The Use of Safety Based Arguments to Support Degradation Product Limits

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The Netherlands

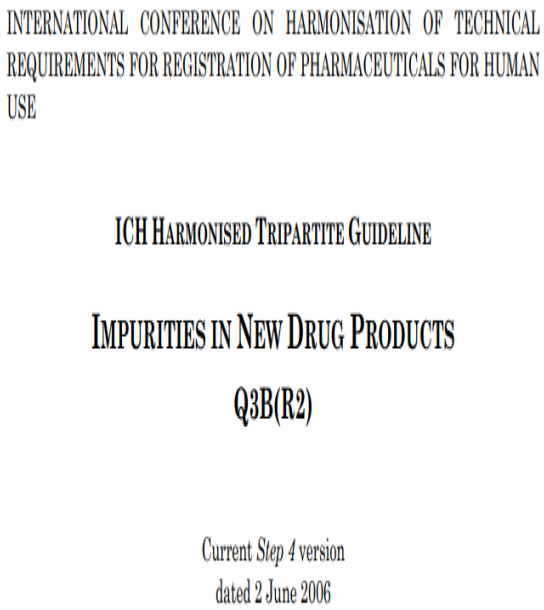
Introduction

- Safety based guidance for impurity levels
- Safety Based Limits
- Early development guidance
- What about metabolites?
- What about Pro-drugs?
- Emerging guidance
- Conclusions

SAFETY BASED GUIDANCE FOR IMPURITIES

ICH Q3B

- This guideline addresses only those impurities in **new drug products** classified as degradation products of the drug substance or reaction products of the drug substance with an excipient and/or immediate container closure system (collectively referred to as "**degradation products**" in this guideline)
  - Each **specified identified degradation product**
  - Each **specified unidentified degradation product**
  - Any unspecified degradation product with an acceptance criterion of **not more than (≤) the identification threshold**
  - **Total degradation products**
- Guidance is only applicable to new drug products, i.e. commercial, **not development phases**


INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

IMPURITIES IN NEW DRUG PRODUCTS

Q3B(R2)

Current *Step 4* version
dated 2 June 2006

ICH Q3B

Attachment 1: Thresholds for Degradation Products in New Drug Products

Reporting Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
≤ 1 g	0.1%
> 1 g	0.05%

Identification Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
< 1 mg	1.0% or 5 µg TDI, whichever is lower
1 mg - 10 mg	0.5% or 20 µg TDI, whichever is lower
>10 mg - 2 g	0.2% or 2 mg TDI, whichever is lower
> 2 g	0.10%

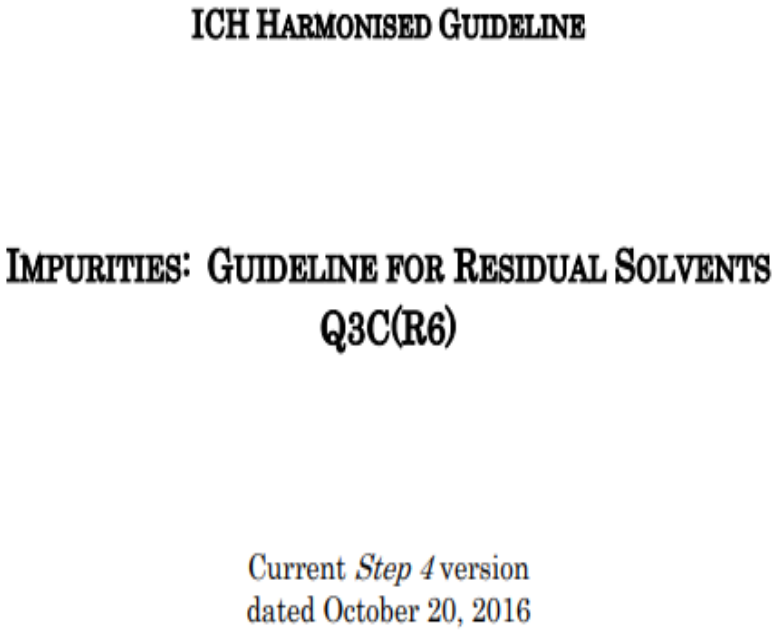
Qualification Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
< 10 mg	1.0% or 50 µg TDI, whichever is lower
10 mg - 100 mg	0.5% or 200 µg TDI, whichever is lower
>100 mg - 2 g	0.2% or 3 mg TDI, whichever is lower
> 2 g	0.15%

Although the TDI (total daily intake) is highlighted; this guidance applies to the dosage form on a concentration basis not the dose delivered/day. In contrast, other ICH Q/M guidance looks at acceptable safety based on daily dosing

