

IPC-USP 7th ANNUAL SCIENTIFIC MEETING 2008



**INORGANIC IMPURITIES
- HEAVY METALS
INDUSTRY
PERSPECTIVE**

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OVERVIEW

- **USP – Definition and Discussion.**
- **Different Pharmacopieas methods ,applications and limitations.**
- **Setting limits and selection of methods.**
- **Alternate approaches.**
- **Lateral guidance.**
- **Harmonisation issues.**
- **Industry expectations.**

USP <231> – DEFINITION

The content of metallic impurities that are coloured by sulfide ion, under the specified test conditions, does not exceed the heavy metals limit Specified (as lead) in the test substance.

METALS- RESPOND TO THIS TEST

USP SPECIFIED						
S. No	Name of the Metal	Symbol	S. No	Name of the Metal	Symbol	Limits
1	Lead	Pb	6	Tin	Sn	Not more than 20ppm
2	Mercury	Hg	7	Cadmium	Cd	
3	Bismuth	Bi	8	Silver	Ag	
4	Arsenic	As	9	Copper	Cu	
5	Antimony	Sb	10	Molybdenum	Mo	

Ph.Eur Specified			
11	Vanadium	V	Not more than 20 ppm (Adding 10 elements above)
12	Palladium	Pd	
13	Platinum	Pt	
14	Gold	Au	
15	Ruthenium	Ru	

HISTORICAL PROSPECTIVE

- 1905 -Inclusion heavy metals in **USP**.
- 1942 –Lead standard and mild acidic conditions.
- **Lead & Copper** - major contaminants in those days are detected undoubtedly by this test.
- **Iron, Chromium, Nickel and Mercury** which are major probable contaminates at current are out of scope.

SOURCES OF HEAVY METALS

➤ Raw materials.

➤ Process aids.

Catalysts – Known special tests E.g.: Palladium content in Ramipril.

➤ Processing equipment.

with increased GMP awareness and scientific approaches the risk of contamination thru process equipment is very minimal.

Material	Chemical composition in %					
	Carbon	Manganese	Silicon	Nickel	Chromium	Molybdenum
SS316	0.039	1.16	0.4	10.39	16.42	2.13

CASE STUDY

FDA STUDY IN 2005

- **Lead content in 27 pharmaceutical products (OTC/Prescription / several dosage forms and strengths) using ICP-MS.**
- **Results: Most of the products lead < 20ppb.**
- **4 products showed elevated lead levels, the highest of 500 ppb.**
- **Products containing calcium and other metals are especially prone to lead contamination.**

POINTS TO PONDER

- Heavy metals test - a Legacy ?
- General marker of Quality ..
- Blanket limit test for Toxic metals not acceptable and non specific for some metals ..
- Alternate methods available..
- Thinking beyond 10 or 15 metals...
- Technological overkill of simple old methods..

PRINCIPLE

- Detected by the precipitation at pH 3.5 in the form of dark-colored sulphides through action of sulphide ions or reagents capable of producing them.
- Comparison is made with a standard containing a known quantity of lead.

METHODS SUMMARY USP- 3 METHODS

USP Method-I Eg:-Stavudine - 0.002%.

Substances that yield clear, colorless preparations under the specified test conditions. Monitor Used.

