Impurities and residues: mutagenic impurities, metal residues, and extractables and leachables

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MCC / AAPS Symposium Pharmaceutical Science, Medicine Registration and Control, “A Scientific Approach”

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Impurities Training Event
Agenda

- Introduction – what is an impurity?
- Impurity Qualification
- Genotoxic (Mutagenic) Impurities
- Metal Impurities
- Extractables and Leachables

Impurities

Introduction

WHAT IS AN IMPURITY?

- **Impurities are substances which differ from the chemical composition of the material or compound.**

WHY ARE THEY PRESENT?

- **Impurities in pharmaceuticals arise as a consequence of a number of factors most relating to the manufacture of the active**
  - Also include impurities arising from storage of the product e.g. Degradants and/or leachables.
- **Impurities should be effectively controlled and where possible eliminated.**
  - Approach taken needs to be **pragmatic** and based on safety hazard.

Qualification

‘The process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.’

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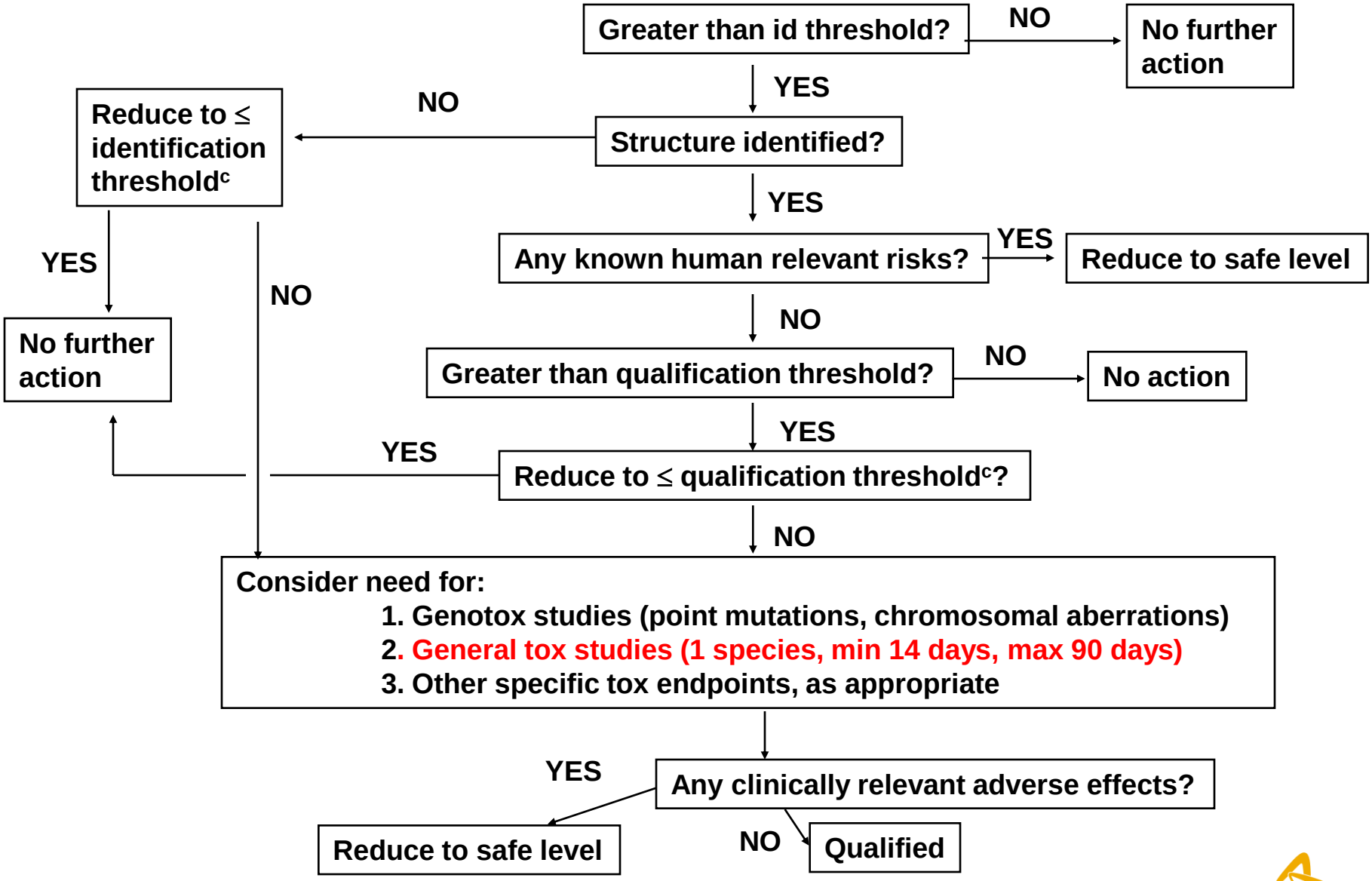
Background to qualification

- Drug substance impurities **must** be qualified in preclinical studies before drug is used in man.
- Risk assessment for man based on preclinical studies will include any contribution to toxicity profile resulting from presence of impurities at levels tested
- Decision tree and thresholds for reporting, identification and qualification of impurities for Marketing Authorisation Applications or New Drug Applications are contained in ICH Q3A(R) and Q3B(R) guidance documents
- For a drug dosed at up to 2g/day, the threshold for qualification for impurities is 0.15% or 1.0mg/day, whichever is lower