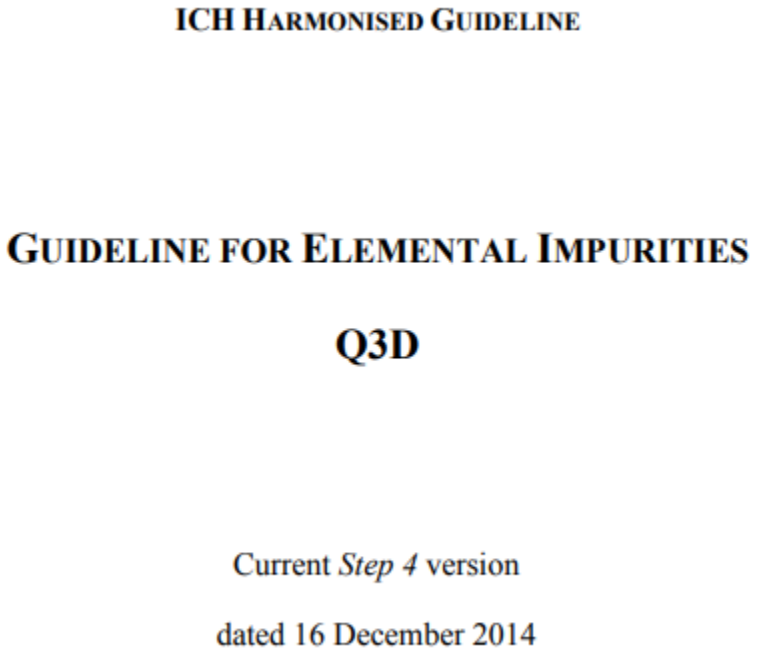
ICH Safety Based Impurity Guidance (ICH 3C)

- Solvents classified into **class1, 2 or 3**
  - Avoidance of class 1 (most toxic)
- Solvents in class 1 or 2 are allocated individual **PDEs based on toxicity**
- Solvents in class 3 allocated a class-based limit of **5000 ppm**
- In practice there is an expectation that levels of class 3 solvents (and also class 2?) should be reduced to levels **as low as reasonably practicable**
  - Thus, **process capability** considerations trump safety considerations
  - No clear guidance provided for **allowable levels during clinical development**



ICH Safety Based Impurity Guidance (ICH Q3D)

- Residual metals classified into **four classes**: class 1, 2a, 2b and 3
- All 24 residual metals are allocated **individual PDEs**
  - Class 1 < Class 2a < Class 2b < Class 3
  - **Risk assessment** can be used to assess likelihood of metals being present
  - Based on risk assessment **testing may be required** (would be typically required for deliberately added Class 2b or 3 metals)
  - Metals that are likely to be present can be omitted from specification if typically the levels are **< 0.3 PDE**, i.e. some **process capability considerations**



ICH HARMONISED GUIDELINE

GUIDELINE FOR ELEMENTAL IMPURITIES

Q3D

Current *Step 4* version

dated 16 December 2014

ICH Safety Based Impurity Guidance (ICH M7)

- Cohort of Concern (CoC) to be avoided e.g. N-nitroso, afflotoxin-like, azoxy
  - **Valsartan withdrawal issue**
- Whole-life TTC (Threshold of Toxicological Concern) of **1.5µg/day**
- **Less than Lifetime limits (LLT)** based on duration of dosing can be applicable during clinical development **AND** for commercial products
- **Allowable intakes (AIs)** for common mutagenic reagents, e.g. hydrazine
  - But concept **not accepted for CoC**
- No requirement to demonstrate levels below TTC, LTL or AI; these are **VSDs (virtually safe doses)**
  - But can be omitted from specification if < 0.3 VSD, i.e. **some process capability considerations**