USP Method-II Eg:- Nevirapine - 0.001%

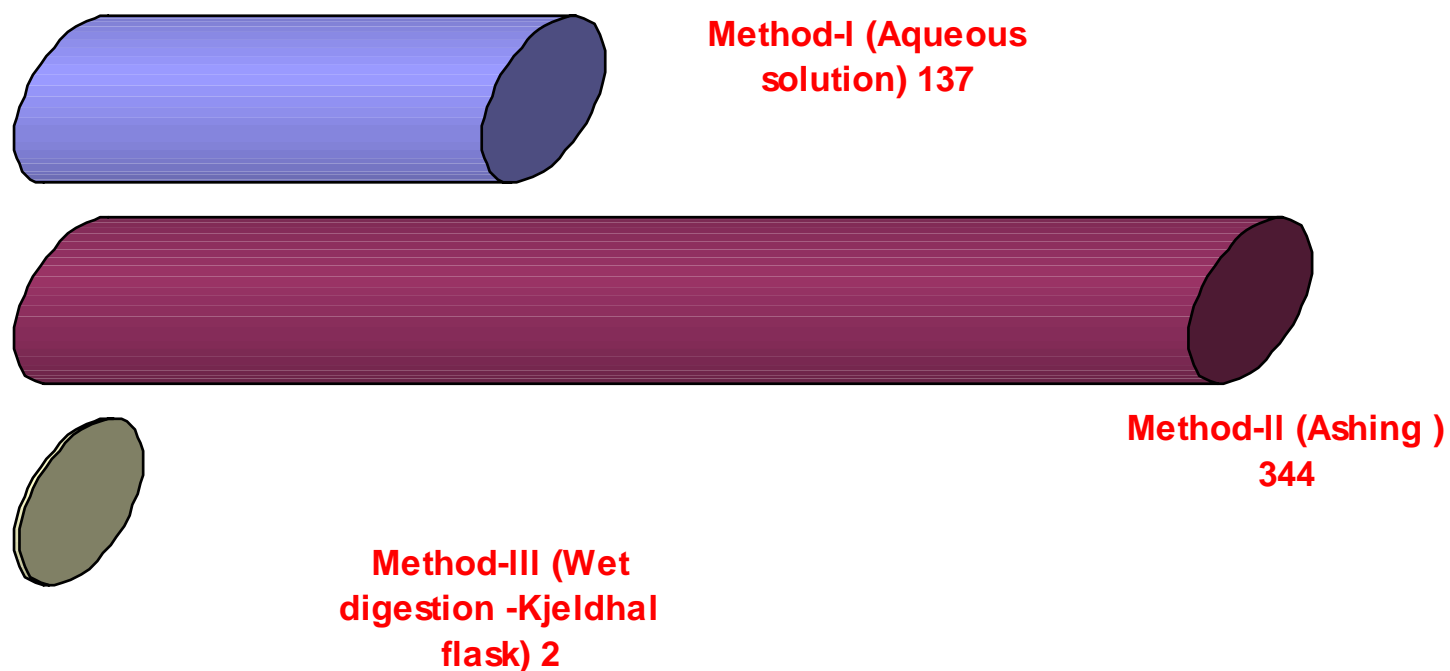
Used for substances that do not yield clear, colorless preparations by Method I, This method does not recover mercury.

USP Method-III Eg:- Alendronate sodium -0.001%

A wet-digestion method, is used only in those cases where neither Method I nor Method II can be used. Monitor Used.

METHODS SUMMARY USP – 3 METHODS

Number of Monographs



METHODS SUMMARY PH. EUR –7 METHODS

Ph.Eur Method A Diltiazem Hydrochloride - 10ppm

Solution in water ,colour \leq degree 6 .

Ph.Eur Method B Ibuprofen - 10ppm

Solution in organic solvent colour \leq degree 6 .

(Monitor is recommended if Sodium sulphide is used in place of Thioacetamide for methods A&B).

Ph.Eur Method C Hydralazine Hydrochloride - 20ppm

Charring method adding MgSO_4 , temperature $\leq 800^\circ\text{C}$ for $\leq 2\text{H}$,Monitor is used.

METHODS SUMMARY PH. EUR –7 METHODS

Ph.Eur Method D

Eg:– Zidovudine - 20ppm

Charring method adding MgO , temperature $\leq 800^{\circ}\text{C}$ for $\leq 1\text{H}$,
Monitor is used.

Ph.Eur Method E

Eg:– Procaine Hydrochloride - 5ppm

Increased concentration lower limits.

