IV Response to USP 232 / ICH Q3D

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Background

Timeline

2013 – USP General Chapter <232> published

2014 – USP reviewed draft ICH Q3D

2015 – USP limits match Q3D (15 elements)

2016 – USP includes 9 additional Q3D elements

2017 – USP *40–NF 35*, *First Supplement* fully aligned with ICH Q3D

IV Stock Products

2012

- **IV-STOCK-37** (discontinued 2014)
- **IV-STOCK-38** – USP precious metals @100 ppm (Ir, Os, Pd, Pt, Rh, Ru)

2014

- **IV-STOCK-40** – USP Oral (Cu, Ni, Mo, V, Cd, Hg, Pb, As)
- **IV-STOCK-41** – USP Parenteral (Cu, Ni, Mo, V, Cd, Hg, Pb, As)

2016

- **IV-STOCK-60** – USP Oral (Dec. 2015 limits)

2018

- 6 new stock products (**IV-STOCK-65, -66, -67, -68, -69, -70**)

IV Stock Products

New IV products grouped by

Element Class: 1, 2A, 2B, 3

Permitted Daily Exposures (PDE)

TABLE 1 (USP 232) / TABLE A.2.1 (ICH Q3D)

Element	Class	Oral PDE µg/day	Parenteral PDE, µg/day	Inhalation PDE, µg/day	
Cd	1	5	2	2	IV-STOCK-65 (10% v/v HNO3)
Pb	1	5	5	5	
As	1	15	15	2	
Hg	1	30	3	1	
Co	2A	50	5	3	IV-STOCK-66 (5% v/v HNO3)
V	2A	100	10	1	
Ni	2A	200	20	5	
Tl	2B	8	8	8	IV-STOCK-67 (10% v/v HCl)
Au	2B	100	100	1	
Pd	2B	100	10	1	
Ir	2B	100	10	1	
Os	2B	100	10	1	
Rh	2B	100	10	1	
Ru	2B	100	10	1	
Se	2B	150	80	130	
Pt	2B	100	10	1	
Ag	2B	150	10	7	IV-STOCK-68 (5% v/v HNO3)
Li	3	550*	250	25	IV-STOCK-69* (5% v/v HNO3 / trace HF)
Sb	3	1200*	90	20	
Ba	3	1400*	700	300	
Mo	3	3000*	1500	10	
Cu	3	3000*	300	30	
Sn	3	6000*	600	60	
Cr	3	11000*	1100	3	

*10x lower

IV Stock Products

Individual Component / Option 1

Assumes ≤10 g/day of drug product

TABLE 3 (USP 232) / Table A.2.2 (ICH Q3D)

Element	Class	Oral Concentration µg/g	Parenteral Conc. µg/g	Inhalation Conc. µg/g	
Cd	1	0.5	0.2	0.2	
Pb	1	0.5	0.5	0.5	
As	1	1.5	1.5	0.2	
Hg	1	3	0.3	0.1	
Co	2A	5	0.5	0.3	
V	2A	10	1	0.1	
Ni	2A	20	2	0.5	
Tl	2B	0.8	0.8	0.8	
Au	2B	10	10	0.1	
Pd	2B	10	1	0.1	
Ir	2B	10	1	0.1	
Os	2B	10	1	0.1	**IV-STOCK-70** (20% v/v HCl)
Rh	2B	10	1	0.1	
Ru	2B	10	1	0.1	
Se	2B	15	8	13	
Ag	2B	15	1	0.7	
Pt	2B	10	1	0.1	
Li	3	55	25	2.5	
Sb	3	120	9	2	
Ba	3	140	70	30	
Mo	3	300	150	1	
Cu	3	300	30	3	
Sn	3	600	60	6	
Cr	3	1100	110	0.3	