ICH HARMONISED GUIDELINE

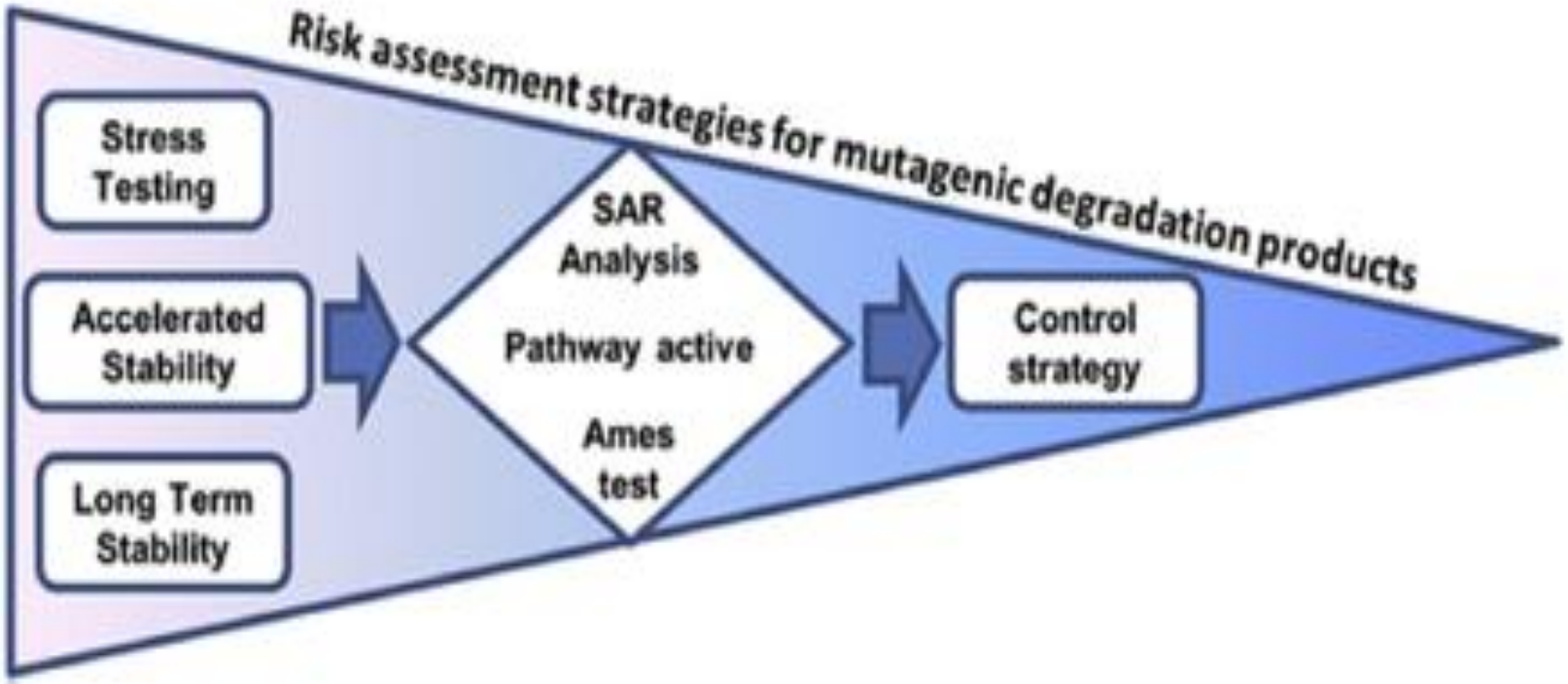
ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC) IMPURITIES IN PHARMACEUTICALS TO LIMIT POTENTIAL CARCINOGENIC RISK

M7(R1)

Current *Step 4* version

dated 31 March 2017

ICH M7: Strategies for Mutagenic Impurities



Limited guidance on mutagenic degradation in ICH M7, so a cross-company consortium tried to provide some basic guidance ……

Kleinman et al. 2015. Org. Proc. Res. Dev., 19, 1447-1457

ICH M7: Strategies for Mutagenic Impurities: Active/Inactive Pathways

- Stress testing bi-products are only important if they reflect/predict those degradation pathways that will occur at accelerated (40C/75%RH) or long term (25C/60%RH) conditions, i.e. they are **"active" degradation pathways**
  - Most bi-products of stress testing are **NOT relevant to ICH storage conditions** and reflect "inactive" degradation pathways
  - Which is why most companies look to **partly degrade, i.e. ca. 20% total degradation** their products rather than completely degrading, i.e. >90%
  - Predictive studies are useful but don't always mimic real time data: Zeneth < Stressed studies (including excipient compatibility) < ICH stability

Kleinman et al. 2015. Org. Proc. Res. Dev., 19, 1447-1457

EARLY DEVELOPMENT GUIDANCE FOR IMPURITIES

What Guidance is there for Early Development?

- Limited … ICH Q3B is only applicable to commercial products
  - But many **EU regulatory agencies still try to apply** this guidance to development….. Even Phase I!
- ICH Q3C is often applied to development projects as **process capability arguments** are expected to apply for commercial products
  - Applicable to solvent based drug product processes
- A **risk assessment** is expected for early phase activities and limits aligned to ICH Q3D are expected for deliberately added metals, i.e. class 2b
  - Impact of **excipients in risk assessment** of drug products is critical
- Surprisingly, ICH M7 is aligned with development AND commercial activities via LTL limits and an **application of Haber's Law**

ICH M7

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 LTL limits allow companies to develop robust strategies for mutagenic (or potentially mutagenic) impurities and degradants at different stages of drug development
  - Uses **Haber's Law**, a fundamental concept in toxicology where **concentration (C) x time (T) = a constant (k)**.
  - Therefore, the carcinogenic effect is based on both dose and duration of exposure
- The risk assessment is **iterative and ongoing** and triggered by changes to API synthesis and process and drug product formulation and process
- This approach is also applicable to commercial products based on their **treatment durations** and importantly **projected life expectancy**

ICH M7

Table 4. Examples of clinical use scenarios with different treatment durations for applying acceptable intakes

