

been harmonised with that in other live attenuated vaccine monographs.

**Labelling:** the route of administration statement has been deleted, since the relevant information is given in the general monograph *Vaccines for human use (0153)*.

### Rotavirus vaccine (live, oral) (2417)

**Thermal stability:** the escape clause has been deleted since it is covered by the revised general monograph *Vaccines for human use (0153)*, published in Supplement 7.3; the wording has been harmonised with that in other live attenuated vaccine monographs.

**Labelling:** the route of administration statement has been deleted, since the relevant information is given in the general monograph *Vaccines for human use (0153)*.

### Smallpox vaccine (live) (0164)

**Thermal stability:** following the revision of the general monograph *Vaccines for human use (0153)*, published in Supplement 7.3, the wording has been harmonised with that in other live attenuated vaccine monographs.

## RADIOPHARMACEUTICAL PREPARATIONS

### **Tetra-O-acetyl-mannose triflate for radiopharmaceutical preparations (2294)**

*Specific optical rotation:* test sensitivity improved; methylene chloride replaced by acetonitrile; specifications subsequently modified.

*Melting point:* test deleted since substance decomposes.

*Impurity B:* test sensitivity improved; consumption of deuterated solvent reduced.

## HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

### **Aniseed (0262)**

*Identification B:* legend of illustration of powdered herbal drug integrated into text of Identification B.

### **Arnica flower (1391)**

*Identification B:* legend of illustration of powdered herbal drug integrated into text of Identification B; letters changed to correspond better to usual presentation.

### **Belladonna leaf (0221)**

*Identification B:* legend of illustration of powdered herbal drug integrated into text of Identification B.

### **Bitter-orange flower (1810)**

### **Lemon verbena leaf (1834)**

*Identification B:* legend of illustration of powdered herbal drug introduced into text of Identification B; letters changed to correspond better to usual presentation.

### **Liquorice dry extract for flavouring purposes (2378)**

*Ochratoxin A:* test introduced; the maximum content has been set for the pure undiluted extract to accommodate the range of extracts available containing different amounts of excipients; the quantity of any added excipients in an individual extract must therefore be taken into account when calculating this limit.

### **Liquorice ethanolic liquid extract, standardised (1536)**

### **Liquorice root (0277)**

*Assay:* calculation formula corrected; it is specified that 18 $\beta$ -glycyrrhizic acid is determined.

### **Marshmallow leaf (1856)**

### **Marshmallow root (1126)**

*Identification B:* legend of illustration of powdered herbal drug integrated into text of Identification B.

### **Ribwort plantain (1884)**

*Identification B:* legend of illustration of powdered herbal drug integrated into text of Identification B; letters changed to correspond better to the usual presentation.

### **Stramonium leaf (0246)**

*Identification B:* legend of illustration of powdered herbal drug integrated into text of Identification B.

### **Thyme oil, thymol type (1374)**

*Title:* changed to specify that the monograph only covers thyme oil of the thymol type.

*Identification:* TLC conditions improved and description of HPTLC conditions added; description of results corrected.

*Chromatographic profile:* mass units replaced by volumes in measuring liquid constituents to facilitate preparation of reference solution (a); disregard limit (reference solution (b)) added; column and temperature profile changed to improve chromatographic separation; introduction of limits for  $\alpha$ -thujene,  $\alpha$ -terpinene and carvacrol methyl ether and modification of limits for p-cymene,  $\gamma$ -terpinene, linalol, terpinen-4-ol, thymol and carvacrol to better distinguish between thyme oil of the thymol type and adulterations.

### **Yarrow (1382)**

*Identification B:* legend of illustration of powdered herbal drug introduced into text of Identification B.

## HOMEOPATHIC PREPARATIONS

### Herbal drugs for homoeopathic preparations (2045)

*Loss on drying:* statement added that the test should be carried out on a fresh plant if it is processed more than 24 h after harvesting.

*Pesticides, Heavy metals:* statements added that the tests can also be performed on the mother tincture according to the requirements of the general monograph *Mother tinctures for homoeopathic preparations (2029)*.

### Mother tinctures for homoeopathic preparations (2029)

*Pesticides:* paragraph added, in line with general monograph *Herbal drugs for homoeopathic preparations (2045)*.

*Heavy metals:* section introduced, as also proposed in general monograph *Herbal drugs for homoeopathic preparations (2045)*.

## MONOGRAPHS

### Alfadex (1487)

*Definition:* content limits widened in line with current policy for LC assays.

