QC SPECIFICATION PART 2

Liquid dosage form for oral use (& powder for reconstitution)

Uniformity of dosage units

Microbial limits

Antimicrobial preservative effectiveness

Dissolution (Suspension)

Redispersibility (time required)

pH

Antimicrobial/Antioxidative preservative content

Extractables

Particle size distribution

Water content (powder for reconstitution)

Parenteral drug products

Uniformity of dosage units (powder for reconstitution)

Sterility

Particulate matter (visible/subvisible particulates)

Antimicrobial/Antioxidant preservative content

Extractables

Particle size distribution (suspensions)

Reconstitution time

pH

Endotoxins

Water content (powders for reconstitution)

Antimicrobial preservative effectiveness

Osmolarity

Redispersibility (suspension)

Oral solid dosage form

Dissolution

Disintegration (dissolution > 80 % in 15 min at pH 1.2 – 6.8)

Hardness/Friability

Uniformity of dosage units

Water content

Microbial limits

Cream, gel, lotion, ointments

Minimum fill

Microbial limit

pH

Syrup, suspension (oral suspension)

Deliverable volume

Microbial limit

Preservative effectiveness

pH

Minimum Fill

⟨755⟩ Minimum Fill

SCOPE

The following tests and acceptance criteria apply to articles such as creams, gels, lotions, ointments, pastes, powders, aerosols, foams, and sprays that are packaged in containers. To minimize the impact of entrained air for products labeled by volume, the fill determination is performed by mass from which the volume is calculated by use of the density of the preparation.

Minimum Fill

ยาที่ไม่ใช่ Aerosols

1) Containers labeled by weight

2) Containers labeled by volume

Stage	Number tested	Acceptance criteria
1	10	Labeled amount $\leq$ 60 g หรือ 60 mL ค่าเฉลี่ยต้องไม่น้อยกว่าที่ระบุทุกภาชนะต้องไม่น้อยกว่า 90 % ที่ระบุ
		Labeled amount > 60 g หรือ 60 mL ค่าเฉลี่ยต้องไม่น้อยกว่าที่ระบุและทุกภาชนะต้องไม่น้อยกว่า 95 % ที่ระบุ
2	20 (รวมเป็น 30)	ค่าเฉลี่ยต้องไม่น้อยกว่าที่ระบุและมีได้ไม่เกิน 1 ภาชนะที่ไม่ผ่านเกณฑ์

Minimum Fill

ยาจำพวก Aerosols หรือ Sprays

เกณฑ์การยอมรับ

น้ำหนักทุกภาชนะต้องไม่ต่ำกว่าที่ระบุ

Water Determination

1. Method I (Titrimetric)
   - Method Ia (Direct titration)
   - Method Ib (Residual Titration)
   - Method Ic (Coulometric Titration)

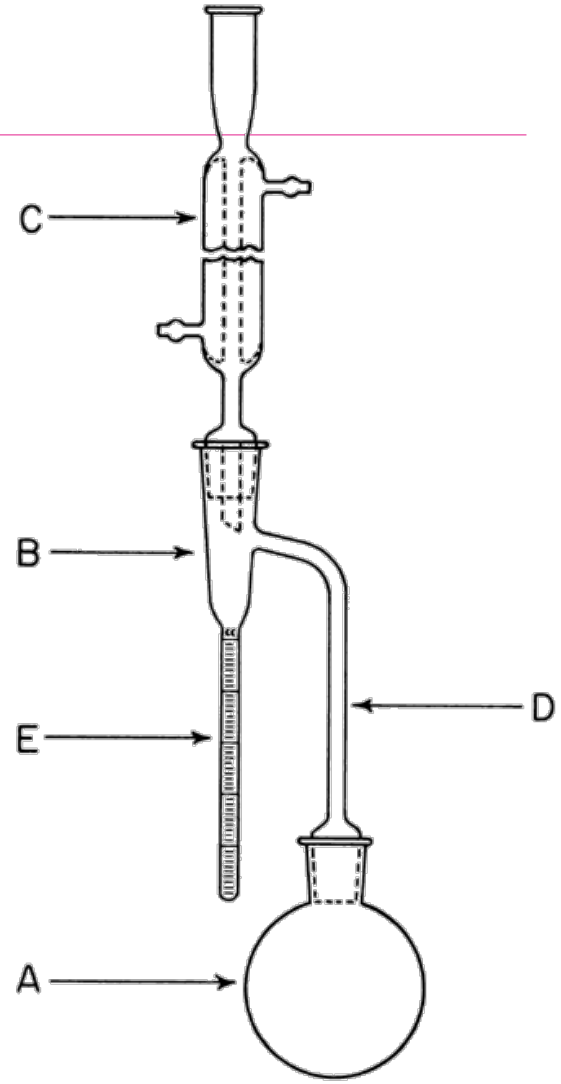
$$H_2O + SO_2 + I_2 \longrightarrow 2HI + SO_3$$