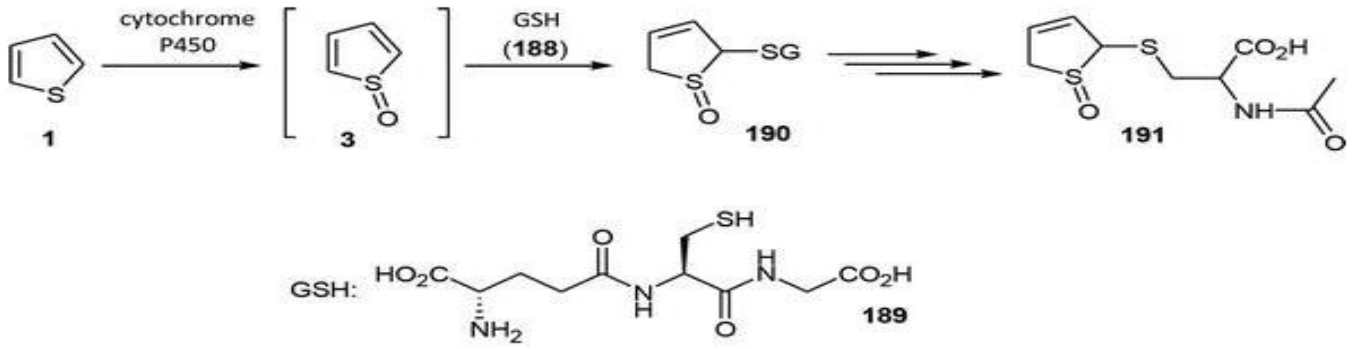
Scenario[1]	Acceptable Intake (µg/day)
Treatment duration of ≤ 1 month: e.g., drugs used in emergency procedures (antidotes, anesthesia, acute ischemic stroke), actinic keratosis, treatment of lice	120
Treatment duration of > 1-12 months: e.g., anti-infective therapy with maximum up to 12 months treatment (HCV), parenteral nutrients, prophylactic flu drugs (~ 5 months), peptic ulcer, Assisted Reproductive Technology (ART), pre-term labor, preeclampsia, pre-surgical (hysterectomy) treatment, fracture healing (these are acute use but with long half-lives)	20
Treatment duration of >1-10 years: e.g., stage of disease with short life expectancy (severe Alzheimer's), non-genotoxic anticancer treatment being used in a patient population with longer term survival (breast cancer, CML), drugs specifically labeled for less than 10 years of use, drugs administered intermittently to treat acute recurring symptoms[2] (chronic Herpes, gout attacks, substance dependence such as smoking cessation), macular degeneration, HIV[3]	10
Treatment duration of >10 years to lifetime: e.g., chronic use indications with high likelihood for lifetime use across broader age range (hypertension, dyslipidemia, asthma, Alzheimer's (except severe AD), hormone therapy (e.g., GH, TH, PTH), lipodystrophy, schizophrenia, depression, psoriasis, atopic dermatitis, COPD, cystic fibrosis, seasonal and perennial allergic rhinitis	1.5

[1] This table shows general examples; each example should be examined on a case-by-case basis. For example, 10 µg/day may be acceptable in cases where the life expectancy of the patient may be limited e.g., severe Alzheimer's disease, even though the drug use could exceed 10 year duration.

METABOLITES

Degradants/Metabolites

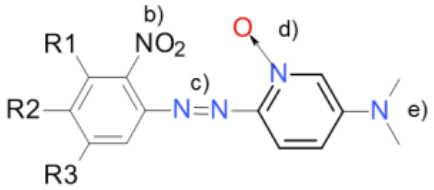
- Most CYP metabolising enzymes are oxidative in nature



- **Sulfoxides and sulfones** are common in sulfide containing pharmaceuticals
- **N-oxides** are common in nitrogen containing pharmaceuticals
  - Nicotine N-Oxide (B), Cotinine N-oxide (C)

T. Thiemann. Thiophene S-Oxides, 2018, DOI: 10.5772/intechopen.79080

Degradants/Metabolites



- Aromatic N-oxides often considered alerting for mutagenicity
  - Impacts metabolites / degradants
  - Basis of this alert is not clear and has been questioned
  - Based on recent work by cross-industry consortium resulted in a downgrade of the general aromatic N-oxide alert
  - Enough public and proprietary data to assign the quindioxin and related chemicals as well as benzo[c][1,2,5]oxadiazole 1-oxide subclasses as alerts

Extending (Q)SARs to incorporate proprietary knowledge for regulatory purposes: is aromatic *N*-oxide a structural alert for predicting DNA-reactive mutagenicity?

