ASCHIMFARMA – AFI
La garanzia della qualità nella supply chain farmaceutica: produttori e importatori di API
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ELEMENTAL IMPURITIES: ASPETTI REGOLATORI E REQUISITI DI QUALITÀ DEI MEDICINALI

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ICH Q3D Guideline for elemental impurities - 2014

- Valutazione specifica per ogni elemento (ma senza speciazione);
- Dose giornaliera accettabile (PDE) invece di specifica sulle sostanze farmaceutiche:
  - obblighi diretti per il produttore di specialità medicinali;
  - Obblighi contrattuali per i produttori di sostanze farmaceutiche.
- *Risk assessment* su tutte le fonti di impurezze elementari.
- L'impianto di produzione come fonte di rischio.
- Controlli di routine solo quando indicato dal *risk assessment*.

Perché nuove norme?

- **Frequently Asked Questions: Rationale for USP's Proposed Standards for Elemental Impurities (updated 14-Jan-2015)**

- **Q. Why has USP waited until now to revise standards for elemental impurities? Was there a specific event that prompted the revision?**

- **A.** USP undergoes regular re–evaluation and revision of all its standards to update their scientific and public health relevance. There was no specific event that triggered the revision of elemental impurities standards, but our scientific experts felt that the elemental impurity standards should be updated to incorporate modern methods and health information. As we have gained a better understanding of the limitations of the current methods, it has become clear that a revision is called for.

- **Q. Have imports posed an increased problem with elemental impurities? How is USP dealing with this?**

- **A.** To date, there have been no known incidents involving elemental impurities in pharmaceuticals. However, there are continuing concerns above the quality of imports. Ultimately, manufacturers are responsible for assuring conformance to FDA requirements and USP standards, no matter what the source. As more ingredients are sourced abroad, the presence of modern, scientifically sound quality standards will help protect both manufacturers and patients in the United States

Diversamente dal *food*....

As of March 2001, 2,265 victims had been officially recognised as having Minamata disease (1,784 of whom had died).

Supporting Document for Action Level for Arsenic in Apple Juice

July 2013

[Docket No. FDA-2012-D-0322]

- Consumption of inorganic arsenic has been associated with cancer, skin lesions, developmental effects, cardiovascular disease, neurotoxicity, and diabetes in humans (Ref. 2). …
- concluded that food can be a major contributor to inorganic arsenic exposure, and the European Food Safety Authority (EFSA) (Ref. 3) concluded that dietary exposure to inorganic arsenic should be reduced. These findings suggest a need to reduce exposure to inorganic arsenic from food.

Normative applicative

- EMA/CHMP/QWP/109127/2015 (26/02/2015): Elemental impurities in marketed products. Recommendations for implementation
  - Date: giugno 2016 (NCE e nuove MA) – dicembre 2017 (prodotti sul mercato)
  - Regole per dossier e documentazione GMP
- FDA June 2016, Elemental Impurities in Drug Products
- EMA/404489/2016: Implementation strategy of ICH Q3D guideline
- EDQM, August 2016, Implementation of ICH Q3D in the Certification Procedure

EDQM, August 2016, Implementation of ICH Q3D in the Certification Procedure

- The EDQM encourages applicants to provide a RMS.

3.1 Risk Management Summary Provided

- Absence of an elemental impurity can be concluded when it is shown with convincing evidence that it is purged to a level which is consistently below 30% of the calculated concentration limit based on the indicated route of administration and based on the option 1 daily intake (as per table A.2.2 of the ICH Q3D guideline), in a minimum of 3 commercial batches or a minimum of 6 pilot batches of the final substance.

- For any elemental impurity intentionally introduced into the last synthetic step of the process, a specification in the final substance is expected (as this is associated with an elevated risk for impurities being carried forward), unless….

- For the analytical methods used: For screening purposes: The analytical methodology used should be mentioned along with minimum validation information such as indication of the specificity and sensitivity of the method (LOD/LOQ).

- **3.2 No Risk Management Summary provided**
- Any elemental impurities (whatever the Class) intentionally introduced in the manufacture of the final substance should be declared and data showing their level in the final substance should be provided.
- For any elemental impurity intentionally introduced into the last synthetic step of the process, a specification in the final substance is expected…
- The method used to control elemental impurities in the final substance should be described in detail (in a format to be annexed to the CEP) and validation data according to ICH Q2 should be submitted.

