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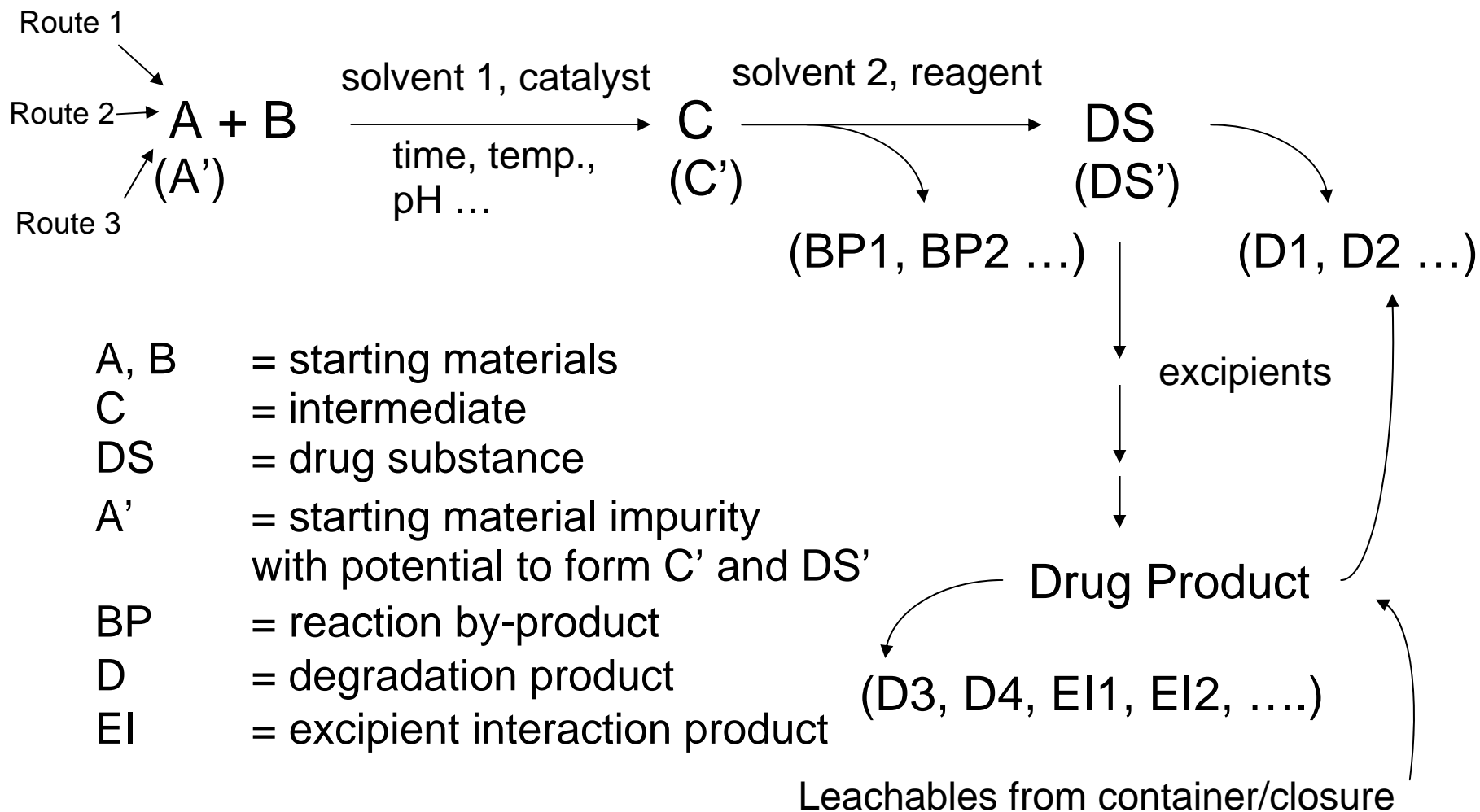
# **Current Issues and Concerns for Impurities in Pharmaceuticals**

**USP WCDG & AOAC-SCS**  
**April 15-16, 2011**

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# Impurity Origins



# ICH Impurities Guidelines

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Q3A(R2) Impurities in New Drug Substances