Design of Stock IV Products

Requested/Approved 232 & Q3D standards

Class 1 elements - ~50 unique combinations

Class 2A elements - ~65 unique combinations

Class 2B elements - ~10 unique combinations

Class 3 elements – ~40 unique combinations

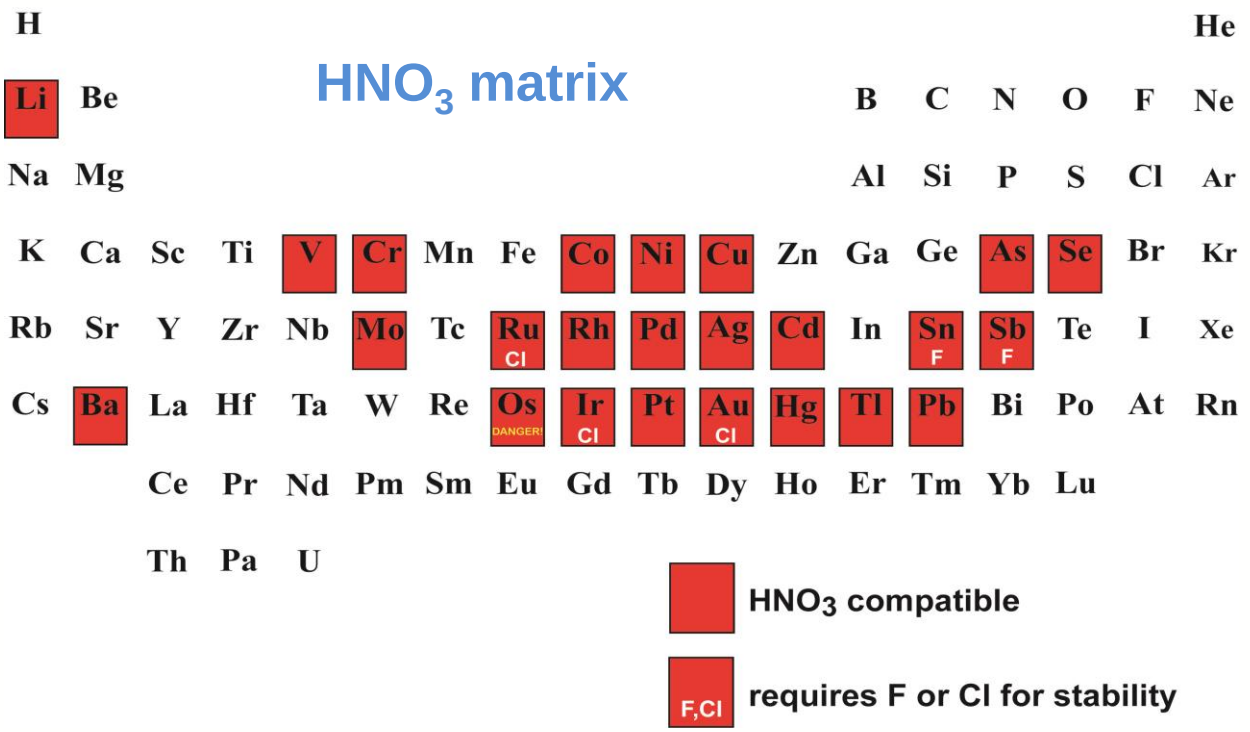
Large variability in requested combinations and concentrations, e.g.,

- ***elements omitted (e.g., Os)***
- ***multiples of limit concentrations (2x, 10x, etc.)***