Letteratura rilevante

- J. F. Kaufman et al., Elemental Impurities in Pharmaceutical Excipients, J. Pharm. Sci. 104 (2015) 4197–4206

- D. Jenke et al., Compilation of Metals and Trace Elements Extracted from Materials Relevant to Pharmaceutical Applications such as Packaging Systems and Devices,, PDA J. Pharm. Sci. and Tech. 2013 (67) 354-375

- A. Teasdale et al., Establishing Limits for Dermal Absorption of Elemental Impurities, Pharmaceutical Technology 39(9), 44–51

Impurezze elementari nelle sostanze farmaceutiche: dati reali

Elemental Impurities in Pharmaceutical Excipients

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(forme orali)
Eccipienti: 31 (190 lotti)
Principi attivi: 8 (15 lotti)

Supporting material: file Excel con tutti i dati

Materials Name	Cd (ppm)	Pb (ppm)	As (ppm)	Hg (ppm)	Co (ppm)	V (ppm)	Ni (ppm)	Al (ppm)
limit option 1 (oral route)	**0.50**	0.50	1.50	**3.00**	5.00	10.00	20.00	-
Ferric Oxide Red Max (5 batches)	**0.00**	0.65	1.17	0.01	57.86	477.85	109.00	604.88
Ferric Oxide Red Median	**0.00**	**0.34**	**0.59**	**0.00**	**36.81**	**457.85**	**98.29**	**486.41**
Ferric Oxide Yellow Max (5 batches)	**0.00**	0.87	1.28	**0.02**	52.52	432.94	102.72	455.52
Ferric Oxide Yellow Median	**0.00**	**0.26**	**0.92**	**0.00**	**40.10**	**408.43**	**51.96**	**407.63**
Ferrous Oxide Black Max (5 batches)		2.59	1.15	**0.00**	149.21	218.15	170.77	1784.10
Ferrous Oxide Black Median	0.00	0.02	0.04	0.00	145.31	0.29	168.22	6.99

Materials Name	Cd (ppm)	Pb (ppm)	As (ppm)	Hg (ppm)	Ba (ppm)	Cr (ppm)	B (ppm)	Al (ppm)
limit option 1 (oral route)	**0.5**	**0.5**	**1.5**	**3**	**140**	**1100**	**-**	**-**
Talc max (10 batches)	0.00	0.28	0.30	0.03	39.54	33.44	6.59	4689
Talc median	0.00	0.21	0.16	0.00	1.63	6.01	0.95	2386.
Calcium carbonate max (26 batches)	0.92	3.07	0.24	0.03	96.94	4.45	4.73	308.53
Calcium carbonate median	0.77	0.07	0.03	0.00	14.50	3.77	0.30	19.93

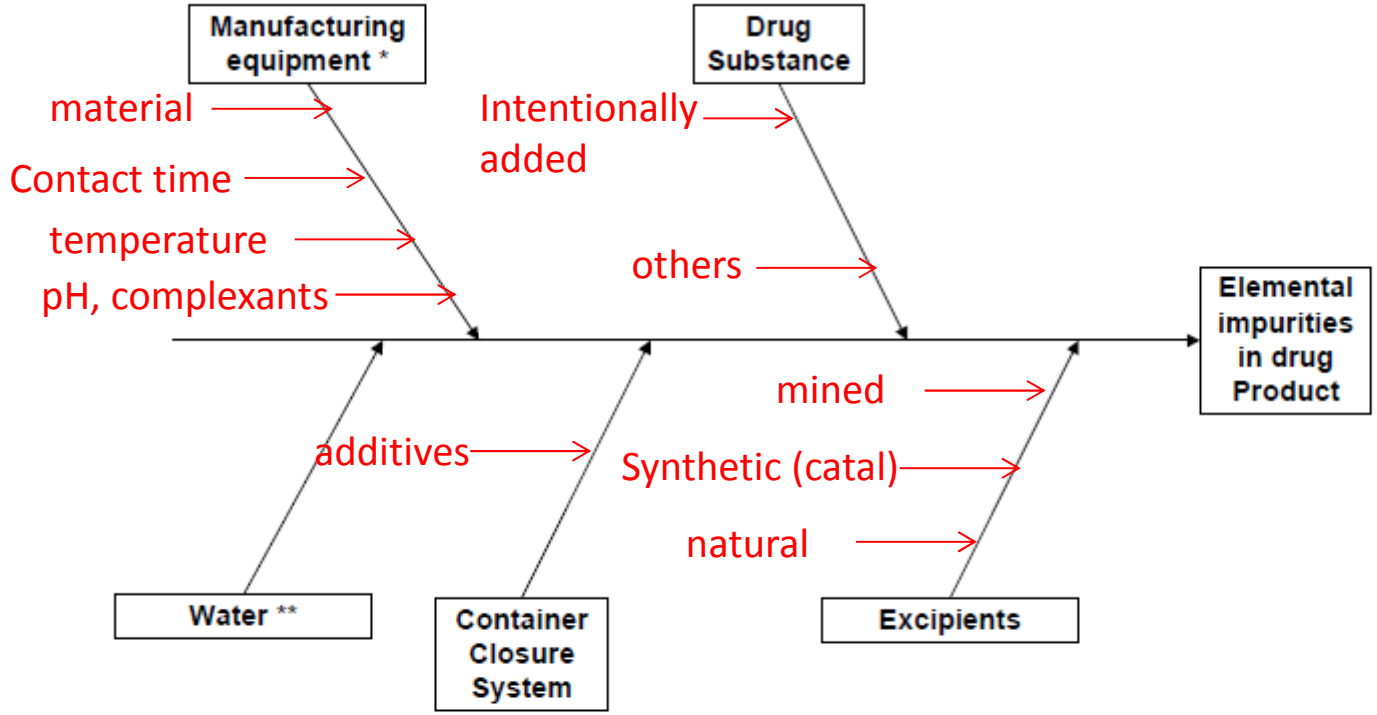
Materials Name	Cd (ppm)	Pb (ppm)	As (ppm)	Hg (ppm)	Li (ppm)	Ba (ppm)	Al (ppm)
limit option 1 (oral route)	**0.5**	**0.5**	**1.5**	**3**	**55**	**140**	**-**
Sodium alginate max (15 batches)	0.03	1.08	1.09	0.01	0.60	222.81	328.27
Sodium alginate median	0.01	0.41	0.40	0.00	0.06	17.87	43.68