Alexander Amberg, Lennart T Anger, Joel Bercu, David Bower, Kevin P Cross, Laura Custer, James S Harvey, Catrin Hasselgren, Masamitsu Honma, Candice Johnson ... Show more

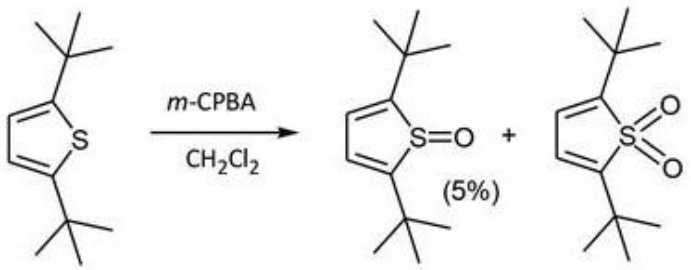
Mutagenesis, Volume 34, Issue 1, January 2019, Pages 67–82, https://doi.org/10.1093/mutage/gey020

Published: 05 September 2018 **Article history ▾**

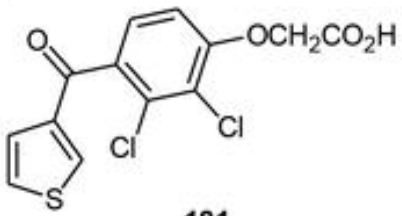
Amberg et al. Mutagenesis, 34, 2019, 67-82

Oxidation/Metabolism

- Oxidation to sulfoxides and sulfones is a common oxidative pathway for thiophene containing heterocyclics



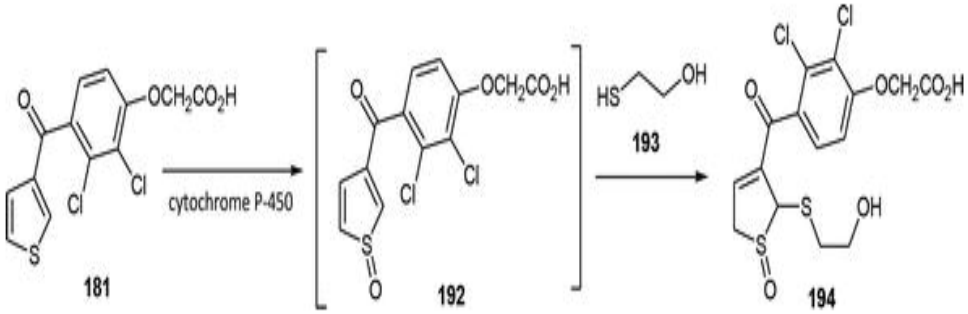
- Many common pharmaceuticals contain this sub-structure, e.g. tenilic acid



181

tienilic acid

- Same oxidative pathways are often seen in CYP mediated metabolism

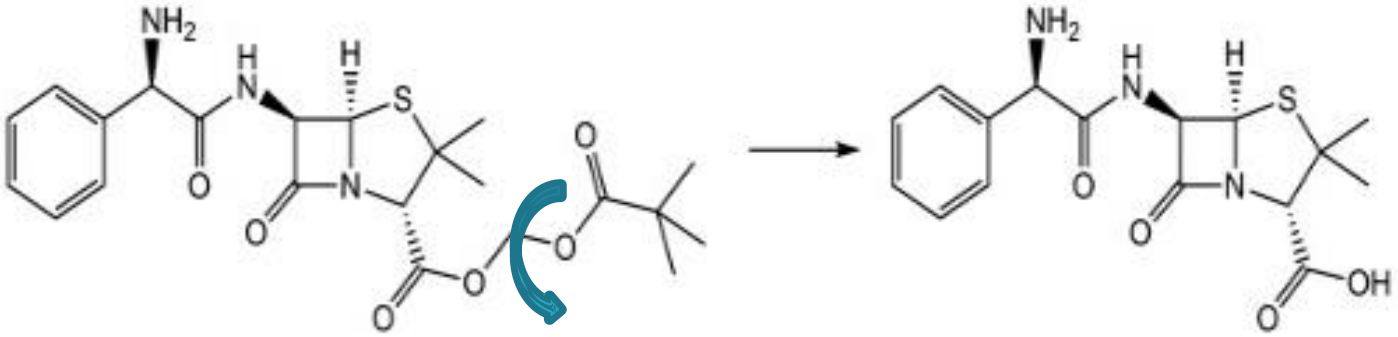


Metabolites

- In certain cases **Meteor** may be as important as **Zeneth**
- As a Meteor prediction that a degradant is also a likely metabolite may give greater flexibility in setting early phase specification limits

