Keeping afloat in a sea of impurities

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What a Chemist needs to know about Safety Assessment

SCI, London, 7/6/07

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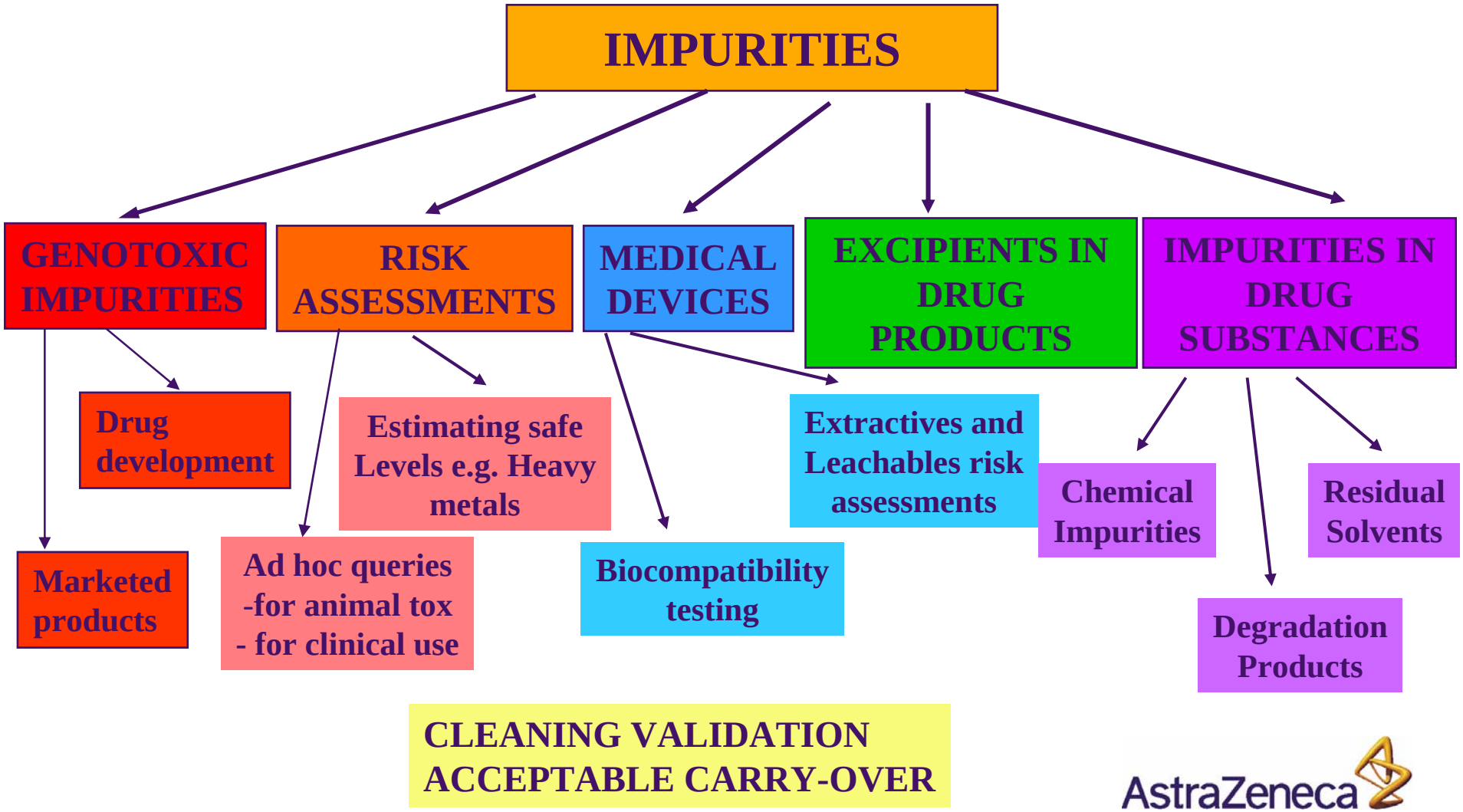
WHERE ARE IMPURITIES IMPORTANT?