$$SO_3 + C_5H_5N \longrightarrow C_5H_5N{\cdot}SO_3$$

$$HI + C_5H_5N \longrightarrow C_5H_5N{\cdot}HI$$

2. Method II (Azeotropic-Toluene Distillation)

3. Method III (Gravimetric)



Loss on Drying

หาปริมาณของสารทุกชนิดที่สามารถระเหยออกไปได้ภายใต้สภาวะที่กำหนด (อุณหภูมิและเวลาที่กำหนด)

“Dry to constant weight” = อบซ้ำจนกระทั่งน้ำหนัก 2 ครั้งสุดท้ายต่างกันไม่เกิน 0.50 มิลลิกรัมต่อกรัมของสารที่นำมาอบ

$$\% \text{ Loss on drying} = \frac{\text{น้ำหนักยาก่อนการทดสอบ} - \text{น้ำหนักยาหลังการทดสอบ}}{\text{น้ำหนักยาก่อนการทดสอบ}} \times 100$$

Deliverable volume

The following tests are designed to provide assurance that oral solutions and suspensions will, when transferred from the original container, deliver the volume of dosage form that is declared on the label of the article. These tests are applicable to products labelled to contain not more than 250 ml, whether supplied as liquid preparations or liquid preparations that are constituted from solids upon the addition of a designated volume of a specific diluent. They are not required for an article packaged in single-unit containers when the monograph includes “Uniformity of Dosage Units” (Appendix 4.28).