ICH Q3a decision tree for qualification studies

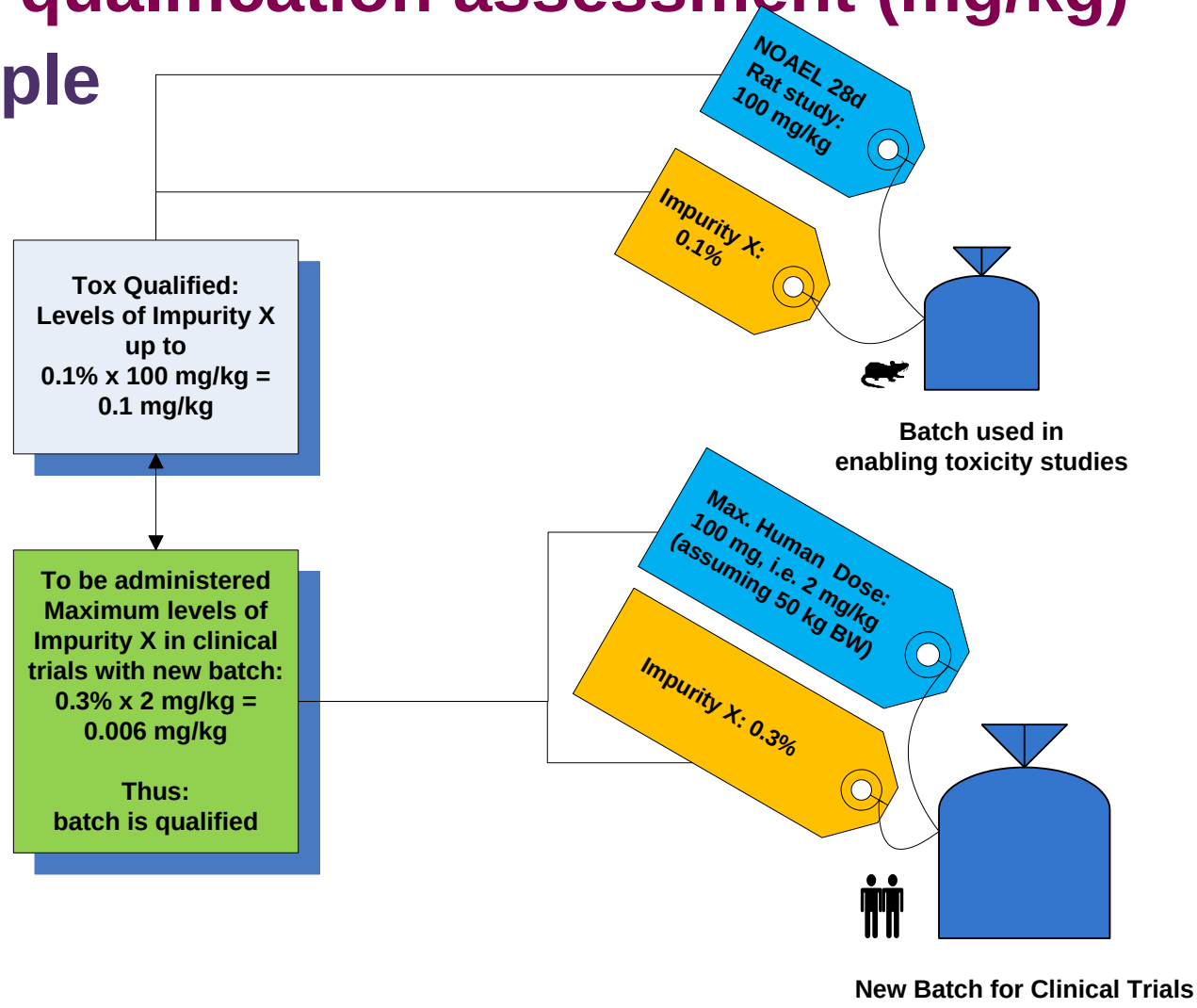


Design of qualification studies

- **Careful design required:** objective is to identify any significant change to safety profile of a drug resulting from the impurity
- Studies should be compared with previous toxicology studies (e.g.. dose levels normally focused on no-effect or low effect levels) NB. taking safety margins into account
- Species selected should enable potential impurity effects to be identified; often species that tolerates highest doses of drug substance – the rat in most cases
- **Study duration** - at least 14 days and up to 3 months (dependent on duration of clinical dosing, duration of existing toxicology studies, whether the impurity or degradation product was present or not in the original toxicology tests (but at low concentrations), and evidence or suspicion of accumulation, e.g. heavy metals).

Basic qualification assessment (mg/kg)

Example



Exposure not level is the key factor

Genotoxic (Mutagenic) Impurities

Current and Future Guidelines - Implications

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Introduction

What is a genotoxin?

- **Genotoxicity defined as: Toxic (damaging) to DNA.**

- **Of specific interest are substances that bind directly to DNA thereby causing mutations which may or may not lead to cancer.**

- **<u>This is mutagenicity</u>**

Introduction – Current Guidelines

- Currently the only formal guideline pertaining to genotoxic impurities is the EMEA (now EMA) guideline.
- Published in mid-2006 this became effective 1st January 2007.
- Supplemented since by a Q&A Process.
  - Industry questions answered by the EMA
- FDA published a draft guideline in Dec 2008
  - Will not be adopted
- Now an ICH topic – ICH M7

Historical Perspective

The beginning

- In 2002 the EU position paper caused a great deal of concern.

- Paper was based on the belief that current controls over genotoxic residues were inadequate.
  - i.e. Not addressed through the ICH quality guidelines.

- Paper structured in similar way to the current EMA guideline.
  - Two sections
    - Quality Assessment and
    - Toxicological Assessment.

Historical Perspective

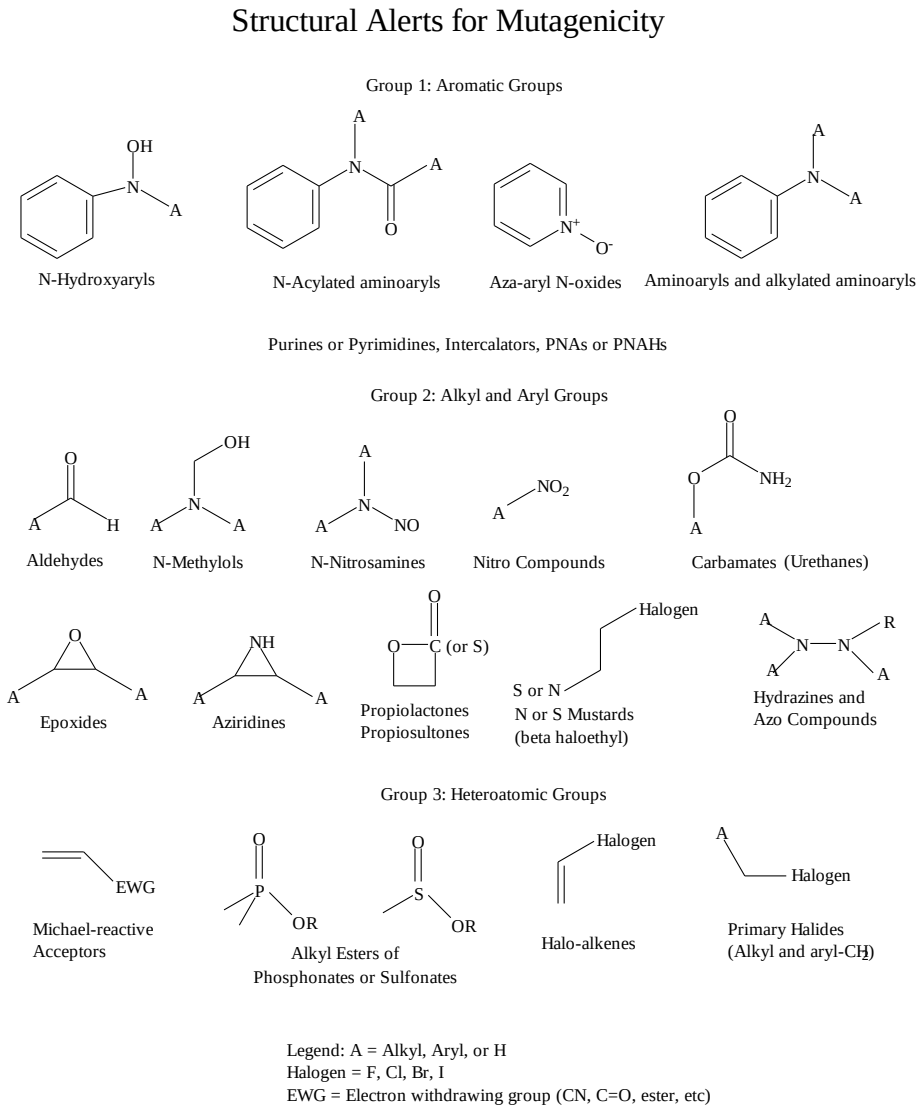
2002 Position Paper

Pharmaceutical Assessment

- **Assumption of no safe limit led to a very conservative approach being proposed.**
  - Avoidance the overriding principle.
    - Justification for use of a genotoxic agent required.
    - Required to update manufacturing process should an alternative route be identified (not containing a genotoxic reagent).
    - Control to "as low as technically feasible."

- **Took little account of existing synthetic methodology.**

- **What is "as low as technically feasible?" –who would decide?**



Historical Perspective

Draft EMEA Guideline – June 2004

- Significant step forward from an industry perspective – far more conciliatory.
  - E.g "as low as technically feasible replaced by "as low as reasonably practical".
  - No longer required to search for a viable alternative at a later date.

GOOD NEWS

- By far the most important change was the inclusion of the acceptable risk concept –the TTC. Set at 1.5µg/day (lifetime exposure).

- Also introduced the idea of flexible limits based on factors such as duration / disease area but no guidance of values.