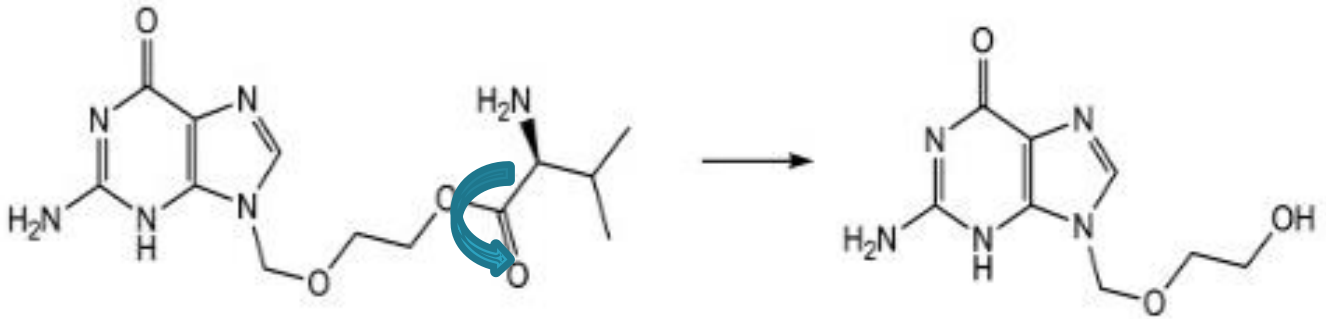
PRO-DRUGS

Pro-Drugs have pre-programmed metabolic liability



Pivampicillin
clogP = 1.77

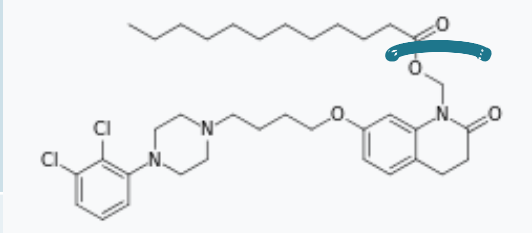
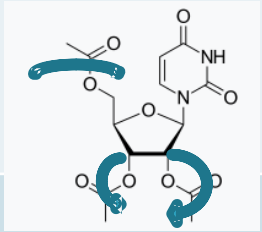
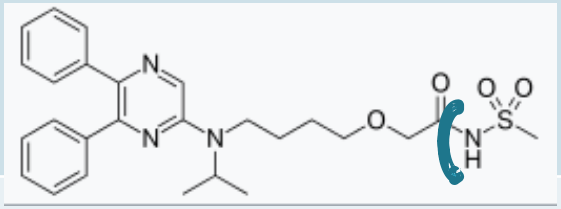
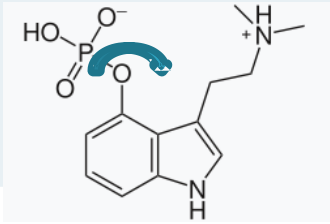
Ampicillin
clogP = –2.30



Valacyclovir

Acyclovir

But they are equally susceptible to chemical hydrolysis

Prodrug	Active Form	Activation	Structure
Aripiprazole Lauroxil	Aripiprazole	Esterases / Hydrolysis	
Uridine Triacetate	Uridine	Esterases / Hydrolysis	
Selexipag	ACT-333679	Esterases / Hydrolysis	
Psilocybin	Psilocin	Phosphatases / Hydrolysis	

Metabolite Limits

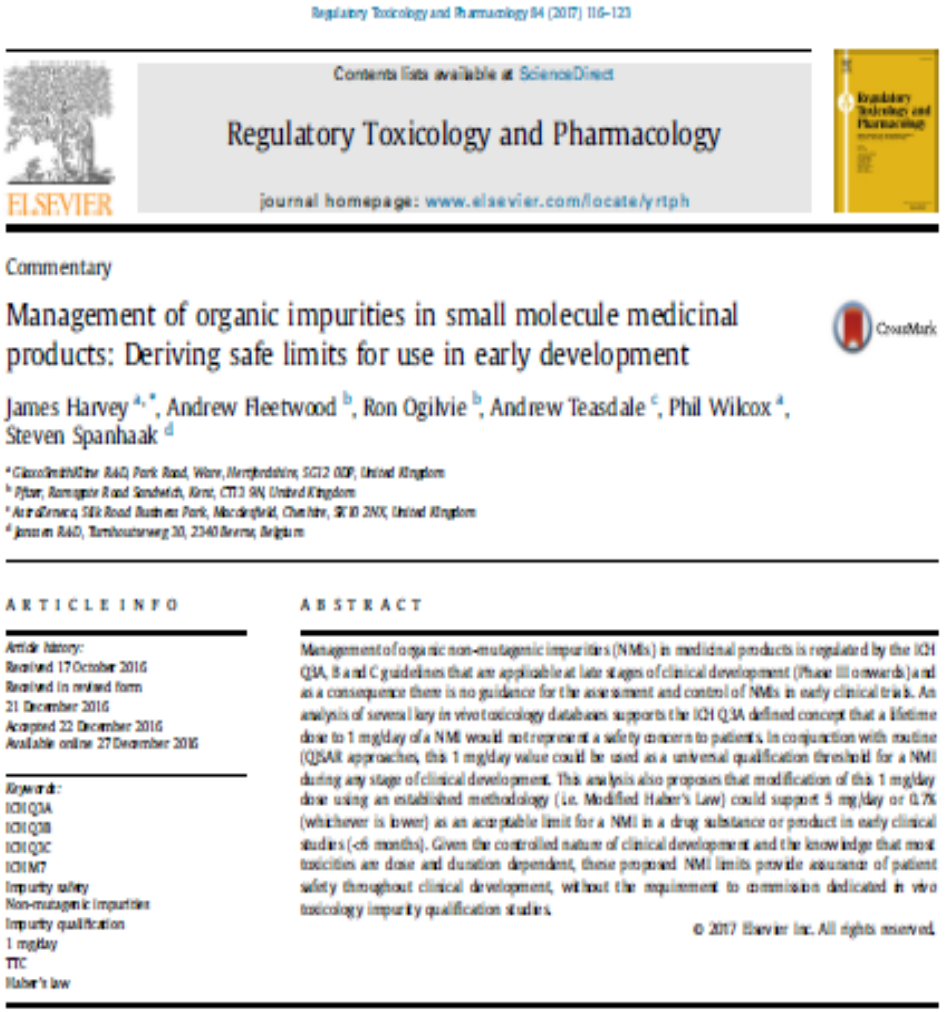
- Metabolites are safe
  - May be supportable up to 10% levels (or above- as is the case with pro-drugs)
- What are allowable levels of metabolite degradants?
  - the latest guidance implies that there may be a 1% limit cut-off in regulator's minds (particularly in EU)
  - "to comply with pharmaceutical quality, specified levels for impurities will **be low, usually close to or below 1%"** (EMA, 2018)… but if supported by process capability a 2% limit for pro-drugs may be achievable
    - So **process capability considerations** will trump safety (as per other ICH quality guidelines)
  - EMA assay limits are 95-105% so only 5% range (95-100%) to work with to encompass end of shelf life degradation losses and process capability of the drug product itself
  - US limits could be greater (90-110%), **but need for global specifications**….