Q3B(R2) Impurities in New Drug Products

Q3C(R5) Guideline for Residual Solvents

Q3D Guideline for Metal Impurities – in progress

# Impurity Controls

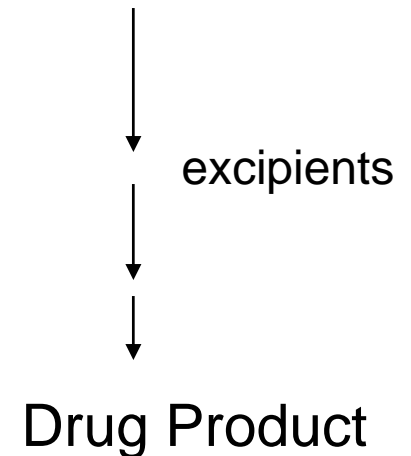
A + B → C → DS

QbD process controls  
Relevant material specifications  
Packaging, handling and storage

ICH Q8: Pharmaceutical Development

ICH Q9: Quality Risk Management

ICH Q10: Pharmaceutical Quality System



# Additional Impurity Controls

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## cGMPs, Validation

- Cross contamination
- Purchased materials – vendor auditing, supply chain control
- Equipment and facilities
- Microbiological contamination

# Additional Impurity Concerns

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## Potentially genotoxic impurities

- Identification
- Assessment
- Control

## Adulterants and Contaminants

- Global supply chain
- EMA (economically motivated adulteration)

## Undeclared active ingredients

- Dietary supplements

# Taking Impurities to another level – Genotoxic Impurities

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## EMA Guidance and FDA Draft Guidance

- For impurities with genotoxic potential
- applies Threshold of Toxicological Concern (TTC) concept to define acceptable risk;
- 1.5 µg/day considered acceptable ( $10^{-5}$  lifetime risk of cancer) where compound specific tox data are not available

EMA / CHMP “Guidelines on the limits of Genotoxic Impurities”, CPMP/SWP/5199/02;  
EMA/CHMP/QWP/251344/2006, London, UK, 28 June 2006.  
<http://www.emea.europa.eu/pdfs/human/swp/519902en.pdf>

Question & Answers on the CHMP Guideline on the Limits of Genotoxic Impurities (London, 26 June 2008 Doc. Ref. EMA/CHMP/SWP/431994/2007)  
<http://www.emea.europa.eu/pdfs/human/swp/43199407en.pdf>

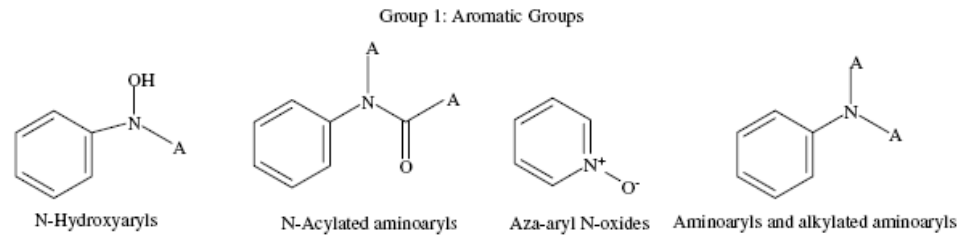
Guidance for Industry, Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches, December 2008  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079235.pdf>

# EMEA and FDA staged TTC limits

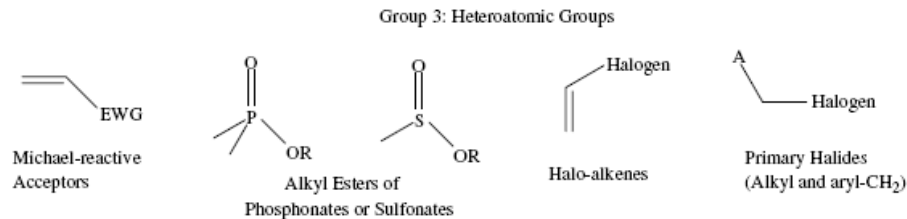
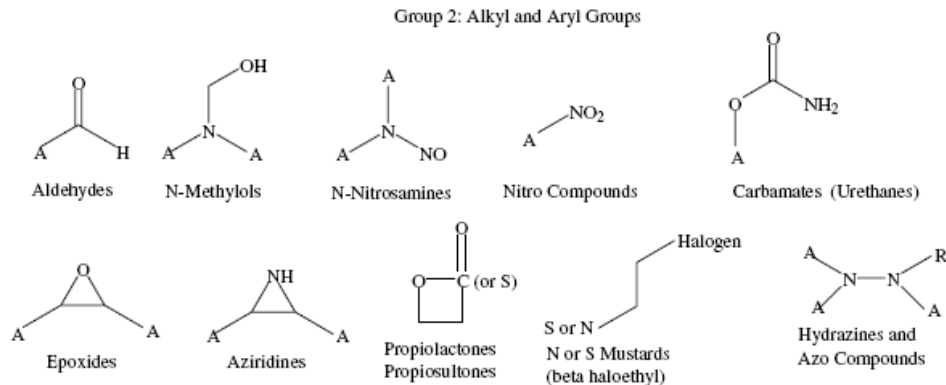
Staged Thresholds of Toxicological Concern  
Genotoxic Impurity Limits,  $\mu\text{g}/\text{day}$