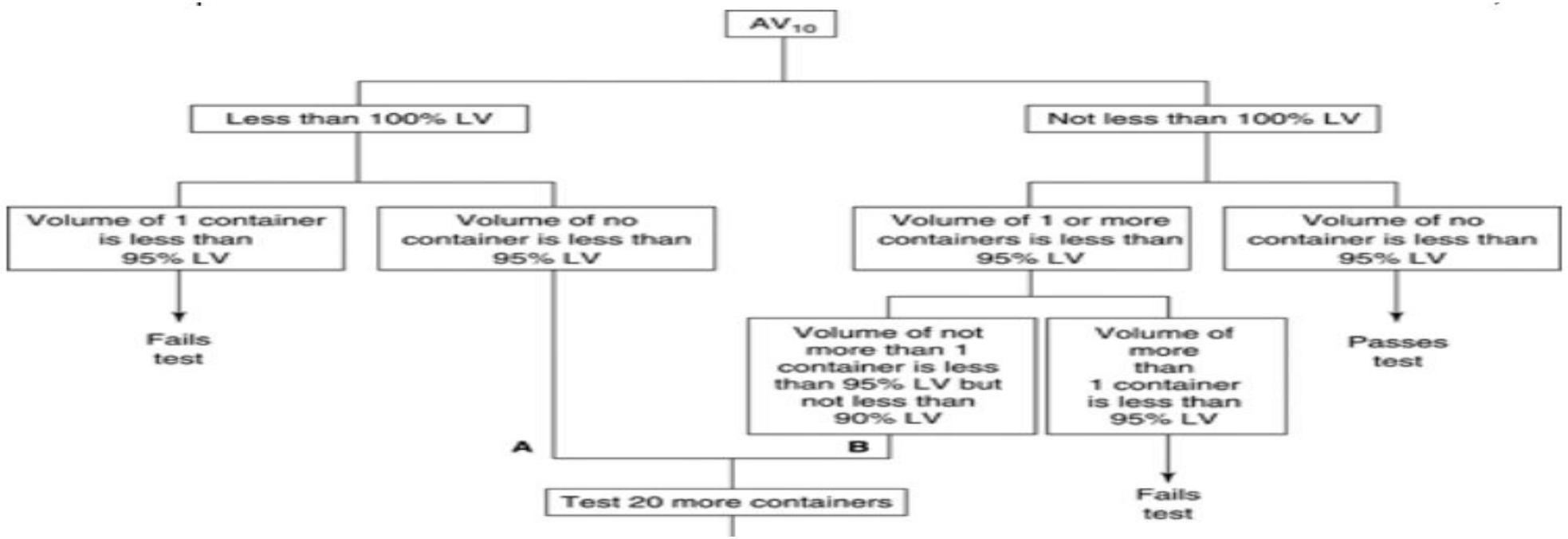
Deliverable volume

Multiple-unit container

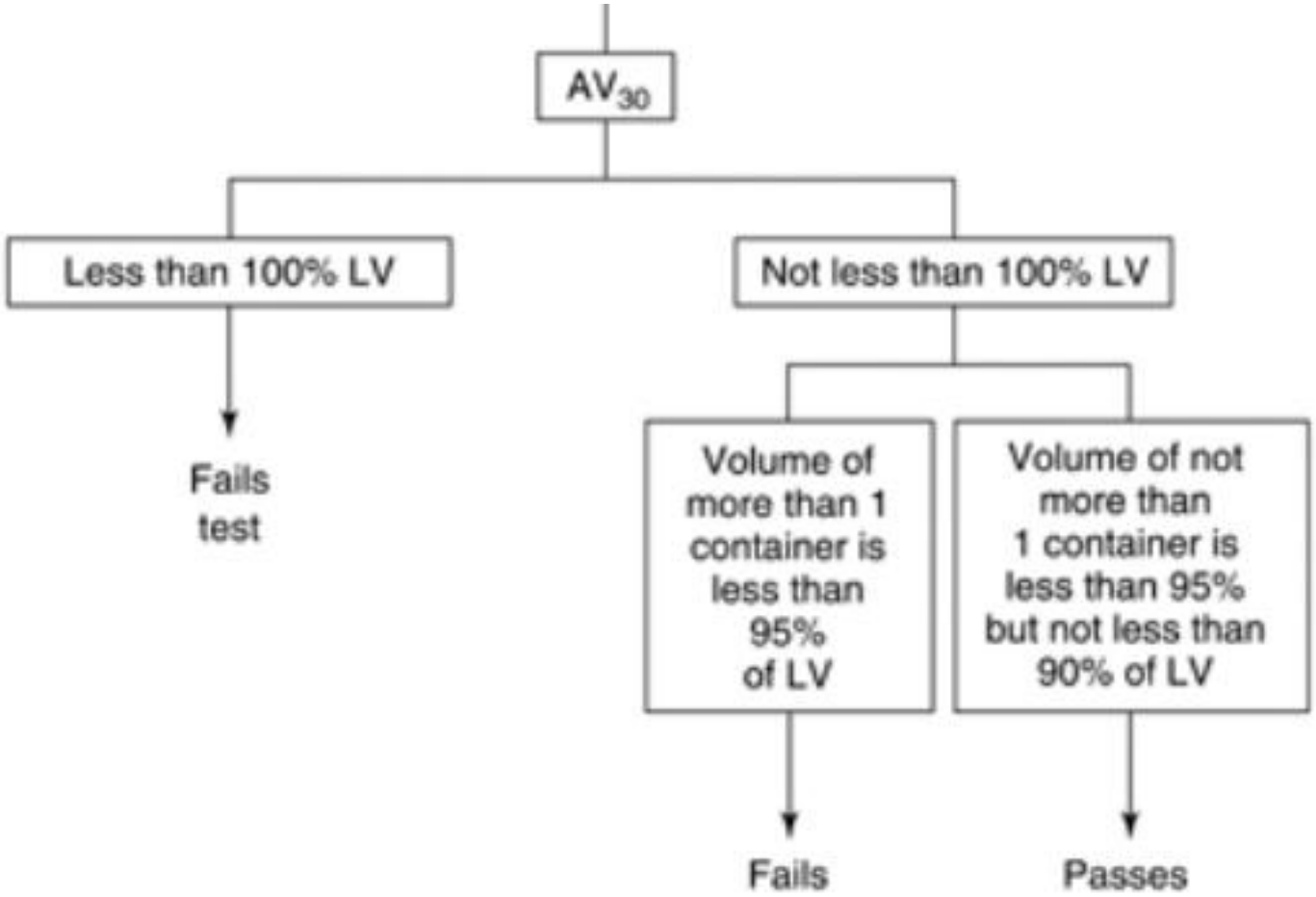
AL_{10} (10 ขวด) = ค่าเฉลี่ยทั้ง 10 ขวด ไม่ต่ำกว่า 100 % และไม่มีขวดไหนน้อยกว่า 95 %

หากไม่ผ่านเงื่อนไขใดเงื่อนไขหนึ่ง (หากไม่ผ่านทั้งสองเงื่อนไขถือว่า Fail)