Altri risultati

- No metalli del gruppo 2A se non aggiunti intenzionalmente.
- Pt in materiali a base di silicone (< 10ppm): catalizzatori nella polimerizzazione.
- Residui molto bassi negli eccipienti di sintesi.
- Residui molto bassi nei principi attivi.

Un esempio di risk assessment di un produttore di medicinali

It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/or formal procedures, e.g., standard operating procedures.) The use of informal risk management processes (using empirical tools and/or internal procedures) may also be considered acceptable.



* The risk of inclusion of elemental impurities can be reduced through process understanding, equipment selection, equipment qualification and Good Manufacturing Practice (GMP) processes.

** The risk of inclusion of elemental impurities from water can be reduced by complying with compendial (e.g., European Pharmacopoeia, Japanese Pharmacopoeia, US Pharmacopeial Convention) water quality requirements, if purified water or water for injection is used in the manufacturing process(es).

- **Componenti (principio attivo, eccipienti, solventi)**
- **Impianto**
- **Contenitori**

IDENTIFICAZIONE DEL RISCHIO: componenti e contenitori

- Elenco di principi attivi ed eccipienti
- Questionario al produttore (per eccipienti: modello IPEC)
- Raccolta delle risposte

Eccipienti: data base delle risposte

CODICE	DENOMINAZIONE SAP	DENOMINAZIONE COMMERCIALE	CAT	RISP. FORN.	As	Cd	Hg	Pb
00505844	2,3 di-tert-butil paracresolo	Butil idrossi toluene (BHT)	EXC					
05147160	Acetone xxx	Acetone	SOL	T				
31784142	Acetone xxx	Acetone	SOL	D+R	< 0.05	< 0.05	< 0.05	< 0.05
35574083	Acido ascorbico	Acido ascorbico	API	R	≤ 0.1	≤ 0.1	≤ 0.01	≤ 0.1
49496474	Acido citrico anidro xxx	Acido citrico anidro	EXC	D+T+R	< 1	< 1	< 1	< 0.5
46178136	Acido citrico anidro yyyy	Acido citrico anidro	EXC	R	0.04 ppb	0 ppb	0 ppb	0.03 ppb
31310983	Acido citrico monoidrato xxx	Acido citrico monoidrato	EXC	R	< 0.2	< 0.1	< 0.02	< 0.3
06320719	Acido citrico monoidrato zzzz	Acido citrico monoidrato fine	EXC	D				
33740592	Acido cloridrico 10%	Acido cloridrico 10%	EXC					
21587878	Acido fumarico	Acido fumarico	EXC	T+R	< 3	< 1	< 1	< 2
39852747	API1	API1	API	D				
49770408	Acido stearico	Steaarina TP micronizzata	EXC					
24982482	Aerosil non compresso	Aereosil 200	EXC					
22671163	Alcool cetilico	Resaphol CE	EXC	D				