Historical Perspective

PhRMA (Mueller) White Paper - 2006

	Duration of Exposure				
	≤1 mo.	>1-3 mo.	>3-6 mo.	>6-12 mo.	> 12 mo.
Allowable Daily Intake (μg/day) for all Phases of development	120 or	40 or	20 or	10 or	1.5
Alternative maximum based on percentage of impurity in API	0.5%	0.5%	0.5%	0.5%	

ICH M7
Format / Content

- Many elements common to EMEA and FDA guidelines
  - Safety and Quality sections (different terminology)
- Specific section addressing Marketed Products.
- New section focused on documentation.
- Case Studies

ICH M7 Step 2
Safety perspective

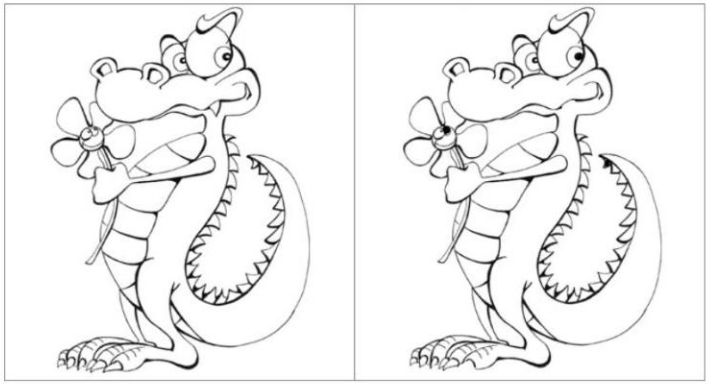
- **Areas of potential significance:**

- Specific focus on mutagenic impurities.
  - Recognised that the primary test is the Ames test.
  - No requirement to specifically look to assess other risks e.g. Clastogenicity.

- SAR evaluation.
  - Heightened scrutiny around the use of in silico systems to assess potential mutagenic risk.
  - May require the use of multiple systems rule based and statistically based (QSAR).
    - May have a big impact on small / medium organisations – these systems are expensive and require expert knowledge
    - No clear evidence to support the view that accuracy improved by use of more than 1 system.

SAR Evaluation -

- Think spot the difference !



- A structure activity relationship (SAR) relates features of the molecular structure of a chemical to a property, effect or biological activity associated with that chemical.

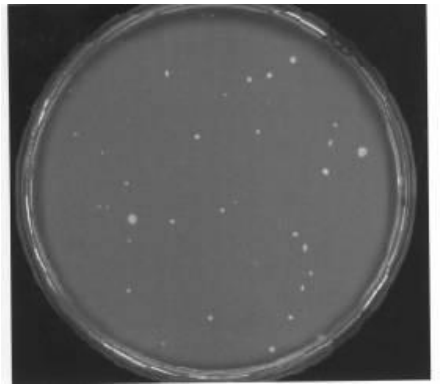
- Predictions made from chemical structure for mutagenicity (Ames test)
  - Best indicator of genotoxicity.

ICH Step 2
Ames Test

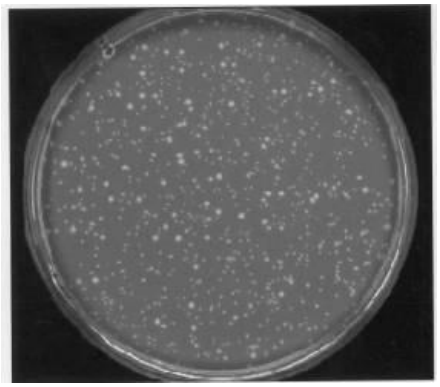
- Examines mutation in Bacterial strains.
- Each strain has specific characteristics aimed at detecting specific types of mutation.
- All have mutations in either histidine or tryptophan operons.
    - Only grow when they mutate.

- **Mutagenicity = growth.**

Control



Mutagen treated



ICH M7 Step 2

Safety perspective

Areas of Significance cont..

- **Greater acceptance of limits based on specific safety data.**
  - Initiative to develop a table analogous to solvents in Q3c.
- **Single set of limits irrespective of route of administration and/or patient population.**
- **Greater use of compound specific risk assessment**
  - Construct of table analogous to that use for solvents

Reagent	Ames Mutagenic / Non-mutagenic		Mutagen, but AI from linear extrapolation not appropriate		not a mutagenic carcinogen, but sometimes treated as one
		carco data problematic*	carcinogenic mechanism not related to mutagenicity, has threshold,(site-specific) or rodent specific mechanism (nat = also prevalent in diet/endogenous metabolism)	mutagenicity has practical threshold (demonstrated in vivo)	
acetaldehyde	M		**X (nat)**		
Acrolein	M	X			
Allyl bromide	M	X			
Aniline	NM		**X**		
Benzyl chloride	M				
Bis-chloromethyl ether	M				
Bromoacetic acid	M				
chloro-nitrobenzene	M				
dimethyl aminopyridine	M				
Dimethyl sulphate	M				
DMCC	M				
Epichlorohydrin	M				
Ethyl chloride	M				
Ethyl methane sulfonate	M			**X**	
Formaldehyde	NM		**X (nat)**		
gycidol	M				
hydrogen peroxide	M		**X**		
Hydroxylamine	NM				
Isopropyl chloride	M?				
methyl chloride	M		**X**		
Methyl Iodide	M		**X**		
Methyl methane sulfonate	M				
N-nitroso pyridine/morpholine/piperazine	M				
p-chloro-aniline	M		**X**		
Phenol	NM				**X**
Phenyl hydrazine	M				

ICH M7 Step 2

Safety perspective

Areas of significance continued..

- **Modification and extension of variable limits based on duration to marketed products.**

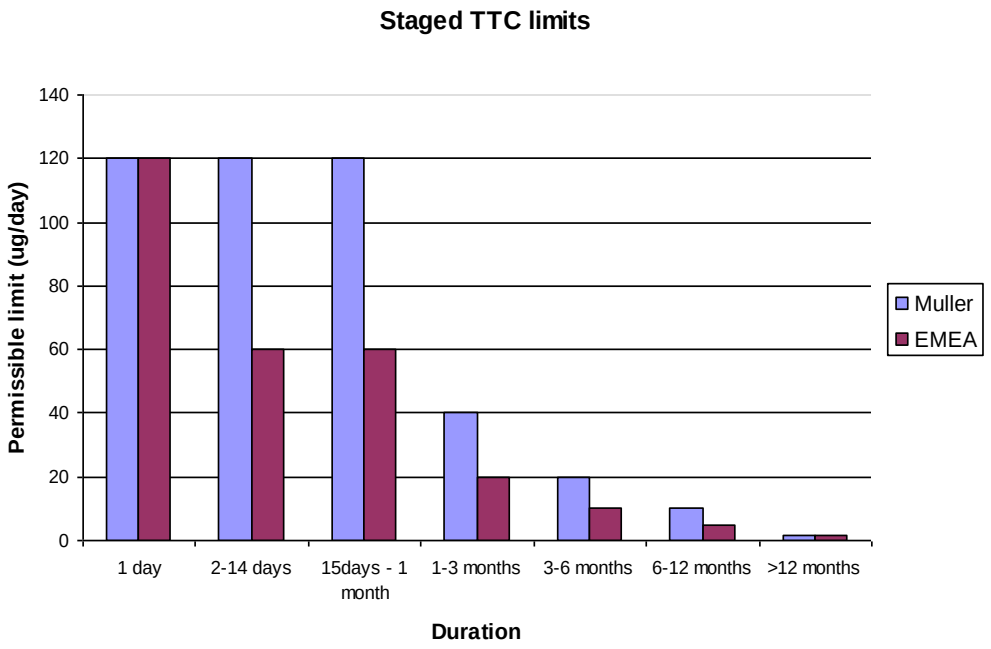


Table 2: Acceptable intakes for an individual impurity

Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5

ICH M7 Step 2

Quality

- **Greater flexibility in terms of mechanism to prove absence.**
  - Options other than to simply test for presence in final API.
  - Ability to more widely use chemical / process based arguments to assess purging. (will examine this further in case studies)