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Outline of presentation

- External guidance on drug impurities - ICH
  - Q3A(R2)
  - Q3B(R2)
  - Q3C(R3)
- Qualification of impurities
- Genotoxic impurities
- Residual metal catalysts
- Summary

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ICH Q3 guidelines

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ICH Impurities Guidelines

- Requirements for assessing safety of impurities covered by 3 quality guidelines from the International Conference on Harmonisation (ICH) :

  Q3A(R2): Impurities in New Drug Substances
  (Current Step 4 version, dated 25 October 2006)
  Q3B(R2): Impurities in New Drug Products
  (Current Step 4 version, dated 2 June 2006)
  Q3C (R3): Impurities: Guideline for Residual Solvents
  (Current Step 4 version, parent guideline, 17/7/97, revised November 2005)

- Drug substance impurities addressed in 2 ways:
  1) chemistry aspects - classification/identification, report generation, setting specifications, analytical procedures;
  2) safety aspects - guidance for qualifying impurities either not present or present in substantially higher levels in drug batches used in safety/clinical studies. Thresholds given below which qualification not required.

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ICH Q3A(R2)
CLASSIFICATION OF IMPURITIES

- **Organic** (process and drug related)
  includes starting materials, by-products, intermediates, degradation products, reagents, ligands and catalysts
- **Inorganic**
  includes reagents, ligands and catalysts, heavy metals or other residual metals, inorganic salts, other materials (eg. filter aids, charcoal etc.)
- **Residual solvents**
  organic or inorganic

Specifically doesn't cover:

1) extraneous contaminants more appropriately addressed under GMP;
2) polymorphic forms
3) enantiomeric impurities

These are addressed in other ICH guidelines eg. Q6A

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ICH Q3A(R2): IMPURITIES IN NEW DRUG SUBSTANCES

Specification for new drug substance should include, where applicable, limits for:

- **Organic impurities**
  - each specified identified impurity
  - each specified unidentified impurity > qualification threshold
  - any unspecified identified impurity ≤ qualification threshold
  - any unspecified unidentified impurity ≤ identification threshold
  - total impurities
- **Residual solvents**
- **Inorganic impurities**

[Specified = included in specification for drug substance]

- Impurities should be qualified (process of acquiring/evaluating data that establishes biological safety of an impurity at the concentration and consequent dose to be administered to humans).

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ICH Q3A(R2): Impurities in New Drug Substances

- Level of impurity present in safety/clinical studies considered qualified (up to level tested).
- Same true for impurities if significant animal and/or human metabolites.
- If no data available to qualify proposed specification level, studies may be needed when following thresholds exceeded*:

Max daily dose	Qualification threshold	Identification threshold	Reporting threshold
≤2g/day	**0.15%**/1.0mg/day (lowest)	**0.10%**/1.0mg/day (lowest)	0.05%
>2g/day	0.05%	0.05%	0.03%

- Higher/lower levels acceptable if justified / necessary (case-by-case)
  - E.g. lower needed if evidence impurity associated with adverse effects in patients; higher if preclinical levels higher or if lower level of concern (consider patient population, drug class effects, technical factors etc).

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ICH Q3B(R2): Impurities in New Drug Products

- Covers DPs of active substance, including reaction products with excipient or container system.
- Degradation products observed in stability studies performed at recommended storage conditions should be identified, qualified and reported when following thresholds exceeded (lowest figure applies)*:

Max daily dose	Qualification threshold	Identification threshold	Reporting threshold
<1mg	**1.0**% or 50µg/TDI	1.0% or 5µg/TDI	0.1%
1mg-10mg	#**1.0**% or 50µg/TDI	0.5% or 20µg/TDI	0.1%
>10mg-100mg	0.5% or 200µg/TDI	0.2% or 2mg/TDI	0.1%
>100mg-1g	0.2% or **3mg**/TDI	0.2% or 2mg/TDI	0.1%
>1g-2g	0.2% or **3mg**/TDI	0.2% or 2mg/TDI	0.05%
>2g	**0.15**%	**0.10**%	0.05%

- Not necessary to identify DPs at levels below these thresholds unless suspected to be unusually potent (catch-22?).