In caso di dichiarazione: «<LOD=X.XX»,
il contenuto si pone uguale al LOD

Nessuna risposta	73
Solo dichiarazione	58
Solo tabella elementi	26
Risultati analitici	7
Dichiarazione + tabella	1
Dichiarazione/tabella + risultati	47
Risposta completa	3
Totale materie prime	215

N.B.: qualche problema i coloranti

VALUTAZIONE DEL RISCHIO

Component	Category	Quantity (mg/tablet)	Dose "x" tablets (mg/day)	Arsenic in component ug/g		As ug in daily dose of formulation		Lead in component ug/g		Pb ug in daily dose of formulation	
		x =	2	Total	Bio Acc	Total	Bio Acc	Total	Bio Acc	Total	Bio Acc
Tablet core:											
Active	Synthetic	100	200	0.00		0.00	0.00	0.00		0.00	0.00
mannitol	Synthetic	120	240	0.00		0.00	0.00	0.00		0.00	0.00
calcium phosphate	Mineral	65	130	0.11		0.01	0.00	0.02		0.00	0.00
modified starch	Plant derived	10	20	0.00		0.00	0.00	0.00		0.00	0.00
cellulose	Plant derived	10	20	0.00		0.00	0.00	0.09		0.00	0.00
magnesium stearate	Synthetic	3	6	0.02		0.00	0.00	0.01		0.00	0.00
titanium dioxide	Mineral	2	4	0.03		0.00	0.00	2.41		0.01	0.00
talc	Mineral	1	2	0.17		0.00	0.00	0.19		0.00	0.00
polyethylene glycol	Synthetic	1	2	0.00		0.00	0.00	1.00		0.00	0.00
ferric oxide red	Mineral	0.1	0.2	0.66		0.00	0.00	0.37		0.00	0.00
purified water*		NA									
Total Tablet weight		312.1	624.2								
Total element				As		0.02	0.00	Pb		0.02	0.00

* NOTE: PF 39.1 Revision Process stimuli "Elemental Impurities in Pharmaceutical Waters" excludes analysis of compendial water meeting monograph conductivity requirements

Permissible Limits	As	Pb
Formulation	Q3D	Q3D
Oral PDE	15	5
Parenteral PDE	15	5
inhaled PDE	2	5

File Excel da http://ipecamerics.org.system/files/Instructions-PDE_Calculator_Elemental_Impurities.df (accesso Settembre 2015)

VALUTAZIONE DEL RISCHIO

- **Se tutti i dati sono disponibili** si conclude secondo ICH Q3D, valutando la necessità di un controllo di routine.

- **Se manca qualche dato**, provvisoriamente si immette il valore massimo della specifica secondo l' opzione 1 (o il valore suggerito dai dati pubblicati);
- Sulla base dei risultati si stabilisce la priorità della valutazione completa (per esempio applicando l'opzione 3) o del sollecito dei dati;
- la priorità è bassa se ciascuna impurezza elementare risulta inferiore al 30 % della PDE.

RISCHIO DOVUTO ALL'IMPIANTO

- Elencare le parti dell'impianto, identificando quelle a contatto con il prodotto;
- Valutare adeguatezza di ispezioni, videoispezioni, manutenzione, cleaning;
- Sulla base dei certificati dei materiali, identificare le possibili impurezze elementari rilasciate;
- Nessuna valutazione ulteriore per solidi orali semplici.
- Valutare rischio in base a matrice, pH, temperatura, tempi di contatto.
- Eventuali prove sperimentali:
  - su singola matrice;
  - su worst case;
  - su simulatore (es. pH 4 – EDTA)

RISCHIO DOVUTO ALL'INTERAZIONE CON IL CONTENITORE

- Nessuna valutazione per solidi orali.
- Sulla base del materiale, del certificato del fornitore, della letteratura (D. Jenke et al., 20139) identificare le impurezze potenziali ed il loro contenuto massimo in caso di completa migrazione.
- Confrontare il contenuto massimo con il limite di controllo:
  - se inferiore in modo consistente, si elencano le impurezze potenziali ed i contenuti limite.
  - se le informazioni sono insufficienti, si procede a test di rilascio (evento raro!)

Riassunto, report e conclusioni finali

- Si sommano i valori ottenuti dai componenti, dall'impianto e dalla valutazione dei materiali di confezionamento;

- Si trae la conclusione finale sulla strategia di controllo e sull'impatto regolatorio.