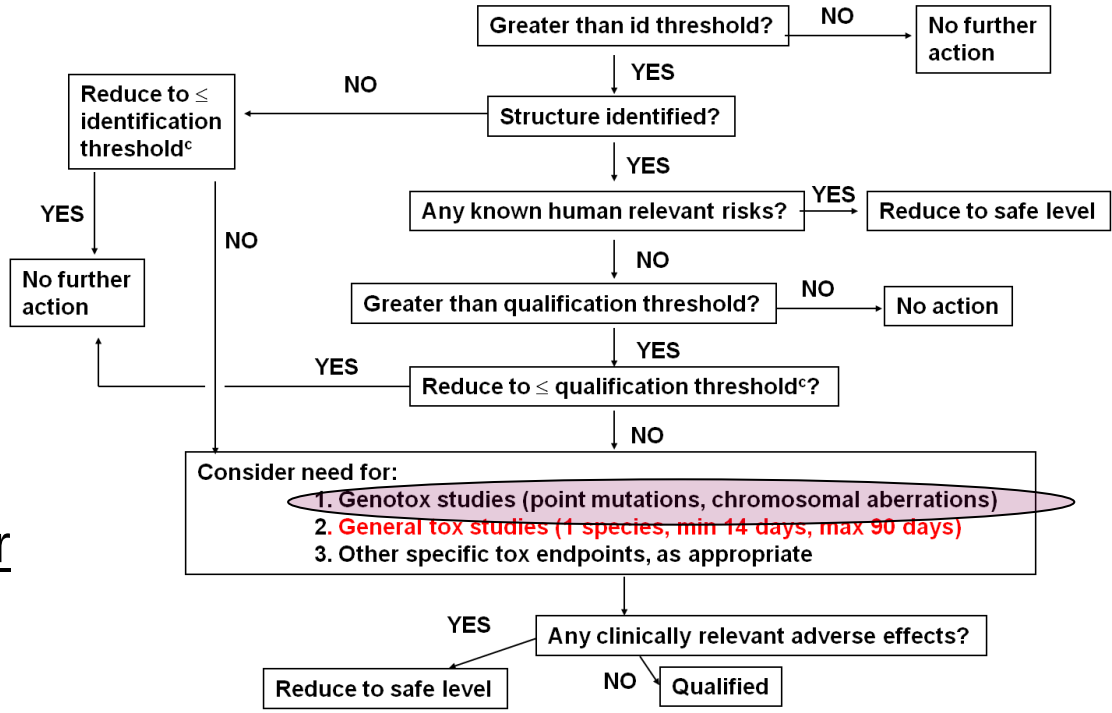
- **Tacit recognition of evolutionary nature of risk assessment.**
  - e.g. Degradants.

- **Emphasis on more detail / clarity in submissions.**
  - What will this mean in practice?
  - Certainly will need to provide more detail relating to SAR evaluations

ICH M7 Step 2

Additional notes

- Relationship to ICH Q3A/ Q3B, following statement added.
  - The ICH M7 guideline recommendations provide a state-of-the-art approach for assessing the potential of impurities to induce point mutations and ensure that such impurities are controlled to safe levels so that below or above the qualification threshold no further qualification for mutagenic potential is required



ICH M7 Step 2
Conclusions

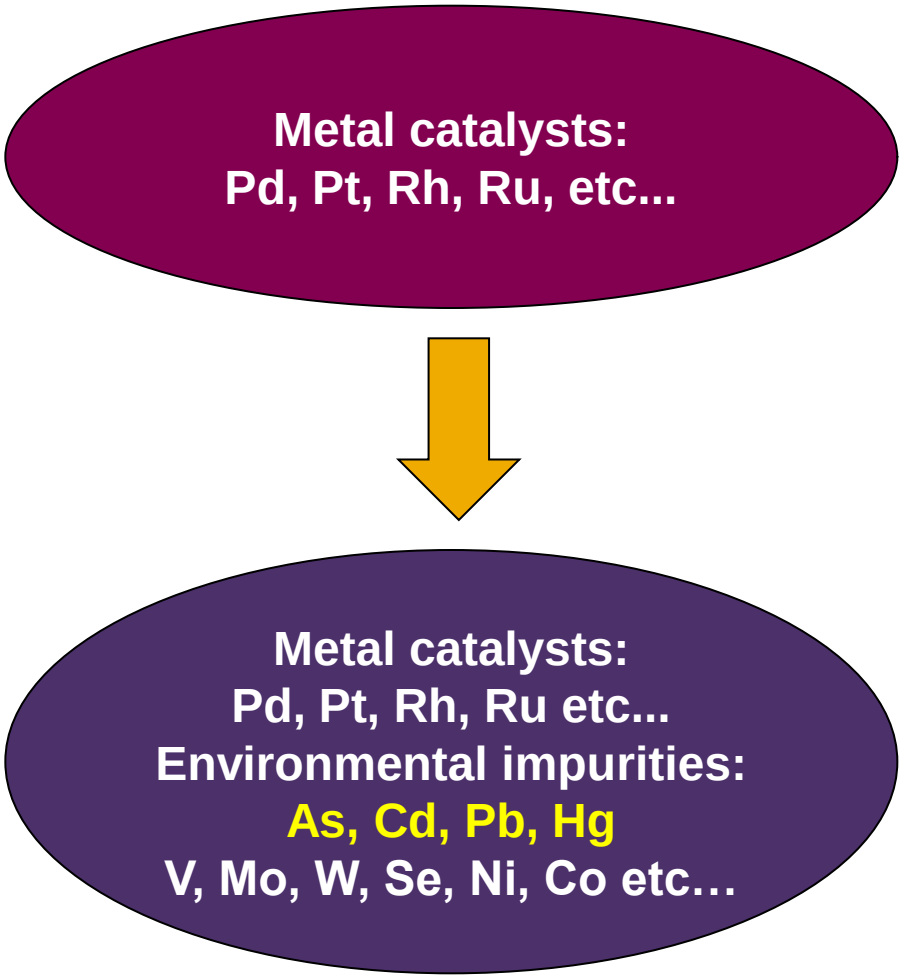
- In general the step 2 document is a positive development.

- Addressed many previous areas of concern from quality and safety perspective.

- Little or no impact on current strategy.

- Main areas of uncertainty
  - SAR evaluation
  - Documentation.

Elemental Impurities
Overview



- **Current regulatory position**
- **New (and evolving!) regulatory position**

Metal Impurities

Current regulatory guidance

- **ICH Q3A Impurities in New Drug Substances (2002)**

'Inorganic impurities are normally detected and quantified using **pharmacopoieal** or other appropriate **procedures**. Carry-over of **catalysts** to the new drug substance should be evaluated during development. The need for inclusion or exclusion of inorganic impurities in the new drug substance specification should be discussed. **Acceptance criteria** should be based on **pharmacopoieal standards** or known **safety data**.'

- **EMEA guidelines for Metal catalysts (2008)**

- recommended specification limits for **metal catalyst/reagent** residues
- focus is control of API and excipients.