ให้สุ่มเพิ่มอีก 20 ขวด (รวมเป็น 30 ขวด) แล้วใช้เกณฑ์ดังนี้



Deliverable volume

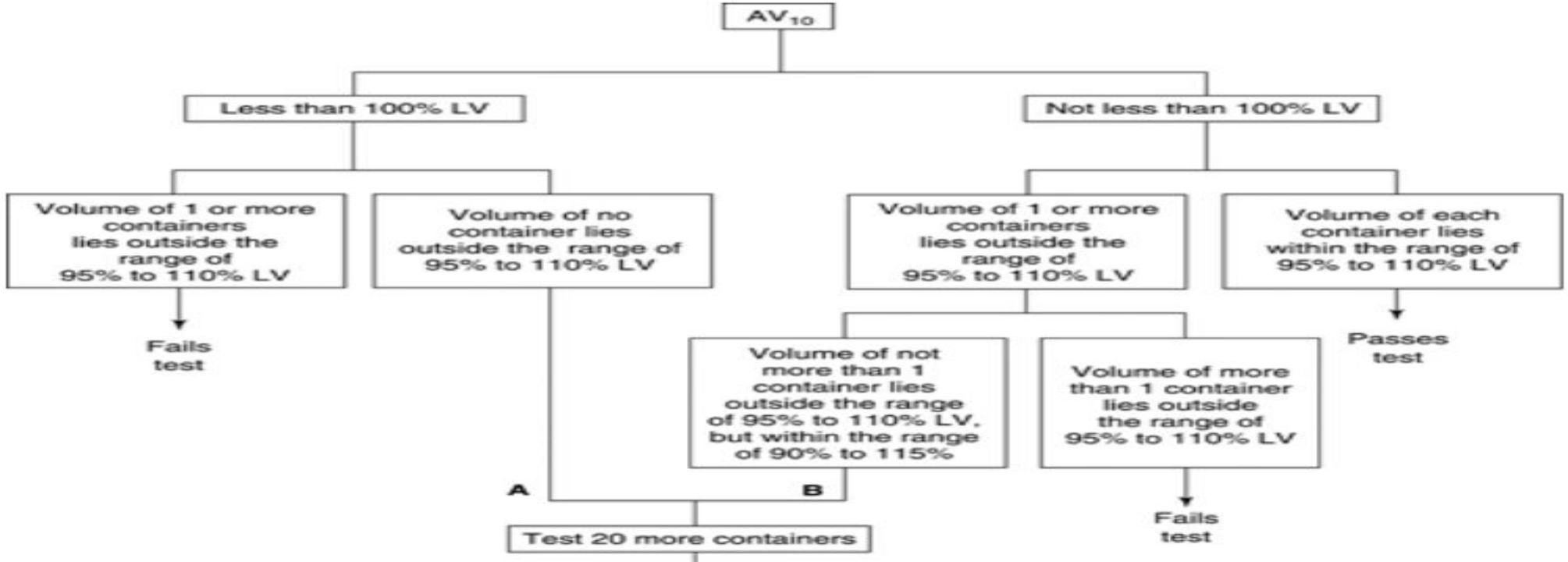


Deliverable volume

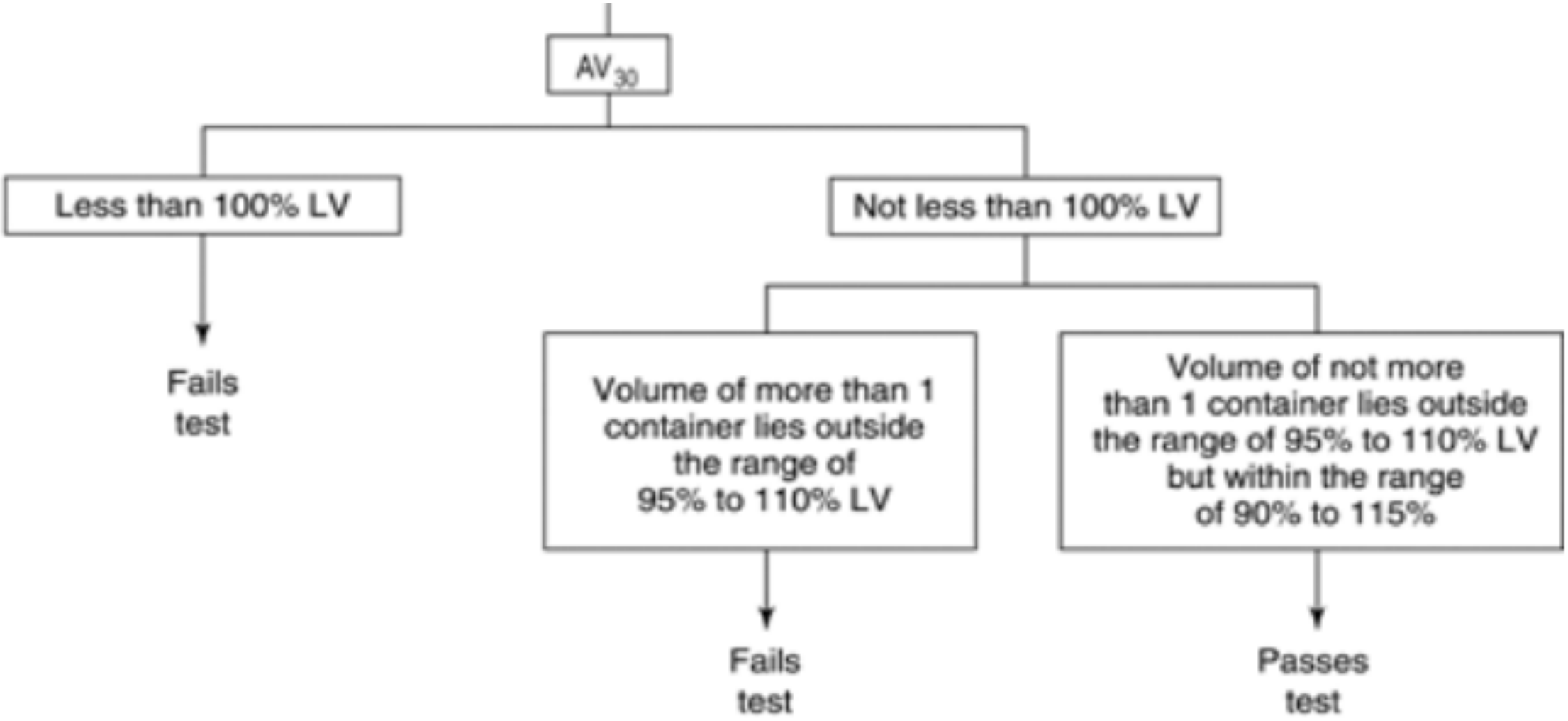
Single-unit container

AL_{10} (10 ขวด) = ค่าเฉลี่ยทั้ง 10 ขวด ไม่ต่ำกว่า 100 % และไม่มีขวดไหนได้เกินช่วง 95 – 110 % ของปริมาณที่กำหนดไว้ในฉลาก

หากไม่ผ่านเงื่อนไขใดเงื่อนไขหนึ่ง (หากไม่ผ่านทั้งสองเงื่อนไขถือว่า Fail) ให้สุ่มเพิ่มมาอีก 20 ขวด (รวม 30 ขวด) แล้วใช้เกณฑ์ดังต่อไปนี้



Deliverable volume



คำจำกัดความที่เกี่ยวข้องกับ Impurity

Concomitant components (existing or happening together)

Proposed Definitions (continued)

- **Concomitant component:** A minor component of an excipient that accompanies the nominal component which is identified either in the title or definition of a monograph. Concomitant components are characteristic of many excipients and are not considered to be impurities if there is no negative impact on drug products. Some but not all concomitant components are defined or specified in excipient monographs. Added substances are not considered concomitant components. (Any component that can be considered a toxic impurity because of significant undesirable biological effect is not considered to be a concomitant component.)

คำจำกัดความที่เกี่ยวข้องกับ Impurity

Foreign substances (extraneous contaminants)

"Introduced by contamination or adulteration, are not consequences of the synthesis or preparation of compendial articles and thus cannot be anticipated when monograph tests and assays are selected. Examples of foreign substance include or a pesticide in an oral liquid analgesic.

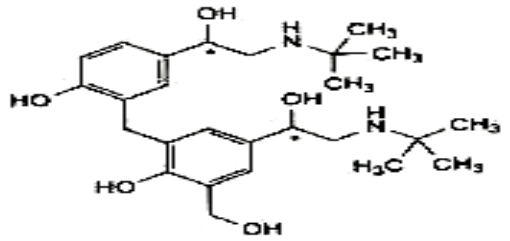
Allowance is made in this pharmacopoeia for the detection of foreign substances by unofficial methods."