EMA. 2018. Reflection paper on the qualification of non-genotoxic impurities (EMA/CHMP/SWP/545588/2017)

EMERGING GUIDANCE FOR STANDARD IMPURITIES

Newly Emerging Guidance Duration Of Exposure

- A life time exposure to **1mg/day** of a non-mutagenic impurity would not represent a safety concern
  - Validation of ICH Q3A limits
- Using **modified Haber's Law**
  - $C^3 \times t = C'^3 \times t'$
- Would support an API limit of **5mg/day or 0.7%** in early clinical studies (<6 months) and **5mg/day or 2.0%** for DP



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Commentary

Management of organic impurities in small molecule medicinal products: Deriving safe limits for use in early development

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TTC
Haber's law

ABSTRACT

Management of organic non-mutagenic impurities (NMIs) in medicinal products is regulated by the ICH Q3A, B and C guidelines that are applicable at late stages of clinical development (Phase III onwards) and as a consequence there is no guidance for the assessment and control of NMIs in early clinical trials. An analysis of several key in vivo toxicology databases supports the ICH Q3A defined concept that a lifetime dose to 1 mg/day of a NMI would not represent a safety concern to patients. In conjunction with routine (Q)SAR approaches, this 1 mg/day value could be used as a universal qualification threshold for a NMI during any stage of clinical development. This analysis also proposes that modification of this 1 mg/day dose using an established methodology (i.e. Modified Haber's Law) could support 5 mg/day or 0.7% (whichever is lower) as an acceptable limit for a NMI in a drug substance or product in early clinical studies (<6 months). Given the controlled nature of clinical development and the knowledge that most toxicities are dose and duration dependent, these proposed NMI limits provide assurance of patient safety throughout clinical development, without the requirement to commission dedicated in vivo toxicology impurity qualification studies.

Newly Emerging Guidance

Qualification on relative-absolute amounts: Drug substance

Scenario:	Allowed Impurity level:	Relative: 0.70%	Absolute: 5 mg/day
	Clinical dose (mg/day):	mg NGI/day	% NGI
1	3000	21	0.17%
2	2000	14	0.25%
3	1000	7	0.50%
4	100	0.7	5.00%
5	10	0.07	50.00%
6	1	0.007	500.00%
7	0.1	0.0007	5000.00%
8	0.01	0.00007	50000.00%

Scenarios 1-3:

For clinical daily doses ranging from 1000 to 3000 mg the allowed relative percentage (0.7%) would result in an absolute amount of impurity that would exceed the absolute 5 mg/day limit thus in these cases the latter is restrictive: In practice meaning that relative levels ranging between 0.17-0.5% would be allowed.

Scenarios 4-8:

For clinical daily doses between 0.01 and 100 mg the allowed relative percentage of 0.7% would result in an absolute amount of impurity that would not exceed the absolute 5 mg/day limit. In contrast allowing an absolute amount of 5 mg would clearly exceed the allowed 0.7%. Thus here relative amounts will be restrictive (0.7%): In practice meaning that absolute levels range between 0.00007 and 0.7 mg.