Introduction

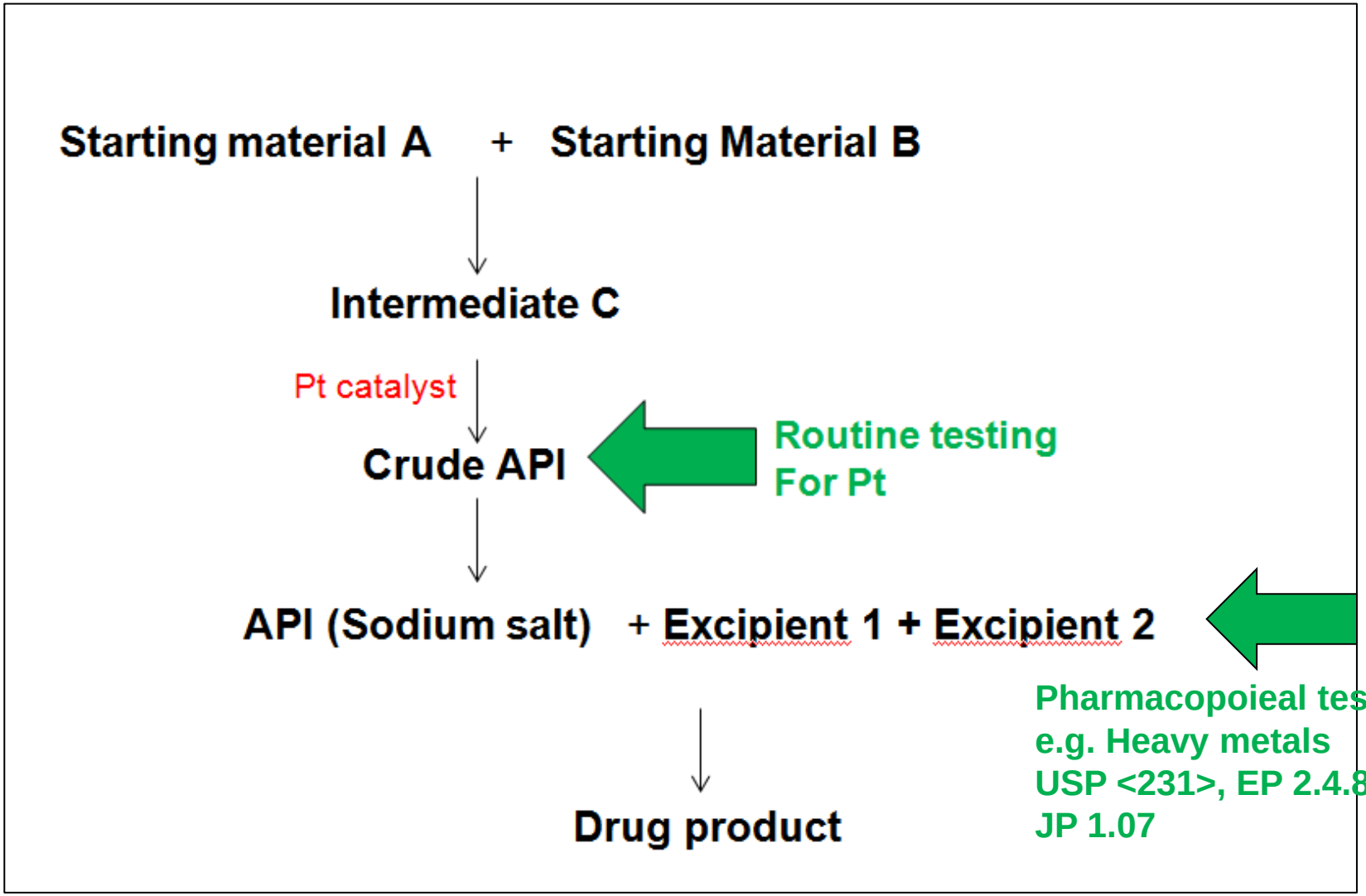
Historical approach to elemental impurity testing

- **Historically risk posed by metals addressed through ‘wet chemical test’ – Heavy metals limit test.**

- **This test relies on the formation of a sulphide precipitate of the metal in question**

- **Issues**
  - Inaccurate
  - Non-specific
  - Some key metals form soluble sulphide salts

Example of a metal impurity control strategy



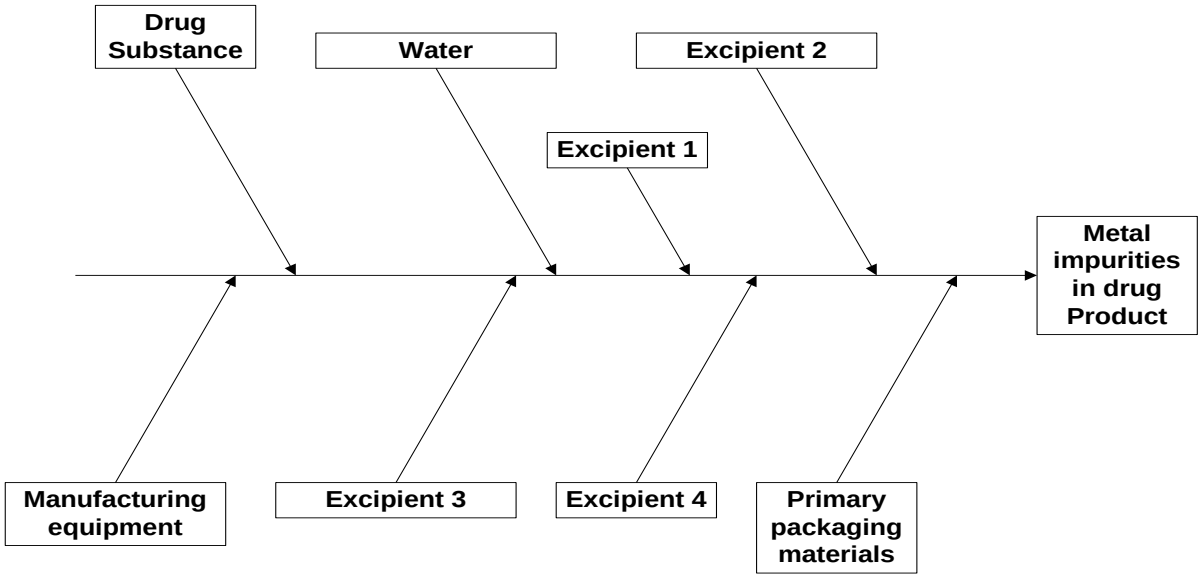
Risks controlled by GMP: purified water, equipment compatibility