Qualification threshold for 10mg/day is 0.5% /200µg TDI

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DEGRADATION PRODUCTS - EXAMPLE OF QUALIFICATION

- DP present at 0.3%
- Max human daily dose of 25mg drug substance
- Total daily intake of impurity is therefore 75µg/subject (or 1.5µg/kg body weight/day for a 50kg subject)
- ICH Q3B(R) gives qualification threshold of 0.5% or 200µg TDI (whichever is lowest) for drug dose of 10-100mg/day.
- Thus, impurity is qualified on this basis.
- NB. At this level, ICH would still require impurity to be identified (threshold 0.18% / 1.8mg/day) and reported (threshold 0.1%).

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ICH Q3C(R3): Impurities: Residual Solvents

- Organic volatile chemicals used/produced in manufacture of active substances/excipients.
- No therapeutic benefit, should be removed as far as possible.
- Classified into 3 groups:

Class 1 (solvents to be avoided)
known/suspect human carcinogens
eg. **benzene** (2ppm), **1,1-dichloroethene** (8ppm)

Class 2 (solvents to be limited)
non-genotoxic animal carcinogens, possible neurotoxicants or teratogens. eg. **acetonitrile** (410ppm), **cyclohexane** (3880ppm), **ethylene glycol** (160ppm), **methanol** (3000ppm)

Class 3 (solvents with low toxic potential)
no health-based exposure limit needed (PDE of ≤50mg/day)
eg. **acetone**, **ethanol**, **DMSO**

- A 4th group lists additional solvents for which no adequate tox data available to generate a PDE; onus on manufacturers to justify levels

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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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General points on qualification

- For impurities with known tox properties / specific alerts, refer to limits in European Pharmacopoeia or USP. Where pharmacopoeial data not available, limits should be based on available literature.
- Assuming tox studies use material containing the impurities, specification for subsequent batches can be modified with reference to doses administered and effects seen (e.g NOEL, NOAEL).
- Appropriate to use mg/kg comparisons to assess 'cover' in early development but need to be aware of mg/m^2 comparisons used by regulators at NDA/MAA.
- Also need to be aware that Japan may expect a margin for qualification of impurities
- If batch of drug for Phase I contains impurities not tested in toxicology, adopt a conservative approach e.g. apply ICH-like qualification threshold (0.2%) or give rationale for accepting higher thresholds.
- Specific qualification or bridging in vivo studies - often last resort (time/resource/risk of generating new findings).

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Qualification example – Drug X

- Question: is clinical batch specification OK for use in man based on preclinical studies on toxicology batch?
- Maximum clinical dose is 25mg/day
- Qualification based on rat 1 month study, No Observed Adverse Effect Level was 5mg/kg/day

Impurity	Level (%) in tox batch	Level (mg/kg) qualified at rat NOAEL	Level (%) qualified for 25mg clinical dose	Level (%) in clinical batch
A	0.02	0.001	0.2	0.09
B	0.04	0.002	0.4	0.60
C	0.06	0.003	0.6	0.11

- Impurities A and C are qualified but impurity B is not in this case.
- Mg/kg body weight comparisons acceptable for development but for MAA/NDA regulators will use mg/m^2 body surface area comparisons: none of these impurities is qualified in terms of mg/m^2.

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Qualification in mg/m^2 & mg/kg

- Background information

  Rat NOAEL is 5mg/kg/day; Level of impurity X is 0.6%

  Maximum clinical dose of drug is 100mg/day (2mg/kg/day)

  Max level of X required for specification is 1.3%

- For the rat:
  0.6% of X @ 5mg/kg is equal to 0.03mg/kg/day
  0.03mg/kg is equal to (0.03 x 6) 0.18mg/m^2/day

- For man:
  1.3% of X at max dose of 2mg/kg/day is equal to 0.026mg/kg/day
  0.026mg/kg/day is equal to (0.026 x 37) 0.962mg/m^2

- **Comparing mg/kg/day (0.03 v 0.026) the level is just qualified**

- **Comparing mg/m^2 (0.18 v 0.962) the level is not qualified**

- In order to qualify in mg/m^2 (with margin of 1),
  tox level should be 0.962 ÷ 6 = 0.161mg/kg/day
  at the drug NOAEL (5mg/kg/day) this would equate to 3.22%.