คำจำกัดความที่เกี่ยวข้องกับ Impurity

Related substances	**สารที่มีโครงสร้างทางเคมีคล้ายคลึงกับโครงสร้างของตัวยาสำคัญ อาจทราบหรือไม่ทราบสูตรโครงสร้างทางเคมี**
Specified impurities	สารเจือปนที่แสดงในข้อกำหนดคุณลักษณะของวัตถุดิบตัวยาสำคัญ ซึ่งมีเกณฑ์การยอมรับที่เฉพาะเจาะจงต่อตัวยานั้นๆ อาจทราบหรือไม่ทราบสูตรโครงสร้างทางเคมีของสารได้
Unidentified impurities	สารเจือปนที่ไม่ทราบสูตรโครงสร้างทางเคมี สามารถบ่งชี้ได้โดยการใช้การเปรียบเทียบ retention time กับ retention time ของสารมาตรฐาน (relative retention time)
Unspecified impurities	สารเจือปนที่ใช้เกณฑ์การยอมรับโดยทั่วไป ซึ่งไม่มีเกณฑ์การยอมรับที่เฉพาะเจาะจงของตัวยาสำคัญนั้นๆ

Impurities in new drug substances

Organic impurities	Inorganic impurities	Residual solvents
Can be identified or unidentified, volatile or non-volatile, and include	Normally known and identified and include	Can be both inorganic or organic liquids used as vehicles for the preparation of solutions or suspensions in the synthesis of a new drug substance.
• Starting materials • By-products • Intermediates • Degradation products • Reagents, ligands and catalysts	• Reagents, ligands and catalysts • Heavy metals or other residual metals • Inorganic salts • Other materials (e.g. filter aids, charcoal)	



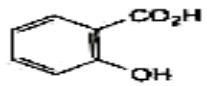
N. 2-[(1,1-dimethylethyl)amino]-1-[3-[[5-[2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-2-hydroxyphenyl]methyl]-4-hydroxy-5-(hydroxymethyl)phenyl]ethanol,

O. unknown structure.

Ph Eur

Salicylic Acid

(Ph. Eur. monograph 0366)



$C_7H_6O_3$ 138.1 *69-72-7*

Action and use
Keratolytic.

Preparations
Coal Tar and Salicylic Acid Ointment
Dithranol and Salicylic Acid Ointment
Salicylic Acid Collodion
Salicylic Acid Cream
Salicylic Acid Ointment
Zinc and Salicylic Acid Paste

Ph Eur

DEFINITION
2-Hydroxybenzenecarboxylic acid.

Content
99.0 per cent to 100.5 per cent (dried substance).

TESTS

Solution S
Dissolve 2.5 g in 50 mL of boiling *distilled water R*, cool and filter.

Appearance of solution
The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 1 g in 10 mL of *ethanol (96 per cent) R*.

Related substances
Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.50 g of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 10 mg of *phenol R* (impurity C) in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *salicylic acid impurity B CRS* in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (c) Dissolve 50 mg of *4-hydroxybenzoic acid R* (impurity A) in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (d) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase.

Reference solution (e) Dilute a mixture of 1.0 mL of each of reference solutions (a), (b) and (c) to 10.0 mL with the mobile phase.

Reference solution (f) Dilute a mixture of 0.1 mL of each of reference solutions (a), (b) and (c) to 10.0 mL with the mobile phase.

Column:
— *size*: $l = 0.15$ m, $Ø = 4.6$ mm;
— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *glacial acetic acid R, methanol R, water R* (1:40:60 *V/V/V*).

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 270 nm.

Injection 10 µL of the test solution and reference solutions (d), (e) and (f).

Identification of impurities Use the chromatogram obtained with reference solution (e) to identify the peaks due to

CHARACTERS

Appearance

White or almost white, crystalline powder or white or colourless, acicular crystals.

Solubility

Slightly soluble in water, freely soluble in ethanol (96 per cent), sparingly soluble in methylene chloride.

IDENTIFICATION

First identification: A, B.

Second identification: A, C.

A. Melting point (*2.2.14*): 158 °C to 161 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *salicylic acid CRS.*

C. Dissolve about 30 mg in 5 mL of *0.05 M sodium hydroxide*, neutralise if necessary and dilute to 20 mL with *water R*. 1 mL of the solution gives reaction (a) of salicylates (*2.3.1*).

impurities A, B and C.

Relative retention With reference to impurity C (retention time = about 9.5 min): impurity A = about 0.6; impurity B = about 0.8.