New elemental/metal impurities guidelines

USP <232/233> and ICH Q3D

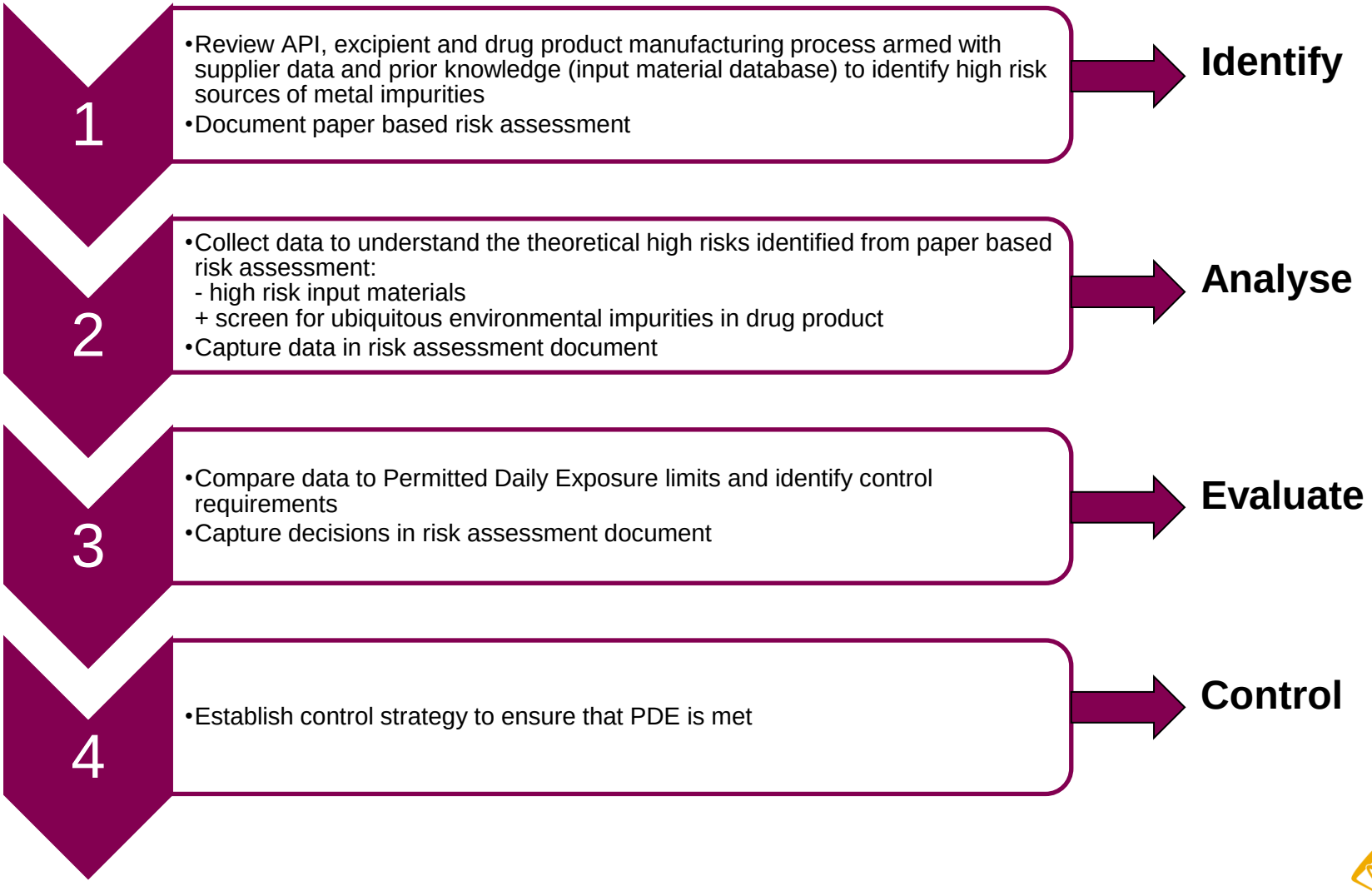
Changes

a) Move to risk based control strategies that consider all potential sources of metal impurities in drug products

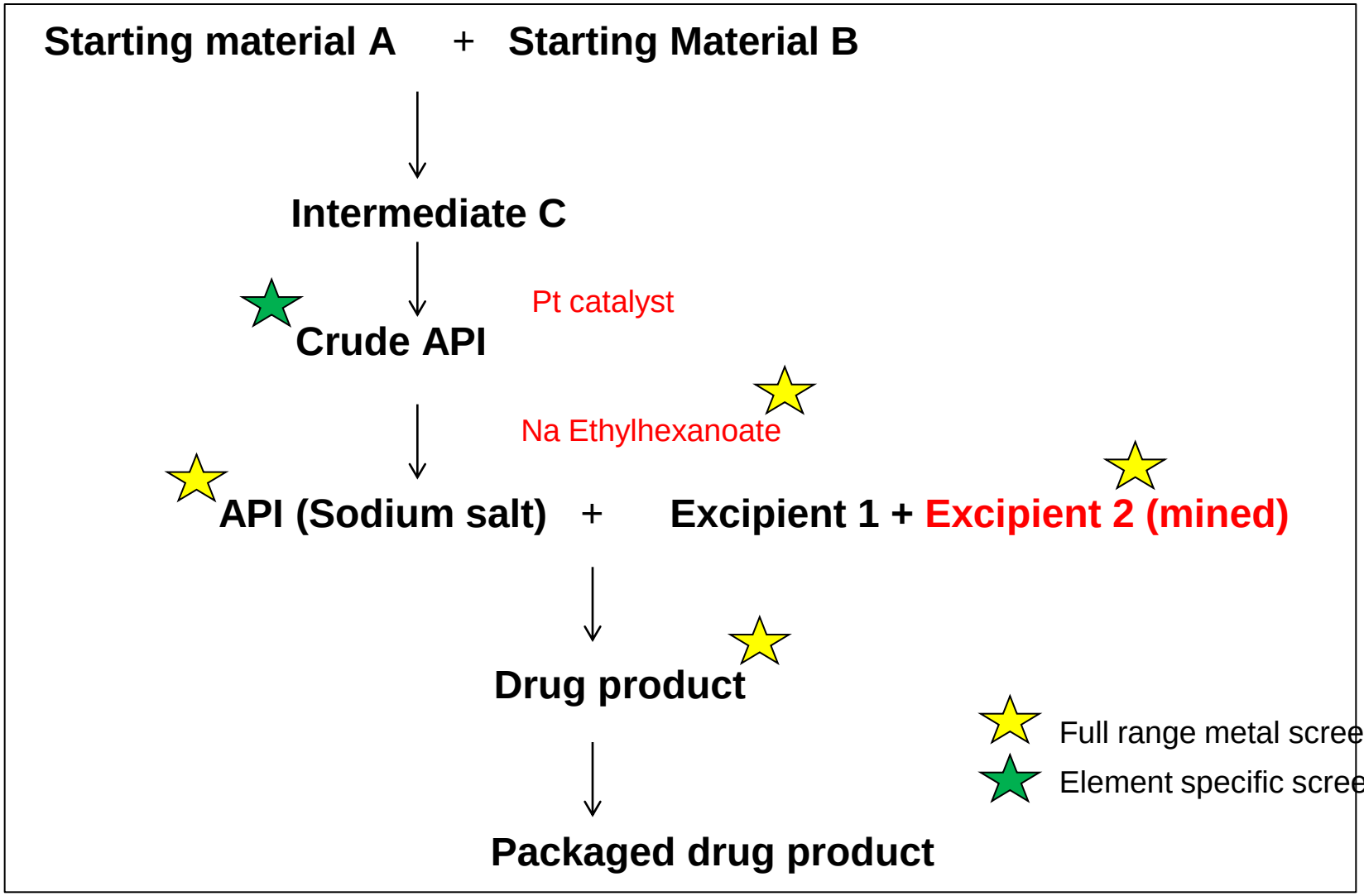


b) decrease in some permitted daily exposure (PDE) limits
c) limits for some ‘new’ elements
d) updated analytical technology

Risk Assessment process: Development of risk based control strategies



Analyse: Example analytical screening by ICP-MS



New Guidelines: compliance deadlines

•**From 1 December 2015, USP <231> Heavy Metals test will be invalid**

• **By 1 December 2015, new and existing marketed products must upgrade from USP <231> to compliance with USP <232> & <233>:**
- Documented risk assessment for potential metal impurities
- Updated specification limits (for metals of concern)
- Updated analytical methodology

• **By –date undefined – all marketed products must comply with the ICH Q3D metal impurities guidance:**
- Documented risk assessment for potential metal impurities
- Updated specification limits (for metals of concern)
- Updated analytical methodology

•**Guidelines are not specifically applicable to clinical development**
- But as metal impurities are now a regulatory hot topic we are likely to receive questions during the clinical trial application process

Evaluate and Control: Challenges

- Lack of harmonisation of global limits (EMEA, USP, ICH timelines).
- Lack of guidance on acceptable risk based control strategy principles.
- Many supplier/manufacturing sites aren't analytically equipped for the required testing

Introduction to Extractables and Leachables

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Overview

- Polymers used in the pharmaceutical industry
- Potential problems with additives
- Definitions
- Route of administration versus interactions
- Guidelines
- Dose & detection limits
- Change control & LCM

Polymers used in Pharmaceutical applications

Polypropylene (PP)
Polyvinylchloride (PVC)
Polyurethane (PU)
Polycarbonate (PC)
- **Rubber (natural & synthetic)**