Ph.Eur Method F

Eg:– Lamivudine - 20ppm

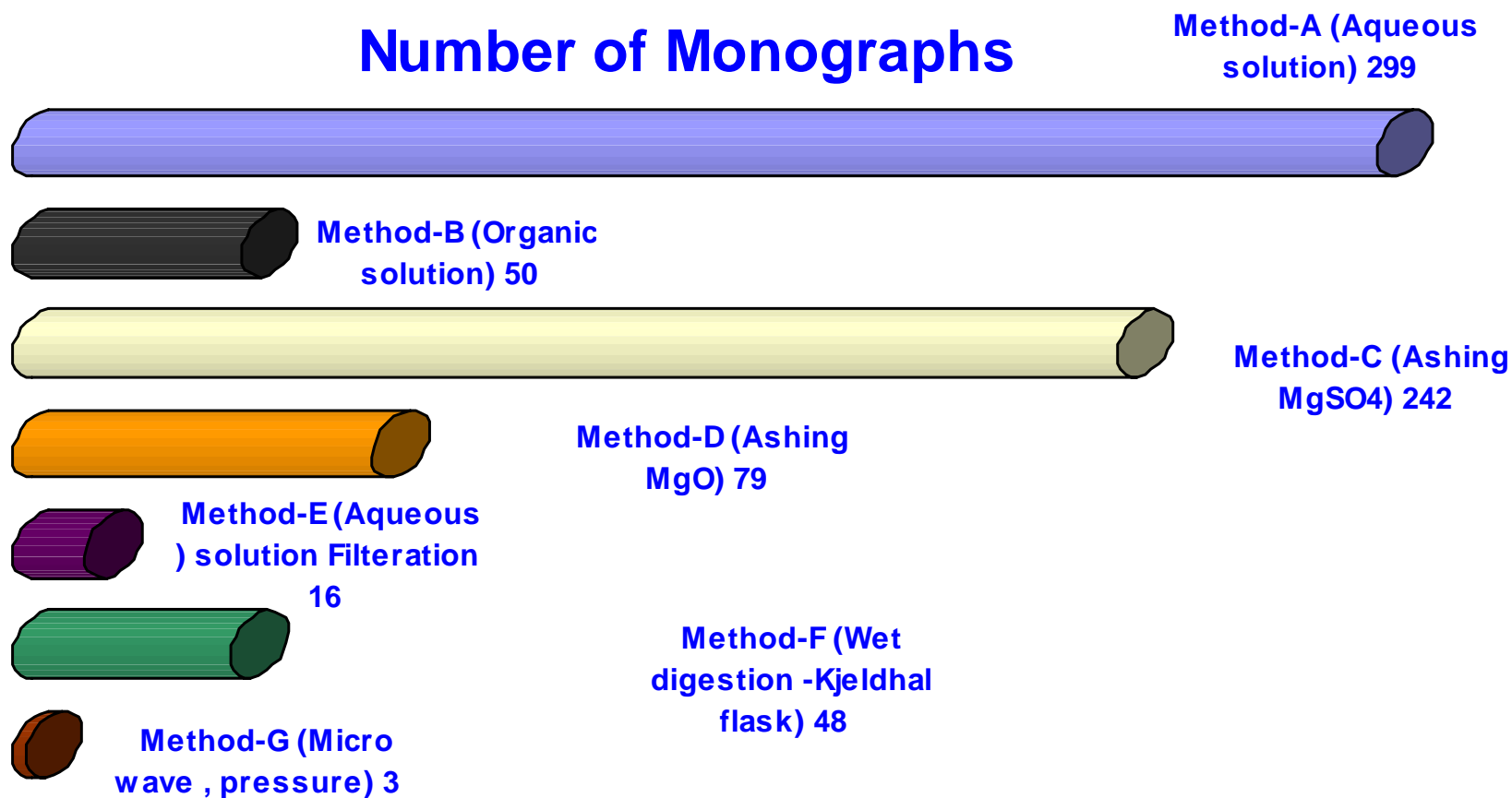
Wet digestion kjeldhal flask, Monitor is used.

Ph.Eur Method G

Eg:– Nevirapine - 20ppm

Microwave pressure digestion fluoropolymer or quartz glass vessels, Monitor is used.

METHODS SUMMARY PH. EUR –7 METHODS



IP - 4 METHODS

Method A

Aqueous solution – Hydrogen sulphide.

Method B

Charring method - Hydrogen sulphide.

Method C

Aqueous solution – Sodium sulphide.

Method D

Aqueous solution – Thioacetamide.

MAZE

Heavy metals test , as a blanket covers 10 metals, inclusive, there are instances, where the test for these metals needs to be done again, either a redundancy or an overlap.

S.No	Monograph	Aluminum	Arsenic	Iron	Lead	Mercury	Selenium	Heavy metals
	General chapter	206	211	241	251	261	291	231
1	Antimony Potassium Tartrate	NS	15	NS	20	NS	NS	NS
2	Calcium Acetate	2	3	NS	10	NS	NS	25
3	Lactase	NS	3	NS	5	NS	NS	30

Lead 5 ppm + Arsenic 3 ppm Heavy metals 30 ppm , what is remaining ?