### Bisoprolol fumarate (1710)

*Related substances:* methods A and B replaced by a single LC procedure that is selective for all potential impurities

### Botulinum toxin type A for injection (2113)

*Bacterial seed lots:* following adoption of monograph *Botulinum toxin type B for injection (2581)*, which includes type F in the Bacterial seed lots section, monograph *Botulinum toxin type A for injection (2113)* has been modified to harmonise both texts.

### Calcifediol (1295) Calcitriol (0883)

*Related substances:* relative retentions for specified impurities and limit for unspecified impurities added, in line with current policy; disregard limit lowered to 0.05 per cent as there is no reason that justifies a higher value.

### Cellulose acetate phthalate (0314)

*Viscosity and assay:* these tests are necessary to define the intrinsic quality of the substance and are therefore placed in the mandatory part of the monograph with a cross-reference to them in the FRC section.

*Definition:* adapted accordingly.

This monograph has been approved within the framework of pharmacopoeial harmonisation.

### Cetirizine dihydrochloride (1084)

*Related substances:* *cetirizine impurity mixture CRS* replaced by *cetirizine for peak identification CRS*.

### Diprophylline (0486)

*Identification:* 2<sup>nd</sup> series deleted to avoid use of ether; Identification C in addition to IR is unnecessary and therefore deleted from 1<sup>st</sup> series; sample preparation method deleted, in line with current policy.

*Related substances:* TLC replaced by LC, reflecting impurity profiles of current batches.

*Impurities:* introduction of section describing impurities controlled by LC.

### Erythromycin (0179) Erythromycin ethylsuccinate (0274) Erythromycin stearate (0490)

*Assay:* a symmetry factor in the range of 0.8 to 1.5, as required by general chapter 2.2.46. *Chromatographic separation techniques*, is not achievable; a deviation from this requirement is allowed, maximum symmetry factor of 5 introduced.

### Fluticasone propionate (1750)

*Water:* methanol-chloroform solvent mixture replaced by methanol.

### Fusidic acid (0798)

*Identification:* introduction of a test for sodium requiring a negative result. Combination of this test and IR spectrum is considered sufficient for identification of the substance; consequently, TLC identification test deleted.

*Related substances:* revised in order to improve separation of impurities and to set more precise limits.

*Impurities:* introduction of a transparency statement.

### Homatropine methylbromide (0720)

*Identification:* 2<sup>nd</sup> identification deleted as the substance is not used in pharmacies; consequently, test C renamed test B.

*Related substances:* mobile phase revised to replace sodium heptanesulfonate monohydrate by sodium pentanesulfonate monohydrate; reference solution for identification of specified impurity A introduced; peak-to-valley ratio added to ensure a good separation of impurity A from homatropine methylbromide; symmetry factor requirement deleted; specifications updated as impurities C, D, E and F considered as other detectable impurities.

**Human antithrombin III concentrate (0878)**

*Test for solubility:* colour of reconstituted solution modified to take into account possible influence of stabiliser.

**Lactose, anhydrous (1061)**

Revision signed off by PDG (Pharmacopoeial Discussion Group) within the framework of pharmacopoeial harmonisation.

*Appearance of solution, Absorbance:* common solution (solution S) prescribed; specified to allow solution to cool before examination.

*Water:* sample weight increased to 1.00 g.

*$\alpha$ -Lactose and  $\beta$ -lactose:* capillary column prescribed instead of packed column that is no longer available; derivatisation procedure optimised and use of cold on-column injection system introduced as alternative to classical injection port.

**Levothyroxine sodium (0401)**

*Appearance:* slightly hygroscopic character of powder added.

*Identification:* tests A, C and D deleted; 2<sup>nd</sup> identification series not relevant for this substance.

*Related substances:* LC replaced by more suitable LC method; list of specified impurities added with limits based on recent batch data.

*Loss on drying:* replaced by test for water.

*Assay:* same LC used as in test for related substances.

**Lincomycin hydrochloride (0583)**

*Definition:* lincomycin B integrated into definition of substance since it has been proven to participate fully in the antimicrobial activity.

*Identification:* 2<sup>nd</sup> series deleted since it had no practical application.

*Related substances:* test introduced and transparency statement added.

*Assay:* GC assay replaced by LC.

**Magnesium chloride 4.5-hydrate (1341)**

*Definition:* content expressed on an 'as-is' basis to overcome out-of-specification results of the assay due to the poor reproducibility of the water determination.

**Methyldopa (0045)**

*Content:* symmetrical limits prescribed in line with current policy.

*Enantiomeric purity:* racemic methyldopa reagent replaced by *racemic methyldopa* CRS following availability problems.