	Single Dose	< 14 days	$\leq 1$ mo.	$\leq 3$ mo.	$\leq 6$ mo.	$\leq 12$ mo.	> 12 mo.
EMEA	120	60	60	30	10	5	1.5
FDA	120	120	60	30	10	5	1.5

# Alerting Structures in Identified Impurities



Purines or Pyrimidines, Intercalators, PNAs or PNAHs

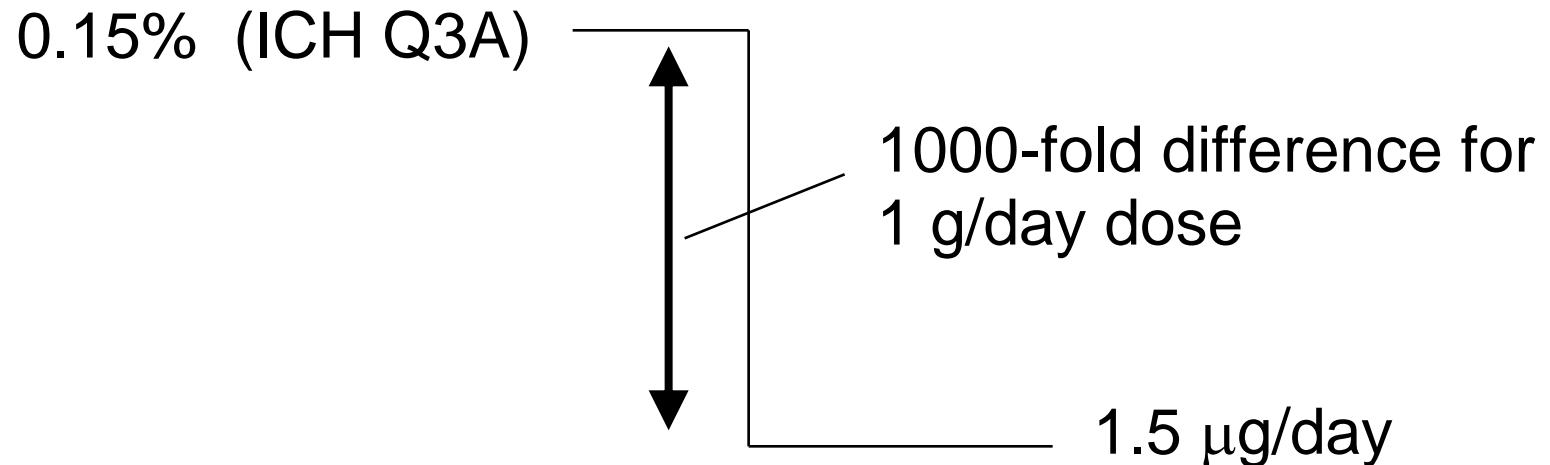


Müller et al., *Reg. Tox. Pharmacol.* 44, 198-211 (2006)

# Much debate about conservative guidances – Is this regulatory overkill?

E. J. Delaney, “An impact analysis of the application of the threshold of toxicological concern concept to pharmaceuticals”, *Reg. Tox. Pharmacol.*, 49, 107-124 (2007)

“The existence of two disparate regulatory impurity standards, one based on ICH Q3A(R) and the other based on TTC, creates a differential *cliff of regulatory concern*.”