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Interesting impurity issues 1

- Email from colleague in QA in Sweden:

  'After micronisation of XXXX suspension we have found some orange plastically peaces in one of our batch. These very small peaces are identified from a rubber-hammer that has been used by the operators to open the mill.'

Stanley 57-531 hammer 18oz

- How does this rubber (polyurethane) material affect the product, regarding both product- and patient safeties?
- Can I have a statement that guarantees the safety of the product?

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Interesting impurity issues 2

- Remnants of pen found in batch of drug substance!!

  Is batch OK to use?

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Genotoxic impurities

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Genotoxic impurities – why do we need guidance?

- Existing Q3 guidelines not clear on how to handle genotoxic impurities
- Standard thresholds not applicable to genotoxic impurities; 'acceptance criteria should be set no higher than the level that can be justified by safety data'
- ICH Q3A(R) – no need to identify structure below 0.1% (1000ppm) or 0.05% (500ppm) if dose >2g/day
- At 1000ppm, 2g dose of drug could contain 2mg genotoxic impurity
- Genotoxicity assays too insensitive to detect effects of an impurity @ 0.1%; very few genotoxic compounds would be detectable at or below this level (also true for carc studies)
- Few genotoxic carcinogens have detection limit in Ames of <5μg/plate (corresponding to 1000ppm in 5mg drug substance)
- If impurity is unidentified below 0.1%, how would its potential genotoxicity be known or suspected?

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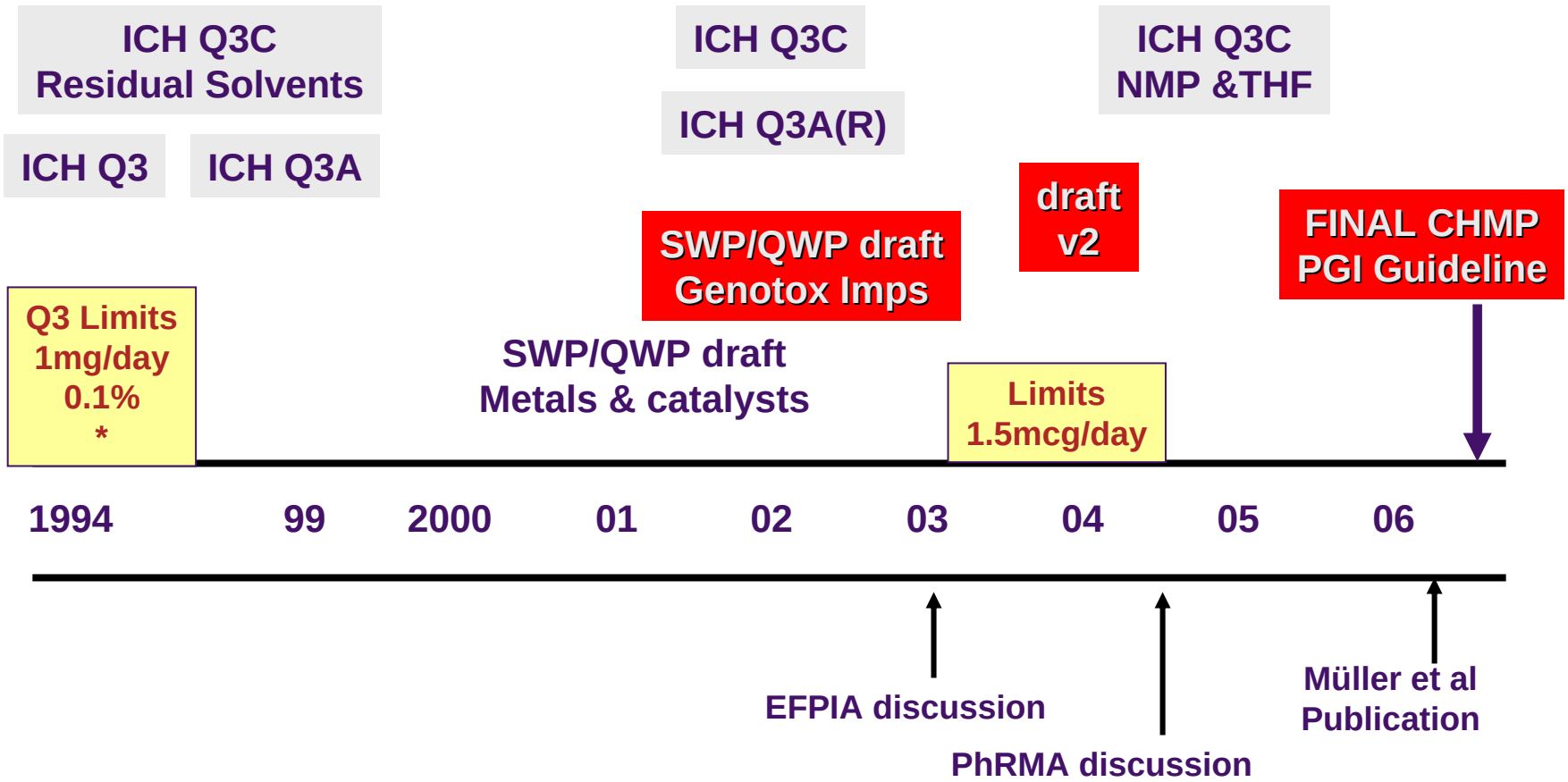
How has the environment changed?