Product Design Criteria

Stability/Compatibility

- Safety (Os)
- 3 year shelf-life



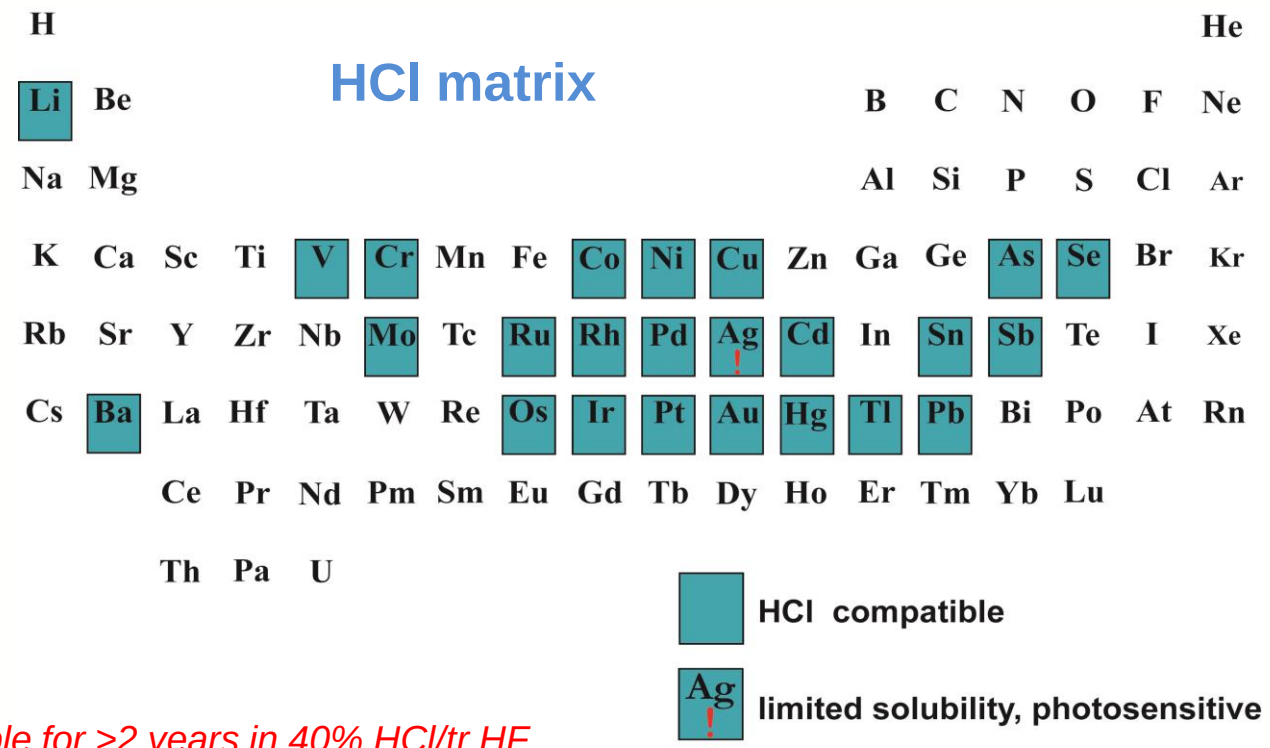
Product Design Criteria

Stability/Compatibility

- Safety (Os)
- 3 year shelf-life

If 2B elements required…

HCl better matrix choice



All 24 elements @100 ug/mL stable for >2 years in 40% HCl/tr HF

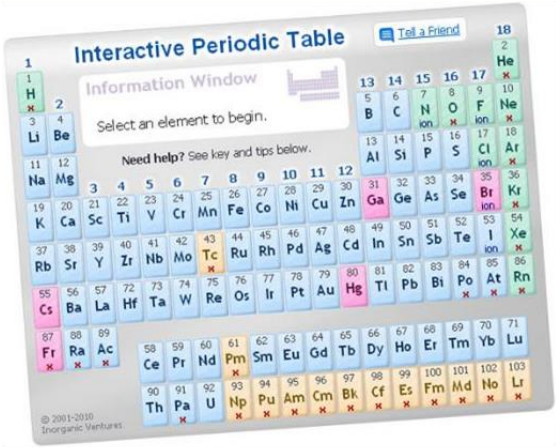
Preparation Tips for 232 / Q3D Standards

Stability/Compatibility

1. Criteria for ≥3 years shelf-life **do not** apply to diluted working standards
2. Avoid osmium in $HNO_{3,}$ but trace HNO_3 (≤5% v/v) does not appear to affect data quality if measured immediately (daily standards)
3. Mercury and gold analyses challenging if matrix is HNO_3
4. Ensure Tl is sourced from oxide ($Tl_2O_3 = Tl^{+3}$) and not nitrate ($TlNO_3 = Tl^{+1}$)

Questions?

Technical Support – Available to Everyone
Online Resources at inorganicventures.com



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- And much, much more.