Harvey et al. 2017. Management of organic impurities in small molecule medicinal products: Deriving safe limits for use in early development. Reg Tox Pharm, 84, 116-123

Newly Emerging Guidance

Qualification on relative-absolute amounts: Drug product			
Scenario:	Allowed Impurity level:	Relative: 2%	Absolute: 5 mg/day
	Clinical dose (mg/day):	mg NGI/day	% NGI
1	3000	60	0.17%
2	2000	40	0.25%
3	1000	20	0.50%
4	100	2	5.00%
5	10	0.2	50.00%
6	1	0.02	500.00%
7	0.1	0.002	5000.00%
8	0.01	0.0002	50000.00%

Scenarios 1-3:

For clinical daily doses ranging from 1000 to 3000 mg the allowed relative percentage (2%) would result in an absolute amount of impurity that would exceed the absolute 5 mg/day limit thus in these cases the latter is restrictive: In practice meaning that relative levels ranging between 0.17-0.5% would be allowed.

Scenarios 4-8:

For clinical daily doses between 0.01 and 100 mg the allowed relative percentage of 2% would result in an absolute amount of impurity that would not exceed the absolute 5 mg/day limit. In contrast allowing an absolute amount of 5 mg would clearly exceed the allowed 2%. Thus here relative amounts will be restrictive (2%): In practice meaning that absolute levels range between 0.0002 and 2 mg.

Harvey et al. 2017. Management of organic impurities in small molecule medicinal products: Deriving safe limits for use in early development. Reg Tox Pharm, 84, 116-123

Regulatory Applicability

- Applied to Phase II project in EU and US
- Applied 0.7% limit for unspecified impurities/degradants and 1% for metabolite (see next section)
- Generally well accepted
  - Ireland indicated that, "Limit for single unknown impurities is proposed at NMT 0.7% which **is not in line with ICH qualification threshold of 0.15%.** Based on batch data and stability data presented, a limit of 0.7% is not supported and **would not allow for adequate control and consistency of the process**. With the exception of *xxxx [metabolite limit]* all other impurities are present at a limit below the 0.10% threshold and **the limit should therefore be tightened accordingly.**"
  - This comment was based on 6 batches of DP!
  - Eventually managed to get them to accept 0.5%..... but no logic for reduction from 0.7% to 0.5%

Newly Emerging Guidance

- "Little available guidance for **qualification of standard impurities**" (cf. ICH 3C, 3D and M7)
- "establishing biological safety of DS or DP with a given impurity profile… is not the same as characterising the **safety profile of an impurity**"
- "a lack of **impurity specific safety** data complicates the qualification process"
- "concerns have been expressed (re: ICH Q3A/3B) from a **scientific and 3Rs perspective**"
  - Can't differentiate toxicity attributable to DS and those attributable to the impurities

1 15 November 2018
2 EMA/CHMP/SWP/545588/2017
3 Committee for Medicinal Products for Human Use (CHMP)

4 Reflection paper on the qualification of non-genotoxic
5 impurities
6 Draft

Draft agreed by Safety Working Party	October 2018
Adopted by CHMP for release for consultation	15 November 2018
Start of public consultation	23 November 2018
End of consultation (deadline for comments)	30 September 2019

Newly Emerging Guidance

- Integrated risk assessment
  - Assess whether risk remains below an **impurity specific TTC** based on Cramer classifications
- Duration of exposure
  - "whether the application of **modified Haber's Law** from life-time to sub-chronic exposure is appropriate remains to be established"
- Structure Activity Relationships
  - "..it would be relevant to look at the **differences** and determine whether any sub-structures that have not been identified in the API **alert for specific types of toxicity**"

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Newly Emerging Guidance

- Use of tox databases
  - Relevance of the **applicability domain** to impurity in question
  - **IMI eTox** database
- In Vitro Approaches
  - **Apply OECD approaches** for novel in vitro test methodology
- Qualification
  - **NOAEL not required** … demonstrate safety at the specified level. WoE approach may be applicable to **demonstrate the absence of risk**
- 3Rs Approach
  - Should **minimise animal usage**

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CONCLUSIONS

Conclusions

- Dawning recognition that ICH Q3A/3B guidelines are not fit for purpose to qualify 'normal' impurities and degradants
  - ICH Q3A/3B still regulates on a **concentration basis** rather than PDE/AI daily exposure basis (*cf*. ICH Q3C/3D/M7)
  - Still a general perspective that safety based limits can be **trumped by process capability** and that these limits should be low (≤1%) to address pharmaceutical quality issues….
  - Even for metabolites?
- Newer approaches (EMA, 2018) consider (a) integrated risk assessment, (b) duration of exposure and (c) Structure Activity Relationships
  - Some positive experience with using **duration of exposure (Harvey et al. 2017) approach** but regulators are still hide bound by process capability considerations even for projects with very limited batch experience <5 batches)

EMA. 2018. Reflection paper on the qualification of non-genotoxic impurities (EMA/CHMP/SWP/545588/2017)