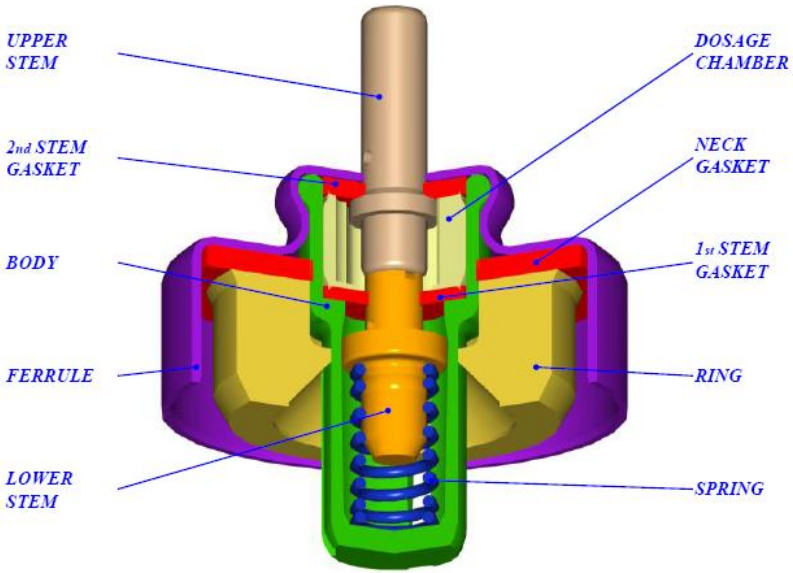
Ethyl vinyl alcohol (EVOH)
(PET)
- **Cyclic Olefin Polymer (COC)**

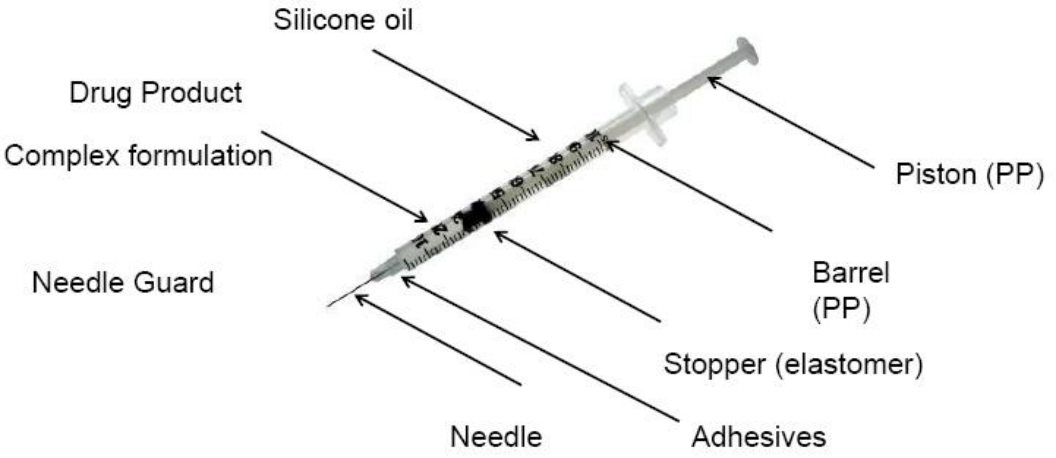
Etc.

Polyethylene (PE)
- **Polysulfone (PS)**

Polymethylmethacrylate (PMMA)
Polyamide (PA)
Polyvinylidendifluoride (PVDF)
Polyethylene Terephthalate

Silicones



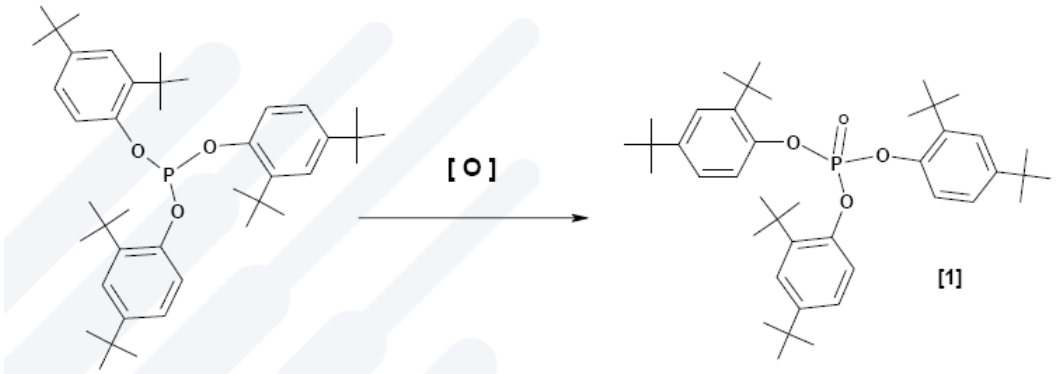


So what's the problem using polymers?

All plastics, elastomers, film coatings etc. are complex formulations which can contain various additives, initiators processing agents etc., e.g.:-

Monomers	oligomers	Accelerators
Antioxidants	Blowing agents	catalysts
Pigments	cross linking agents	curing agents
Fillers	Lubricants	plasticisers
Vulcanising agents		

Some of these can degrade or react further with the formulation.



Irgafos 168 used as an antioxidant in PP & PE

These may end up as Leachables by migrating into the container closure systems, may be of toxicological concern !

What are Extractables and Leachables?

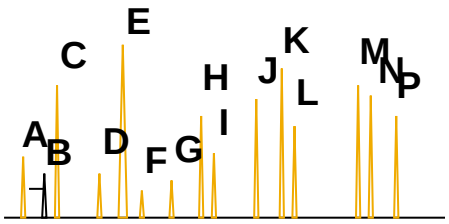
Definitions

- Extractables: chemical compounds that are forcibly removed from drug product container closure systems, packaging, or from devices under rigorous laboratory conditions (e.g. reflux)
  - If low levels are found then Leachables may not be needed

- Leachables: chemical compounds that migrate from drug product container closure systems, packaging, or from devices under normal-use/stability
  - May use simulation studies, e.g. placebos, chopped up polymer etc to accelerate the formulation of leachables

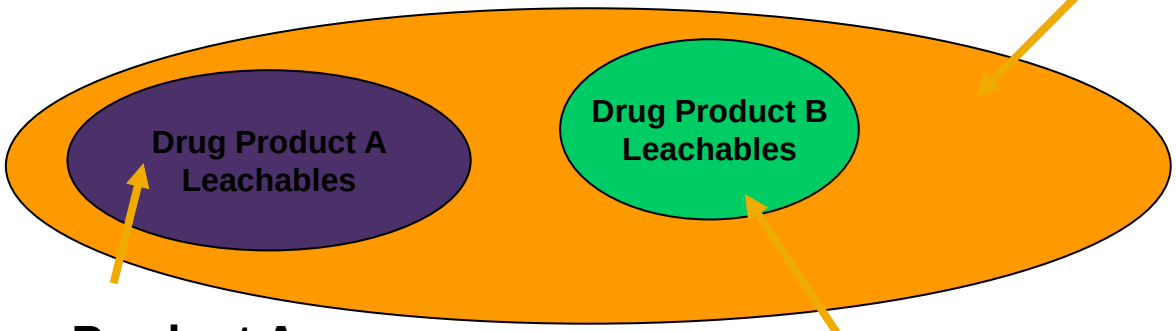
Extractables and Leachables

Different products will have unique leachables profiles from the same packaging system

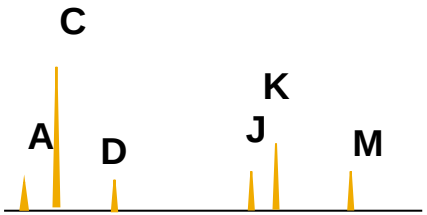


Extractables

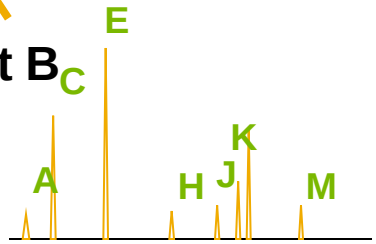
Forced Extraction Testing



Product A



Product B



Note: Some new Leachables may be seen outside the "design space"!