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Final CHMP Guideline on the Limits of Genotoxic Impurities

- Scope:

  '…general framework and practical approaches on how to deal with genotoxic impurities in new active substances. It also relates to new applications for existing active substances, where assessment of the route of synthesis, process control and impurity profile does not provide reasonable assurance that no new or higher levels of genotoxic impurities are introduced as compared to products currently authorised in the EU containing the same active substance. The same also applies to variations to existing Marketing Authorisations pertaining to the synthesis. The guideline does, however, not need to be applied retrospectively to authorised products unless there is a specific cause for concern.'

- Adopted by CHMP 28th June 2006.
- Came into effect 1st January 2007

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Final CHMP Guideline

- **Current regulatory assumption**: in vivo genotoxic compounds have potential to damage DNA at any level of exposure; thus, there is **no discernible threshold** and **any level of exposure carries a risk**
- But evidence for thresholds does exist for chemicals interacting with non-DNA targets (& effective protective mechanisms for low doses of DNA-reactive chemicals)
- Impossible to define 'safe' exposure to non-threshold genotoxins; need concept of 'acceptable risk'
- Pragmatic approach needed – concept of '**Threshold of Toxicological Concern**' (TTC); established by FDA ('Threshold of Regulation') initially for chemicals migrating from packaging into foods
- TTC intended to be 'low enough to ensure that public health is protected, even in the event that a substance…is later found to be carcinogenic'

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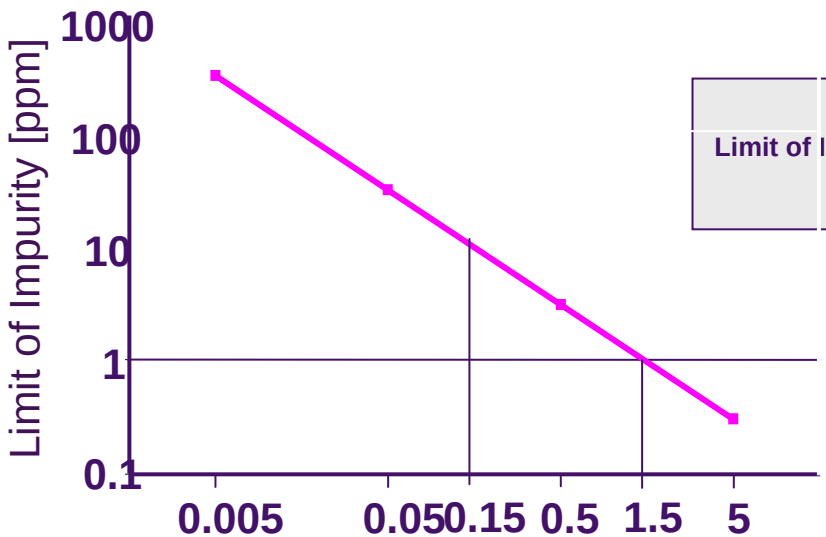
Final CHMP Guideline