NS – Not Specified.

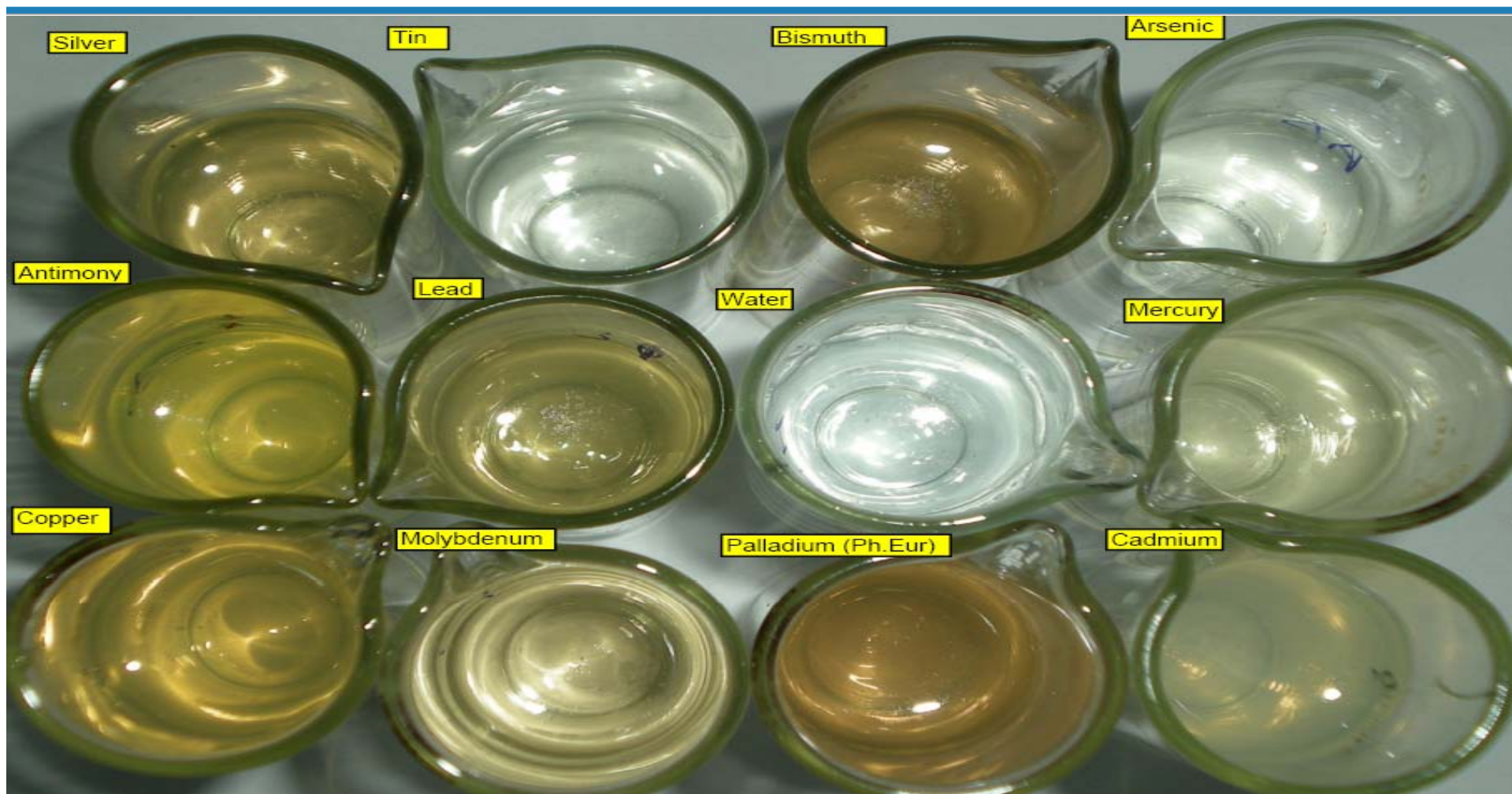
SUITABILITY OF METHOD

(“Stimuli to the Revision Process,” Pharmacopeial Forum, Vol. 21, No. 6, 1995, Katherine Blake).