*Heavy metals:* method C replaced by method F in line with current policy; limit decreased (10 ppm) in view of daily intake (more than 0.5 g/day) and duration of treatment (more than 30 days).

**Metoprolol succinate (1448)**

*Related substances:* impurity C indicated as specified impurity; explicit criterion for unspecified impurities introduced.

**Metoprolol tartrate (1028)**

*Related substances:* impurities indicated as specified impurities or other detectable impurities; explicit criterion for unspecified impurities introduced; relative retentions of specified impurities introduced.

**Miconazole nitrate (0513)**

*Related substances:* explicit acceptance criterion for unspecified impurities introduced, in line with general monograph *Substances for pharmaceutical use (2034)*; relative retentions of specified impurities now given.

**Nitrofurantoin (1135)**

*Identification B:* sample preparation method no longer specified in line with current policy.

*Related substances:* use of *nitrofurantoin* for *peak identification* CRS introduced, in line with current impurity policy; paragraph for identification of impurities A and B and relative retentions of impurities introduced; explicit acceptance criterion for unspecified impurities introduced; disregard limit adapted to the requirements of general monograph *Substances for pharmaceutical use (2034)* (maximum daily dose < 2 g/day).

**Oxaliplatin (2017)**

*Impurity D:* limit raised to 0.15 per cent.

*Related substances:* preparation of certain solutions revised to minimise quantities of CRSs used; limits for impurities A, B and C and sum of unspecified impurities raised to 0.15 per cent; limit for unspecified impurities revised to 0.10 per cent.

**Pimozide (1254)**

*Related substances:* explicit criterion for unspecified impurities introduced, in line with general monograph *Substances for pharmaceutical use (2034)*; relative retentions of specified impurities now given.

**Pramipexole dihydrochloride monohydrate (2416)**

*Water:* range of limits revised.

**Prilocaine (1362)**

*Identification:* 2<sup>nd</sup> series deleted to avoid use of ether and because substance is not used in pharmacies; description of sample preparation modified to avoid use of ether.

*Solution S:* following deletion of test for optical rotation, solution S deleted and specific description introduced for solution to be used in test for appearance of solution.

*Optical rotation:* test deleted.

*Related substances:* test revised in order to improve separation of all impurities, to cover all impurities (including impurity B) with a single test and to update limits in view of current batch data.

**Heavy metals:** method C replaced by method H in line with current policy.

**Assay:** preparation of solution modified to reduce volume of titrant, in line with Technical Guide.

**Impurities:** impurities A, C, D, E and F moved to Other detectable impurities.

### **Prilocaine hydrochloride (1363)**

**Identification C:** ether replaced by a safer solvent.

**Optical rotation:** test deleted.

**Related substances:** test revised in order to improve separation of all impurities, to cover all impurities (including impurity B) with a single test and to update limits in view of current batch data.

**Heavy metals:** method C replaced by method H in line with current policy.

**Assay:** preparation of solution modified to reduce volume of titrant, in line with Technical Guide.

**Impurities:** impurities A, C, D, E and F moved to Other detectable impurities.

### **Sodium ethyl parahydroxybenzoate (2134)**

**Title:** English title corrected to harmonise with *Sodium methyl parahydroxybenzoate (1262)* and *Sodium propyl parahydroxybenzoate (1263)*.

**Definition:** content limits modified as the assay is now performed by LC.

**Identification:** test A deleted from 1<sup>st</sup> identification series because test B and former test E are sufficient; former test D

deleted from 2<sup>nd</sup> identification series, test E consequently renamed D.

**Related substances:** TLC replaced by LC in line with current policy.

**Heavy metals:** test modified in line with current general chapter.

**Assay:** titration replaced by LC used in test for related substances.

**Impurities:** impurity A is specified.

### **Sodium fusidate (0848)**

**Identification:** in identification A (infrared absorption spectrophotometry), comparison with a reference spectrum of fusidic acid after conversion of sodium fusidate to fusidic acid has been replaced by direct comparison with *sodium fusidate CRS*; identification B (thin-layer chromatography) has been deleted and consequently identification C renamed B.

**Related substances:** revised in order to improve separation of impurities and to set more precise limits.

**Impurities:** introduction of a transparency statement.

### **Sufentanil (1569)**

#### **Sufentanil citrate (1269)**

#### **Terconazole (1270)**

**Related substances:** explicit acceptance criterion for unspecified impurities introduced, in line with general monograph *Substances for pharmaceutical use (2034)*; relative retentions of specified impurities now given.