- Data from analysis of 730 carcinogens estimates daily exposure to ≤0.15µg/day for most (genotoxic) carcinogens not likely to exceed lifetime cancer risk of 1 in 10^6 (1 in a million)
- For pharmaceuticals, limit based on 1 in 10^5 risk (1.5µg/day) as drugs have a benefit, not normally used for lifetime and precedent of benzene in Q3C
- Exceptions eg. aflatoxin-like and N-nitroso compounds – need case-by-case assessment
- Higher exposures OK if justifiable e.gs. For drug use for <30 days, terminal patients, lack of alternatives, other significant sources of exposure) – case by case



$$\text{Limit of Impurity [ppm]} = \frac{1.5\ \mu g}{\text{Daily Dose of Drug [g]}}$$

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Does the guideline apply to development as well as registration?

- Not clear from guideline but…
- Some pharma companies been put on clinical hold at IND stage by Neuropharm division of FDA - applied limit of 1ppm to imps resembling an alkylating agent regardless of dose
- Default could be 1.5µg/day in development unless higher level justifiable!
- In 2004, US PhRMA Genotoxicity Taskforce set up to look specifically at clinical development
- Produced a White Paper now published as Müller et al. (2006).

A rationale for determining, testing, and controlling specific impurities in pharmaceuticals that possess potential for genotoxicity

Lutz Müller [a,*], Robert J. Mauthe [b], Christopher M. Riley [c], Marta M. Andino [d], David De Antonis [d], Chris Beels [e], Joseph DeGeorge [f], Alfons G.M. De Knaep [g], Dean Ellison [f], Jane A. Fagerland [h], Rebecca Frank [i], Betsy Fritschel [j], Sheila Galloway [f], Ernie Harpur [k], Charles D.N. Humfrey [l], Alexander S. Jacks [i], Nirdosh Jagota [m], John Mackinnon [e], Ganapathy Mohan [k], Daniel K. Ness [n], Michael R. O'Donovan [l], Mark D. Smith [o], Gopi Vudathala [k], Larry Yotti [p]

Regulatory Toxicology and Pharmacology 44 (2006) 198–211

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Müller et al. – focus on limits for PGIs during drug development

- Paper recognises several key points:
  - primary concern is non-thresholded DNA-reactive carcinogens
  - commitment to application of As Low As Reasonable Practicable (ALARP)
  - rational specification limits proposed taking into account duration of clinical trials, maturity of synthetic scheme, availability of analytical methods and potential risks
  - single assay (e.g. bacterial reverse mutation assay) usually sufficient to conclude absence of genotoxicity
- Defines 5 Classes of PGIs

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PhRMA proposed classification

- **Class 1:** Impurities known to be genotoxic (mutagenic) and carcinogenic
- **Class 2:** Impurities known to be genotoxic (mutagenic), but with unknown carcinogenic potential
- **Class 3:** Alerting structure, unrelated to parent structure and of unknown genotoxic (mutagenic) potential
- **Class 4:** Alerting structure, related to the parent API
- **Class 5:** No alerting structure or indication of genotoxic potential

Qualification of Impurities

- **Step 1:** Identify and classify structural alerts in parent compound and impurities
- **Step 2:** Establish a qualification strategy
- **Step 3:** Establish acceptable limits