Regulatory Concern – FDA – Route v Packaging Interaction

Examples of Packaging Concerns for Common Classes of Drug Products.			
Degree of Concern Associated with the Route of Administration	***Likelihood of Packaging Component-Dosage Form Interaction***		
	High	***Medium***	***Low***
Highest	**Inhalation Aerosols and Solutions;** **Injections and Injectable Suspensions**	**Inhalation powders** **Sterile Powders and Powders for Injection;**	
High	**Nasal Aerosols and Sprays** **Ophthalmic Solutions and Suspensions;** **Transdermal Ointments and Patches;**		
Low	**Topical Solutions and Suspensions;** **Topical and Lingual Aerosols;** **Oral Solutions and Suspensions**	**Topical Powders; Oral powders**	**Oral Tablets** **Oral (Hard and Soft Gelatin) Capsules**

Regulatory Concern – detection limits

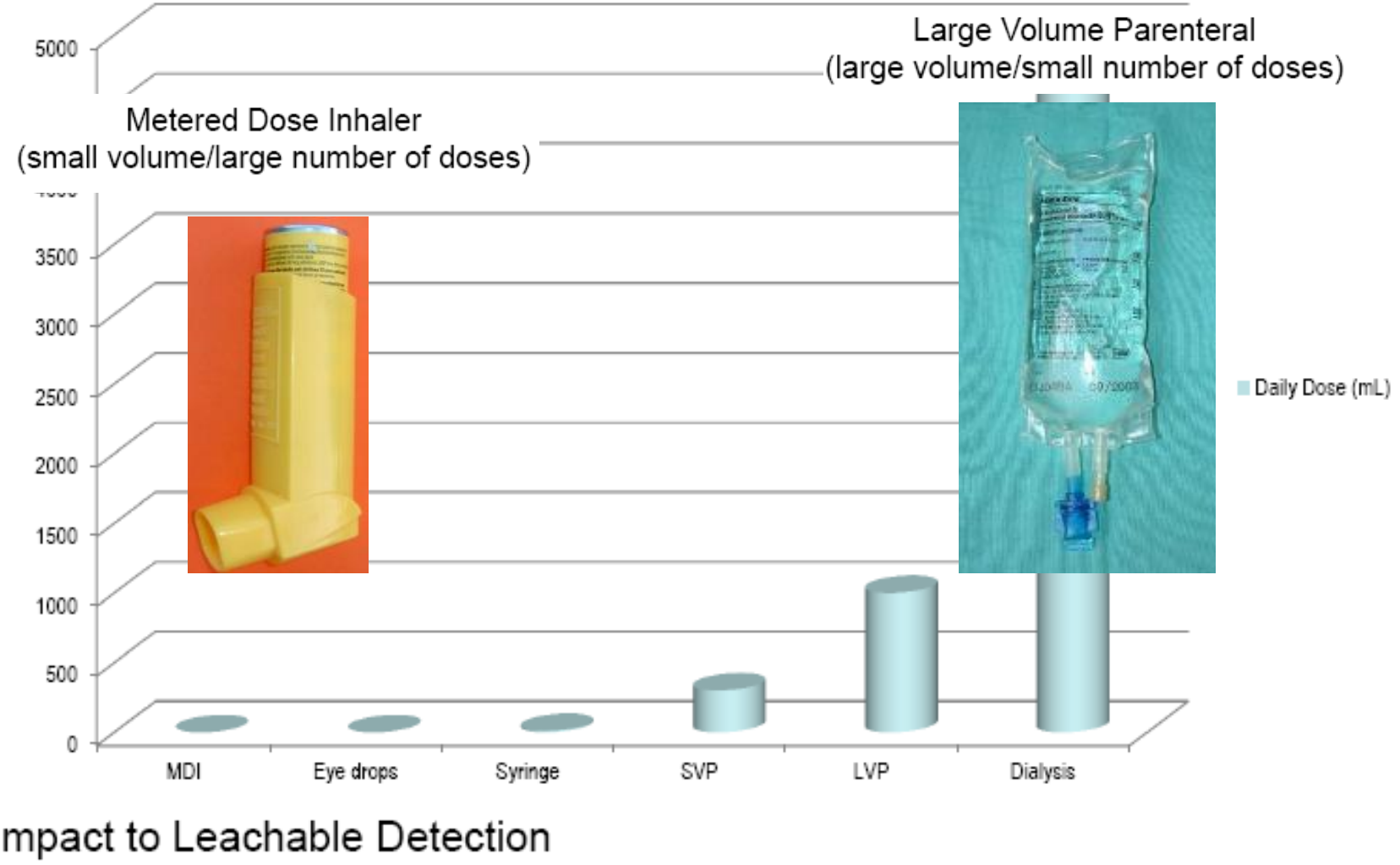
Authorities have increased scrutiny and focus on E&L compounds over last several years

- **PQRI guidelines exist for E&L in Orally Inhaled & Nasal Drug Products (OINDPs)**
  - **Safety Concern Threshold (SCT) <0.15 ug/day (ref TTC concept in PGIs 1.5ug/day)**
  - **Compounds seen at ≤ 5ug/day just need SARs evaluation**
  - **Compounds above this threshold must be toxicology justified**
  - **PAH's, Nitrosamines & 2-mercaptobenzothiazole are exceptions**

- **PODP (Parenteral, Ophthalmic Drug Products) guidelines are in preparation by the PQRI and the SCT is likely to be 1.5ug/day**

- **Solid dosage forms do not normally require E&L data & just require materials of construction & specification**

Analytical Concern – detection & quantification – may vary with dose!

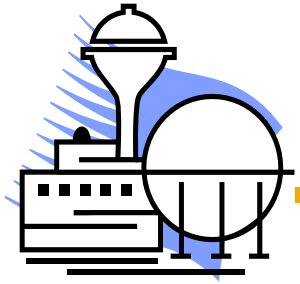


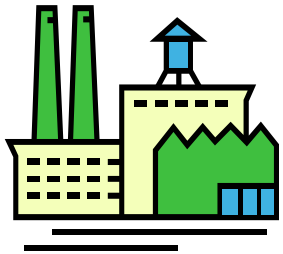
Impact to Leachable Detection

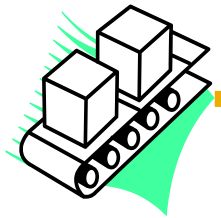
Change Control & LCM

- Complex supply chains – Support to Operations

N-4	N-3	N-2	N-1	(N) End user
Monomer Synthesis	Polymer Manufacturing	Master batcher	Molding Shop (Converter)	Packaging Containers/ Device Components







Bulk Chemicals
Storage Stabilizers

Catalysis
Stabilizers
Antioxidants
Processing aids
Others

Stabilizers
Antioxidants
Processing aids
Antistatic
Others

Lubricants
Colorants

Conclusions - Impurities in Pharmaceuticals

- Safe medicines can be achieved through appropriate control of impurities.
- Such control should be predicated on control to safe levels, not total avoidance.
- There is a strong regulatory framework that supports the assessment process.
- Care is though needed to ensure the approach taken in commensurate with the risk.
- By utilising a risk based approach it is possible to ensure actual risks are identified and mitigated.