# Debate, cont.

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D.Snodin, G. Vudathala, "Genotoxic Impurities: A case for a regulatory rethink", AAPS Newsmagazine, Feb. 2009, pg. 20

- Generic TTC is an overly conservative approach
- Lack of transparency of database
- Lack of justification for high-to-low dose linear extrapolation
- Numerical errors(?)
- Inconsistency among regulatory authorities
- Humans exposed to many endogenous genotoxins
- Chemistry and purification rationale not likely to be accepted

# ICH M7

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## Issues to be resolved

- What are acceptable levels of genotoxic impurities during drug development?
- What are acceptable levels of genotoxic impurities for marketing?
- Should those impurities be regulated differently that are likely to have threshold effects?
- Should levels of genotoxic impurities be regulated using a Threshold of Toxicological Concern (TTC) approach?
- Structurally related genotoxic impurities are likely to have similar mechanisms of action. Should these be summed in calculating a TTC?
- What process of qualification testing should be followed for impurities that are metabolites?
- What additional data are needed to support having no special restrictions, or a higher acceptable daily intake than the TTC, for a genotoxic impurity?

Final Concept Paper, M7: Genotoxic Impurities, *Endorsed by the ICH Steering Committee on 9 June 2010*

# Development Strategy

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While the debate continues, a strategy is needed to progress compounds in development.

Lilly: D. Pierson et al., *Org. Process Res. Dev.* 13 (2009) 285-291.

AZ, purge factors: A. Teasdale, *Org. Process Res. Dev.* 2010, 14, 943–945

GSK, QbD: Z. Cimarosti et al., *Org. Process Res. Dev.* 2010, 14, 993–998

Vertex, Risk assessment: A.R. Looker et al., *Org. Process Res. Dev.* 2010, 14, 1032–1036

Review: D.L. Robinson, *Org. Process Res. Dev.* 2010, 14, 946–959

Tox viewpoint: D.J. Snodin, *Org. Process Res. Dev.* 2010, 14, 960–976

BOOK: *Genotoxic Impurities – Strategies for Identification and Control*, A. Teasdale, Ed., Wiley, Hoboken, NJ, 2010.

# Genotoxic Impurity Questions

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- Which impurities from the synthetic process need to be assessed for genotoxicity?
- Can genotoxic impurities be avoided in the design of the synthetic route or introduced as early in the route as possible?
- Which degradation impurities need to be assessed for genotoxicity?
- Which impurities need to be determined analytically?
- What methods and validation are appropriate?
- What impurity specifications are needed?

# Impurities to evaluate

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"This discussion can be limited to those impurities that might **reasonably be expected** based on knowledge of the chemical reactions and conditions involved." – EMEA guidance

"**If an impurity** that is present at levels below the ICH qualification thresholds **is identified**, the impurity should be evaluated for genotoxicity and carcinogenicity" – FDA draft guidance

Guidances provide a disincentive to identify impurities below ICH thresholds – contradictory to a QbD approach to achieve process/product understanding

# Case by case evaluation within a general strategy

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1. Assess synthetic route impurities and known degradation products (including major stress degradation products)
2. For known or identified mutagens/carcinogens, evaluate risk of impurity appearing in drug substance or product
3. Develop methods to determine higher-risk impurities
4. Analyze samples to determine impurity levels, demonstrate absence, and determine rejection efficiencies
5. Use a risk-based approach to determine whether impurity specification controls are needed

# Genotoxicity assessment

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Assessment for potential genotoxicity can involve:

- Evaluation for alerting structures in “actual and potential” impurities
- *in silico* toxicology prediction, e.g., DEREK, MCASE
- *in vitro* testing for genotoxicity, e.g, Ames test

# Regulatory risk

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Specification control of GTI