“Approximately 50% of the metals may be lost during the ash process. . . Note that mercury, which is one of the more toxic heavy metals, was not recovered from either set of samples” Because of the loss of metals during ignition, the validity of test results obtained with the current USP, JP and EP general test procedures is questionable.”

COLOUR – CONUNDRUM

EXPERIMENT–USP LISTED HEAVY METALS AT 20PPM LEVEL IN METHOD I



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ALTERNATE METHODS

➤ **ICP-OES**

➤ **AAS**

➤ **ICP-MS**

ALTERNATE METHODS

15 metals (**USP** and **Ph.Eur**) were spiked in a sample at 0.4ppm level and digested in microwave and recovery for them are as followed when analysed on ICP OES.

S. No	Name of the Metal	Wavelength	% Recovery
1	Lead	220.353	95%
2	Mercury	253.652	103%
3	Bismuth	223.061	98%
4	Arsenic	228.812	115%
5	Antimony	259.805	86%
6	Tin	189.926	116%
7	Cadmium	228.802	104%
8	Silver	328.068	101%
9	Copper	324.754	104%
10	Molybdenum	202.030	107%
11	Vanadium	292.402	89%
12	Palladium	340.458	105%
13	Platinum	214.423	106%
14	Gold	242.795	112%
15	Ruthenium	240.272	103%