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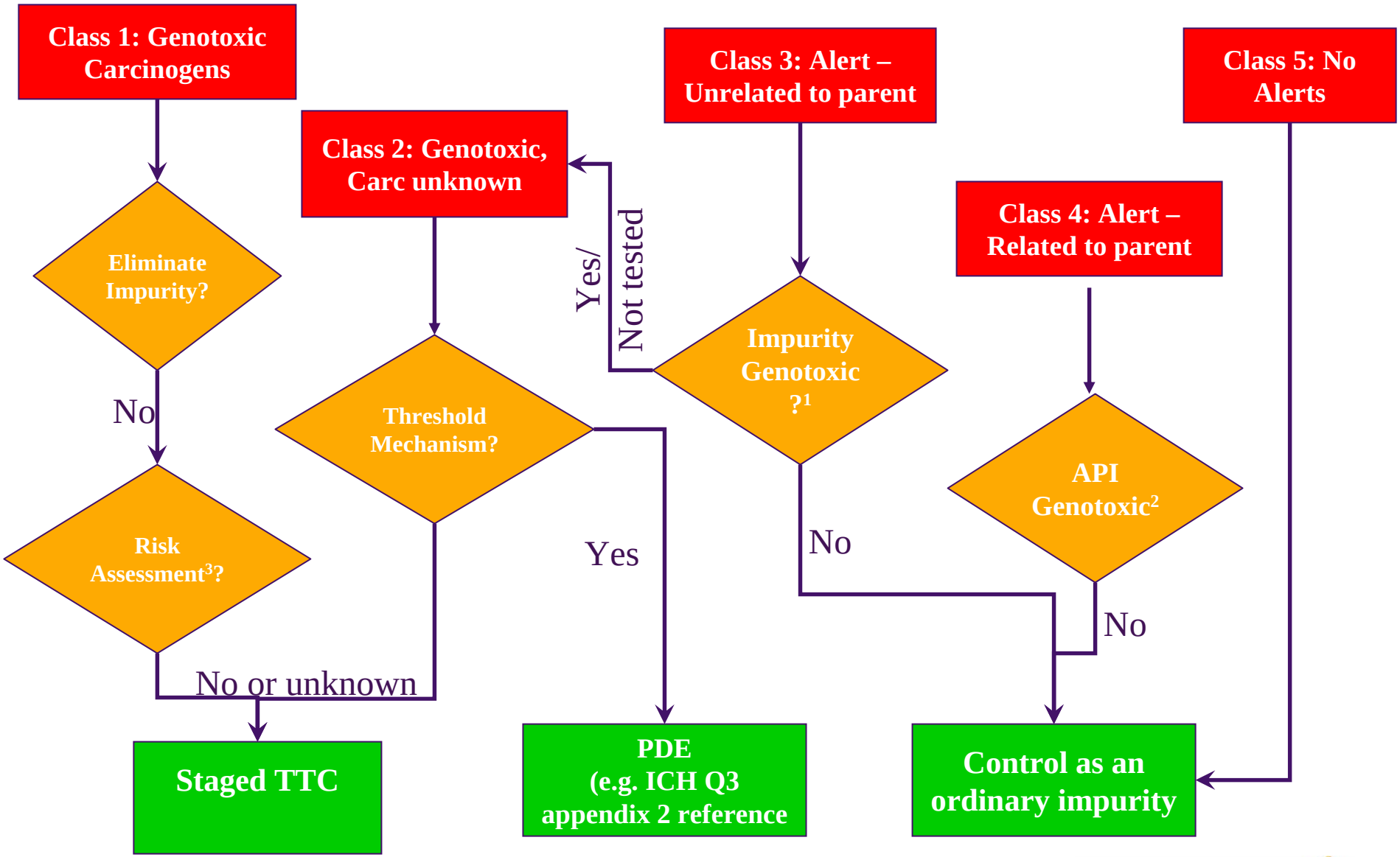
Proposed categorization, qualification and risk assessment of impurities



[1]Either tested neat or spiked into API and tested at ≥ 250 µg/plate
[2]If API is positive, risk benefit analysis required
[3]Quantitative risk assessment to determine ADI

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Allowable daily intake for genotoxic impurities during clinical development, a staged TTC approach

	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%	

Known carcinogens should have compound-specific risk calculated
Risk level for up to 12 months is 1 in 10^6, for >12 months is 1 in 10^5