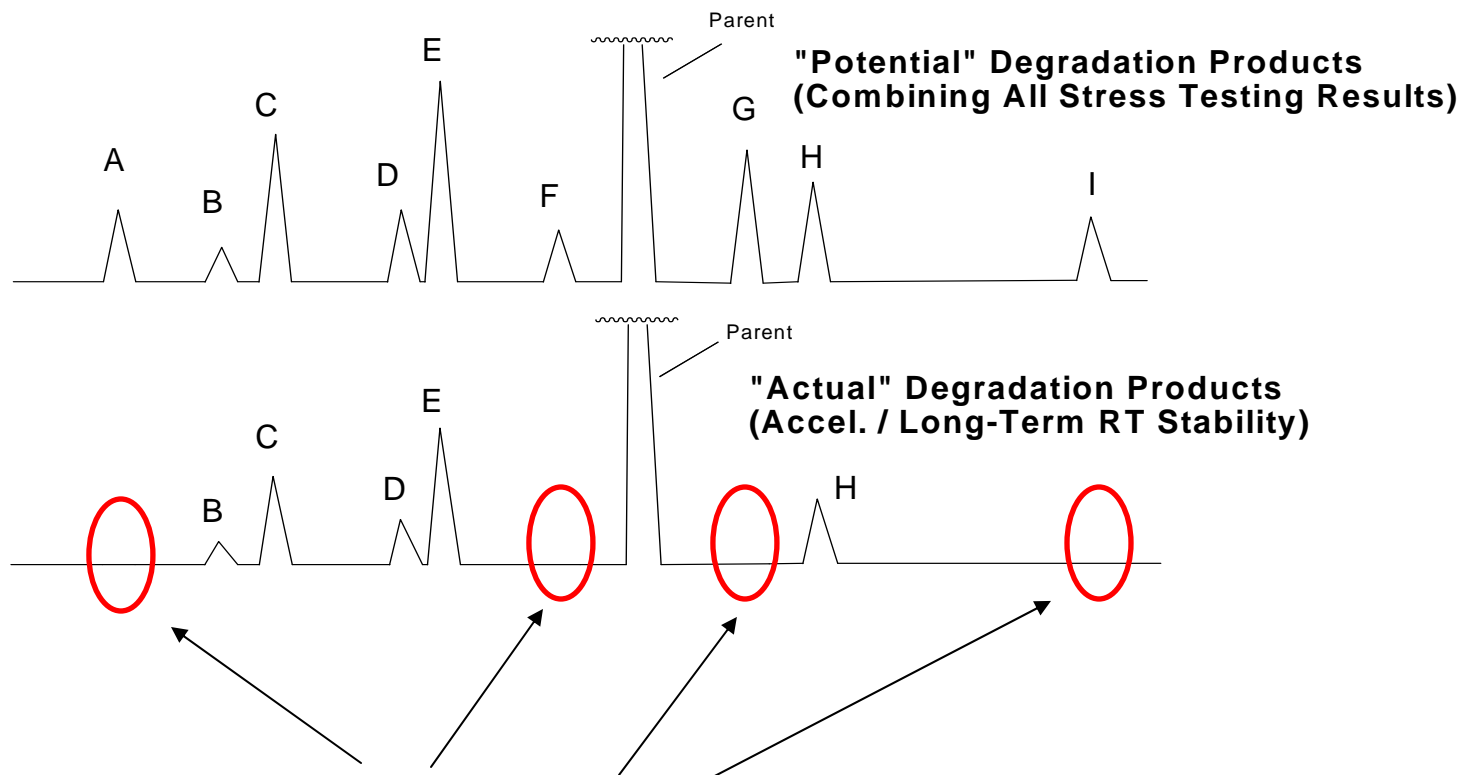
Process data supporting  
removal of GTI

Chemical reactivity or  
process purification  
rationale for removal



Probability of  
regulatory acceptance

# Impurity identification during stress testing



Do potential degradation products need to be examined at TTC levels if they contain alerting structures?

\*S.W. Baertschi, IIR Conference on Genotoxic Impurities, Philadelphia, PA, December 8-9, 2008

# Genotoxic degradation products

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- Analytical method needed for appropriate level
- Is degradation product GTI present?
- Does degradation product GTI form with time?
- Can degradation product GTI formation be prevented through formulation design, packaging, or storage conditions?
- Establish specification if necessary

# Retrospective application of genotoxic impurities guidance

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For products approved before guidance:

## **FDA Draft Guidance – Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches**

- Specific safety signal for increased cancer risk
- Supplement application that proposes a significant change (e.g. new indication, new dosage regimen, longer duration of use, etc.)
- Manufacturing supplements to NDAs, BLAs, and ANDAs such as new formulations or synthetic routes