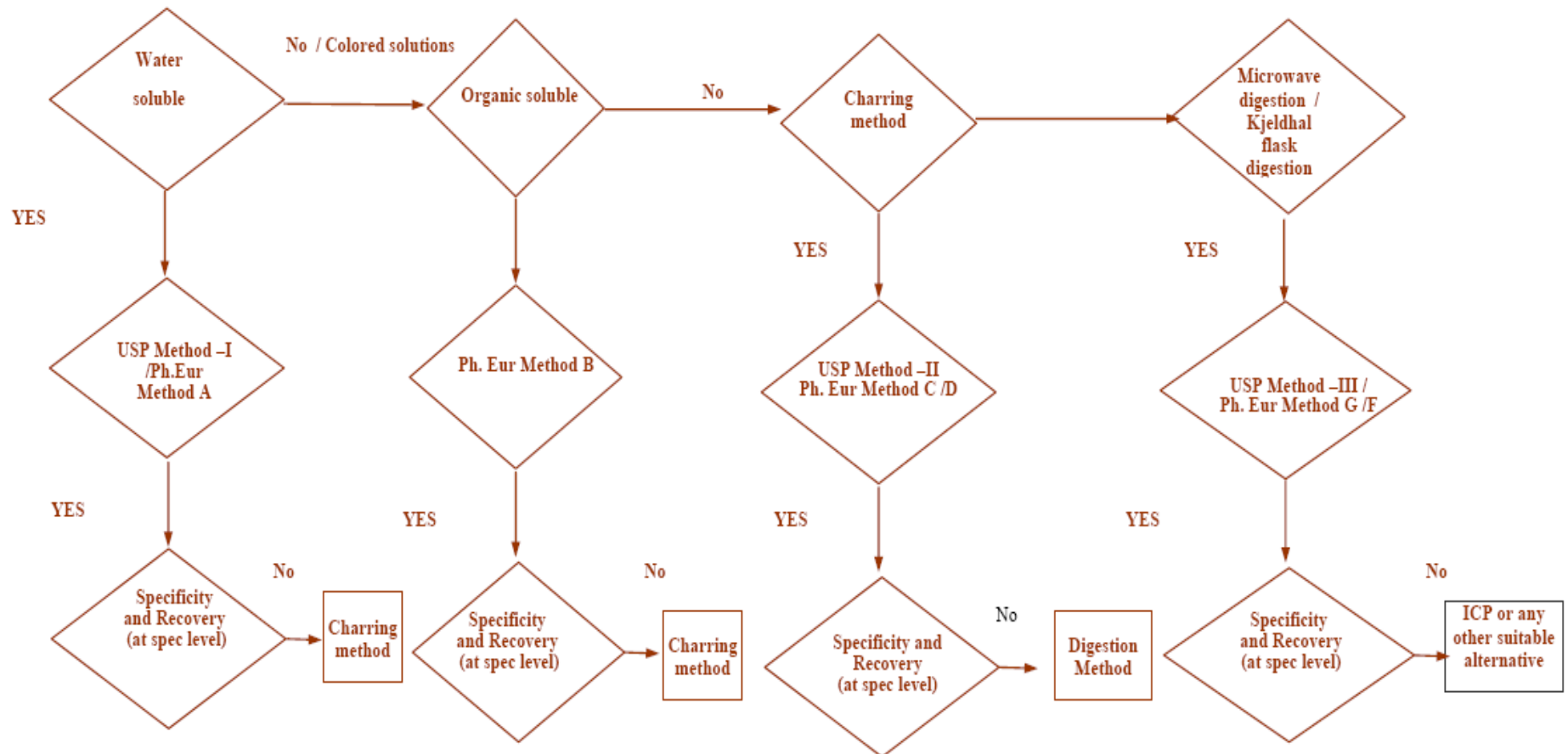
STAYING WITH CURRENT SCENARIO

➤ Choosing limits for non pharmacopieal products

Daily intake > 0.5g/day , treatment < 30 days	Heavy metals test , Limit 20 ppm
Daily intake > 0.5g/day , treatment > 30 days	Heavy metals test , Limit 10 ppm
Daily intake < 0.5g/day , treatment > 30 days	Heavy metals test , Limit 10 ppm if the substance is used parenterally , other wise 20 ppm
Daily intake < 0.5g/day , treatment < 30 days	No Heavy metals test

Technical Guide for the Elaboration of Monographs European Pharmacopeia.

SELECTION OF METHOD



LATERAL GUIDANCE

DRAFT GUIDELINE ON THE SPECIFICATION LIMITS FOR RESIDUES OF METAL CATALYSTS

- Highly toxic/known Toxic Metals (**Class 1A and 1B**)
- Significantly Toxic (**Class 1C**)
- Metals with low safety concern (**Class 2 Metals**)
- Metals with minimal safety concern (**Class 3 Metals**)

LATERAL GUIDANCE

S. No	Classification	Oral Exposure		Parenteral Exposure	
		PDE (µg/day)	Conc ppm	PDE (µg/day)	Conc ppm
1.	Class-1A: Metal of Significant Safety Concern. Platinum (Pt) Palladium (Pd)	100	10	10*	1*
2.	Class-1B Iridium (Ir) ,Rhodium (Rh), Ruthenium (Ru) Osmium (Os)	100**	10**	10**	1**
3.	Class-1C Molybdenum(Mo), Nickel(Ni), Chromium (Cr) Vanadium(V)	300	30	30*	3*
4.	Class-2 Metals with Low Safety Concern. Copper(Cu), Manganese(Mn)	2500	250	250	25
5	Class-3 Metals With Minimal Concern. Iron (Fe) , Zinc (Zn)	13000	1300	1300	130

*Specific limits have been set for inhalation exposure to platinum; Chromium VI and nickel

** Sub class limit: the total amount of listed metals should not exceed the indicated limit

LATERAL GUIDANCE

Assumptions:

- Limits are arrived by assuming MDD is 10 gm/day.
- Other major calculating factors adopted from Q3C.

Pros :

- Provides limits for the specified metals.
- Gives option for skip testing if 30% of set limit is achieved in 3 consecutive batches.

Cons:

- Not included Arsenic , Lead and Mercury which rank first three in ATSDR (Agency for Toxic Substances and Disease Registry) list.
- List not complete some other toxic metals are lagging Ex: Tin.

HARMONISATION ISSUES

- Common method/s for Heavy Metals / In-Organic impurities.
- Different methods / Different chemicals / Different equipment making the Heavy Metals test onerous process reducing to two or three harmonised methods will help out.
- Common guidance with list of possible elements along with limits to be harmonised as Q3C for Residual solvents.
- Common limits for all Regions and Monographs.

EXPECTATIONS OF INDUSTRY

- Approach of the Heavy metals <231> to be re-defined as per current scenario.
- Test to be made subjective rather than objective and blanket limit to be avoided.
- Test with documental evidence and single test for all the common metals.
- Common guidance with list of possible elements along with limits to be harmonised as Q3C.

ACKNOWLEDGMENTS

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THANK YOU