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Basic stepwise approach to assess PGI risk in drug substances

Step 1
Identification and Fate of PGIs in synthetic route of drug substance

Step 2
Structural Assessment (SAR) of identified structures

Step 3
Hazard Evaluation and Classification

Step 4
Quantification of Level present in drug substance

Step 5
Risk Assessment e.g. drug dose/PGI concentration(s)/staged TTC

Step 6
Communication

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Residual metals

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Draft CPMP Note for Guidance on Metal catalysts

- Draft re-released for comment June 2002, again in January 2007!
- Oral/parenteral concentration limits (ppm) proposed for 14 metals in active substances or excipients; Pt, Pd, Ir, Rh, Ru, Os, Mo, V, Ni. Cr, Cu, Mn, Zn and Fe
- Limits derived from estimated oral/parenteral PDEs (from literature data) after application of a variable % figure to account for variation in dietary intake of each metal and polypharmacy.
- Limits assume intake of 10g drug/day (as in ICH Q3 docs; if limits not achievable, option to base limits on actual intake (minimum of 1g/day)
- EFPIA comments on June 02 draft expressed many concerns eg. comprehensiveness of searching, interpretation, variation in % PDE, no consideration of technical feasibility, omitted metals used as catalysts, statement that 'no therapeutic benefit from residual metals' but some are essential minerals etc, etc…
- Following discussion with EFPIA an industry-led re-draft was proposed and is reflected in latest draft

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Latest redraft by EFPIA

Metals divided into 3 classes (a la Q3C):

- Class 1 (metals of significant safety concern)
  - Known/suspected human carcinogens, genotoxic and sometimes nongenotoxic animal carcinogens or possible causative agents of other irreversible toxicity e.g. neurotoxicity or teratogenicity
  - Metals suspected of other significant but reversible toxicities
  - Examples: Ir, Pd, Pt, Ru, Rh, Os, Mo, V, Cr and Ni
- Class 2 (metals with low safety concern)
  - Trace metals required for nutritional purposes or present in foodstuffs or readily available supplements
  - A health-based exposure limit is appropriate
  - Examples: Cu and Mn
- Class 3 (metals with minimal safety concern)
  - Metals ubiquitous in the environment or plant and animal kingdoms
  - No health-based limit necessary
  - Recommended nutritional intakes of $\geq$10mg/day
  - Examples: Fe and Zn

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Latest EFPIA proposals

	Oral exposure		Parenteral exposure	
	PDE (μg/day)	**Concentration (ppm)**	**PDE (μg/day)**	**Concentration (ppm)**
Class 1A: Pt, Pd	100	10	10*	1*
Class 1B: Ir, Rh, Ru, Os	100**	10**	10**	1**
Class 1C: Mo, Ni, Cr, V	300	30	30*	3*
Class 2: Cu, Mn	2500	250	250	25
Class 3: Fe, Zn	13000	1300	1300	130

* Separate limits for inhalation exposure to Pt, Cr(VI) and Ni;
** Subclass limit

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Summary

- Existing Q3 impurity guidelines identify requirements for impurities, degradation products and residual solvents for drug registration; not necessary for drug development where higher levels of impurities can be justified based on toxicological qualification
- Impurity qualification depends on comparing dose in animals at NOAEL or LOAEL with dose in man at highest clinical dose.
  - mg/kg OK for development but be aware mg/m^2 needed for NDA
- EMEA/CHMP genotoxic impurities guideline came into operation 1 January 2007 with 1.5µg/day TTC default limit; many companies using staged TTC from Müller et al (2006) for drug development
- 'New' guidelines being developed for residual metals (final in 2007?)
- Safety Assessment support also covers other imporant areas including excipients, medical devices and cleaning limits in drug manufacturing facilities.
- Impurities in biologics not covered here but important to consider where relevant

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As with most things we do in Safety Assessment, it's all about RISK ASSESSMENT!!

Checklist:

- Swimming Pool -
- Metal Ladder -
- Bare feet -
- Electric drill -
- Goggles - Check