## **Question & Answers on the CHMP Guideline on the Limits of Genotoxic Impurities** 17 December 2009

- Specific cause for concern, such as new knowledge – formation of alkyl mesitates cited as an example of a concern identified post-approval for mesilate salt drug substances

# Monograph Evolution/Modernization

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Monograph development and revision processes attempt to keep pace with evolving regulatory expectations and with up-to-date technology

- Ordinary impurities → ICH impurities (TLC to gradient HPLC)
- Organic Volatile Impurities → ICH residual solvents
- In progress - Heavy metals → Metal impurities (sulfide precipitation to plasma spectrochemistry)

What about toxic or genotoxic impurities at trace levels (often requiring LC-MS methodology)?

# Current Pharmacoepial Approaches to Genotoxic Impurities

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## PhEur – Production Statements

Additional requirements drawing attention to particular aspects of the manufacturing process

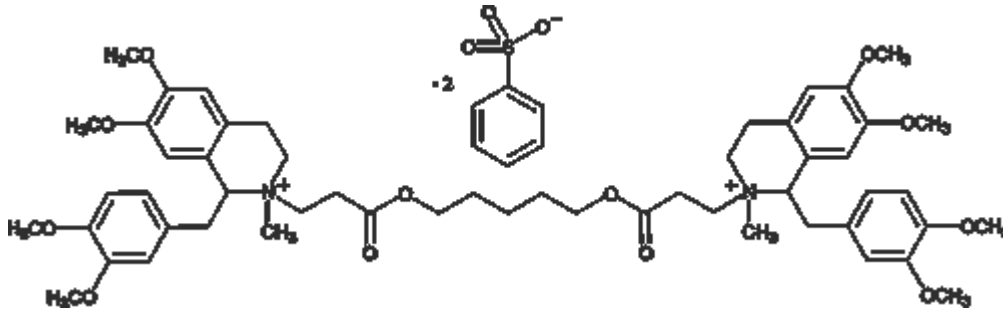
## Mesilate salts

The production method must be evaluated to determine the potential for formation of alkyl mesilates, which is particularly likely to occur if the reaction medium contains lower alcohols. Where necessary, the production method is validated to demonstrate that alkyl mesilates are not detectable in the final product.

## USP

Monographs rarely include tests and limits for sulfonate ester impurities or other trace impurities

# Atracurium Besylate



## USP 33

Atracurium besylate monograph includes test for methyl benzenesulfonate with an acceptance limit of 100 ppm

HPLC with complex gradient profile (3 linear ramps, 45 minute analysis time) and UV detection at 217 nm.

## PhEur 6.0

Similar method to USP but limit is 10 ppm

# Potential PhEur policy on genotoxic impurities in monographs

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Product approved post-guideline

- Monograph should be based on marketing authorisation(s)

Product approved pre-guideline

- Follow specifications in dossier for marketing authorisation
- Action needed only where there is study data demonstrating genotoxicity of the impurity
- **Structural alerts alone insufficient to trigger follow-up measures**

PHARMEUROPA Vol. 20, No. 3, July 2008

# TOP TEN DEFICIENCIES - New Applications for Certificates of Suitability (End 2009)

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## **TOP 4 (3.2.S.3.2): Genotoxic impurities:**

Compliance with the *CHMP Guideline on the Limits of Genotoxic Impurities, EMEA/CHMP/QWP/251344/2006* must be **demonstrated for substances obtained by a manufacturing process not yet approved in Europe**. The guideline is not applied retrospectively to authorised products unless there is recent data demonstrating the genotoxicity of a specific compound relevant to the application. For substances which fall within the scope of the guideline, a **specific discussion as part of the overall discussion on impurities should be provided with regard to impurities with potential genotoxicity**.