System suitability Reference solution (e):

— the 3rd peak in the chromatogram corresponds to the peak due to impurity C in the chromatogram obtained with reference solution (d);

— *resolution*: minimum 1.0 between the peaks due to impurities B and C; if necessary, adjust the quantity of acetic acid in the mobile phase.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.1 per cent);

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.05 per cent);

— *impurity C*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.02 per cent);
— *unspecified impurities*: for each impurity, not more than the area of the peak due to impurity B in the chromatogram obtained with reference solution (f) (0.05 per cent);
— *total*: not more than twice the area of the peak due to impurity A in the chromatogram obtained with reference solution (f) (0.2 per cent);
— *disregard limit*: 0.3 times the area of the peak due to impurity A in the chromatogram obtained with reference solution (f) (0.03 per cent). Do not disregard the peak due to impurity C.

Chlorides (2.4.4)
Maximum 100 ppm.
Dilute 10 mL of solution S to 15 mL with *water R*.

Sulfates
Maximum 200 ppm.
Dissolve 1.0 g in 5 mL of *dimethylformamide R* and add 4 mL of *water R*. Mix thoroughly. Add 0.2 mL of *dilute hydrochloric acid R* and 0.5 mL of a 25 per cent *m/m* solution of *barium chloride R*. After 15 min any opalescence in the solution is not more intense than that in a standard prepared as follows: to 2 mL of *sulfate standard solution (100 ppm SO_4) R* add 0.2 mL of *dilute hydrochloric acid R*, 0.5 mL of a 25 per cent *m/m* solution of *barium chloride R*, 3 mL of *water R* and 5 mL of *dimethylformamide R*.

Loss on drying (2.2.32)

water *R* and 5 mL of dimethylformamide *R*.

Loss on drying (2.2.32)
Maximum 0.5 per cent, determined on 1.000 g by drying in a desiccator.

Sulfated ash (2.4.14)
Maximum 0.1 per cent, determined on 2.0 g.

ASSAY
Dissolve 0.120 g in 30 mL of *ethanol (96 per cent) R* and add 20 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, using 0.1 mL of *phenol red solution R* as indicator.
1 mL of *0.1 M sodium hydroxide* is equivalent to 13.81 mg of $C_7H_6O_3$.

STORAGE
Protected from light.

IMPURITIES
Specified impurities *A, B, C.*

A. 4-hydroxybenzoic acid,

B. 4-hydroxyisophthalic acid,

C. phenol.

Inorganic Impurities

Heavy metal <231> ตัดออกไปเรียบร้อยแล้ว

USP: Elemental Impurities-Limits <232>, Elemental Impurities-Procedure <233>

Residue on ignition <281>

Atomic absorption spectrophotometer

Inductively Coupled Plasma (ICP-OES, ICP-AES)

Inductively Coupled Plasma - Mass Spectrometer (ICP-MS)

Residual solvents

Class 1 solvents: Solvents to be avoided

Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.

Class 2 solvents: Solvents to be limited

Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity.

Solvents suspected of other significant but reversible toxicities.

Class 3 solvents: Solvents with low toxic potential

Solvents with low toxic potential to man; no health-based exposure limit is needed. Class 3 solvents have PDEs of 50 mg or more per day.

Residual solvent

Class 1 solvents (Solvent to be avoided)

TABLE 1. Class 1 solvents in pharmaceutical products (solvents that should be avoided).

Solvent	*Concentration limit (ppm)*	*Concern*
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethene	8	Toxic
1,1,1-Trichloroethane	1500	Environmental hazard

Residual solvent

Class 2 solvents (Solvent to be limited)

TABLE 2. Class 2 solvents in pharmaceutical products.

Solvent	*PDE (mg/day)*	*Concentration limit (ppm)*
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cumene[1]	0.7	70
Cyclohexane	38.8	3880
Cyclopentyl methyl ether[2]	15.0	1500
1,2-Dichloroethene	18.7	1870
Dichloromethane	6.0	600
1,2-Dimethoxyethane	1.0	100
N,N-Dimethylacetamide	10.9	1090
N,N-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethyleneglycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3000
2-Methoxyethanol	0.5	50
Methylbutyl ketone	0.5	50
Methylcyclohexane	11.8	1180
Methylisobutylketone[3]	45	4500
N-Methylpyrrolidone[4]	5.3	530

Residual solvent

Class 3 solvents (Solvent with low toxic potential)

TABLE 3. Class 3 solvents which should be limited by GMP or other quality-based requirements.

Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethyl ketone
tert-Butylmethyl ether	2-Methyl-1-propanol
Dimethyl sulfoxide	2-Methyltetrahydrofuran[7]

การรายงานค่า

ATTACHMENT 1
Thresholds

Maximum Daily Dose[1]	Reporting Threshold[2,3]	Identification Threshold[3]	Qualification Threshold[3]
≤ 2g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
> 2g/day	0.03%	0.05%	0.05%

ตัวอย่างการรายงานค่า

Example 1: **0.5 g Maximum Daily Dose**

Reporting threshold = 0.05%
Identification threshold = 0.10%
Qualification threshold = 0.15%

"Raw" Result (%)	Reported Result (%) Reporting threshold =0.05%	Calculated Total Daily Intake (TDI) (mg) of the impurity (rounded result in mg)	Action	
			Identification (Threshold 0.10% exceeded?)	Qualification (Threshold 0.15% exceeded?)
0.044	Not reported	0.2	None	None
0.0963	0.10	0.5	None	None
0.12	0.12[1)]	0.6	Yes	None[1)]
0.1649	0.16[1)]	0.8	Yes	Yes[1)]

ตัวอย่างการรายงานค่า

Example 2: 0.8 g Maximum Daily Dose

Reporting threshold = 0.05%
Identification threshold = 0.10%
Qualification threshold = 1.0 mg TDI

"Raw" Result (%)	Reported Result (%) Reporting threshold =0.05%	Calculated Total Daily Intake (TDI) (mg) of the impurity (rounded result in mg)	Action	
			Identification (Threshold 0.10% exceeded?)	Qualification (Threshold 1.0 mg TDI exceeded?)
0.066	0.07	0.6	None	None
0.124	0.12	1.0	yes	None[1)2)]
0.143	0.14	1.1	yes	Yes[1)]

Impurities in new drug products

1.3 Scope of the guideline

This guideline addresses only those impurities in new drug products classified as degradation products of the drug substance or reaction products of the drug substance with an excipient and/or immediate container closure system (collectively referred to as "degradation products" in this guideline). Generally, impurities present in the new drug substance need not be monitored or specified in the new drug product unless they are also degradation products (see ICH Q6A guideline on specifications).

Impurities arising from excipients present in the new drug product or extracted or leached from the container closure system are not covered by this guideline. This guideline also does not apply to new drug products used during the clinical research stages of development. The following types of products are not covered in this guideline: biological/biotechnological products, peptides, oligonucleotides, radiopharmaceuticals, fermentation products and semi-synthetic products derived therefrom, herbal products, and crude products of animal or plant origin. Also excluded from this document are: (1) extraneous contaminants that should not occur in new drug products and are more appropriately addressed as good manufacturing practice (GMP) issues, (2) polymorphic forms, and (3) enantiomeric impurities.

การรายงานค่า

Attachment 1: Thresholds for Degradation Products in New Drug Products

Reporting Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
≤ 1 g	0.1%
> 1 g	0.05%

Identification Thresholds

Maximum Daily Dose[1]	Threshold[2, 3]
< 1 mg	1.0% or 5 µg TDI, whichever is lower
1 mg - 10 mg	0.5% or 20 µg TDI, whichever is lower
>10 mg - 2 g	0.2% or 2 mg TDI, whichever is lower
> 2 g	0.10%

Qualification Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
< 10 mg	1.0% or 50 µg TDI, whichever is lower
10 mg - 100 mg	0.5% or 200 µg TDI, whichever is lower
>100 mg - 2 g	0.2% or 3 mg TDI, whichever is lower
> 2 g	0.15%

Notes on Attachment 1

1 The amount of drug substance administered per day

2 Thresholds for degradation products are expressed either as a percentage of the drug substance or as total daily intake (TDI) of the degradation product. Lower thresholds can be appropriate if the degradation product is unusually toxic.

3 Higher thresholds should be scientifically justified.

ตัวอย่างการแปลผล

Example 1: 50 mg Maximum Daily Dose

Reporting threshold: 0.1%
Identification threshold: 0.2%
Qualification threshold: 200 µg

'Raw' Result (%)	Reported Result (%) (Reporting Threshold = 0.1%)	Total Daily Intake (TDI) of the Degradation Product (rounded result in µg)	Action	
			Identification Threshold 0.2% exceeded?	Qualification Threshold 200 µg TDI exceeded?
0.04	Not reported	20	None	None
0.2143	0.2	100	None	None
0.349	0.3[1]	150	Yes	None[1]
0.550	0.6[1]	300	Yes	Yes[1]

ข้อสอบเสริม

ชุด A ข้อ 20.

ข้อสอบเสริม

สารปนเปื้อนใดที่ไม่ได้มาจากธรรมชาติหรือกระบวนการผลิตหรือสังเคราะห์

A. Related substance

B. Foreign substance

C. Ordinary impurities

D. Inorganic impurities

E. Residual solvents