PA/PH/CEP (10) 65 Strasbourg, June 2010

# ANDA Deficiencies

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Common deficiencies with respect to impurities and degradation products include:

“Impurities that are structural alerts for genotoxicity need to be controlled at the Threshold of Toxicological Concern (TTC) of 1.5 mcg/day...”\*

\*A. Srinivasan, D.S. Gill, R. Iser, Pharm. Tech., **35** (2), 58-67 (2011)

# Needs for Genotoxic Impurities Regulation

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Clarity

Consistency

Risk-based

# Adulterated or Substandard Materials

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## Supply chain controls

- Quality systems
- Audits
- Inspections

## Analytical controls

- Do we know what we're looking for?
- Appropriate screening
- Looking for and assessing “changes” in materials

# Considerations for adulterated or substandard products

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Risk assessment and design of analytical controls or screening methods

- Substantial vs. minute contaminant levels
- Harmful vs. innocuous contaminant
- Detectable vs. transparent to normal QC/monograph tests
- Homogeneous vs. localized distribution throughout a batch
- Introduction of contamination in relation to final product
  - pre-API
  - API
  - excipients
  - drug product

# Is the USP monograph “quality-indicating”

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Consider monograph as a whole:

- Identification – distinguishes among similar materials?
- Assay – specific for desired compound(s)?
- Impurities – discriminating for impurities (and potential adulterants)?
- Other tests that are indicative of quality?

# Screening programs

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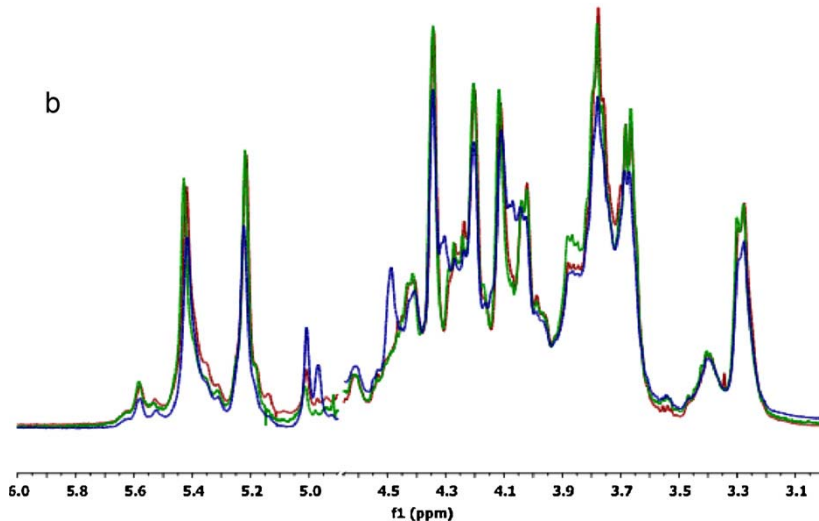
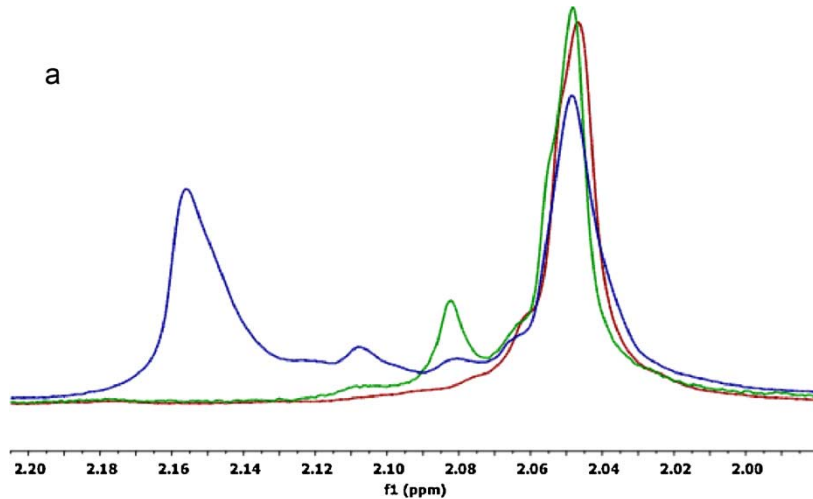
What are we screening for?

- Known potential adulterants
- Classes of potential adulterants
- “Sameness” to existing product
- What threshold levels need to be detected

How rapid and/or portable does screening need to be?

Where should screening be conducted and who should do it?

# Chemometric calibration models for heparin quality by $^1\text{H}$ NMR



$^1\text{H}$  NMR spectra of heparin samples

Pure heparin (brown, 0.14% DS and 0% OSCS)

Heparin containing DS impurity (green, 4.12% DS and 0% OSCS)

Heparin containing OSCS contaminant (blue, 2.71% DS and 14.0% OSCS)

(a) In the 2.20–1.95ppm region; (b) in the 6.00–3.00ppm region.

Q. Zhang et al., *J. Pharm. Biomed. Anal.*, 54 (2011) 1020–1029

# Heparin Screening by NMR

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118 samples used for building and 60 for validating model

## Chemometric methods

principal components analysis (PCA)

partial least squares discriminant analysis (PLS-DA)

linear discriminant analysis (LDA)

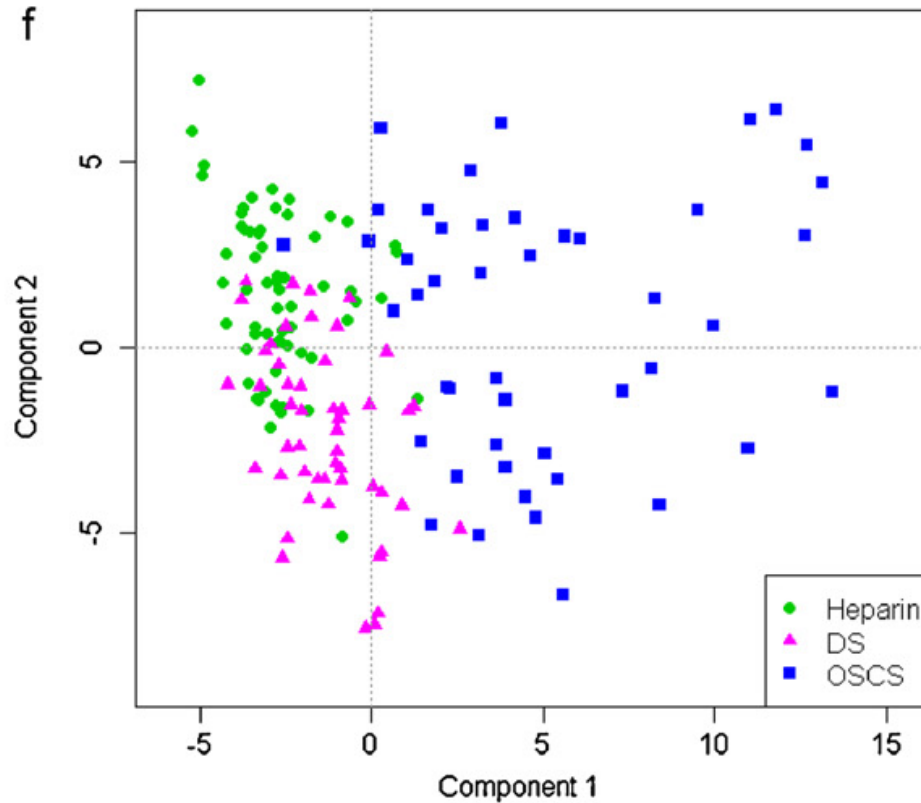
k-nearest neighbor (kNN) method.

Under optimal conditions, a perfect classification (100% success rate) was attained on external test sets for the Heparin vs OSCS model.

The predictive rates for the Heparin vs DS, Heparin vs [DS + OSCS], and Heparin vs DS vs OSCS models were 89%, 93%, and 90%, respectively.

Q. Zhang et al., J. Pharm. Biomed. Anal., 54 (2011) 1020–1029

# Class discrimination using PLS-DA



Second vs. first latent variable from PLS-DA analysis

Q. Zhang et al., J. Pharm. Biomed. Anal., 54 (2011) 1020–1029

# DEG in Glycerin

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Chemometric calibration models for NIR and Raman –  
1% DEG (7-25% estimated as range for EMA)

Not sufficient sensitivity for USP requirements

User interface developed to automate analysis and give  
a P/F result

Threshold for decision making – 5% false failure, 5%  
erroneous pass

J.F. Kauffman et al., Am. Pharm. Rev. 13(1), 58-63 (2010)

# Risk Assessment – Melamine contamination

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FDA Guidance  
Pharmaceutical Components at Risk for  
Melamine Contamination - August 2009

Adenine (USP)  
Albumin (IID)  
Amino acids derived from casein protein hydrolysates  
Ammonium salts  
Calcium pantothenate (USP)  
Caseinate or sodium caseinate (IID)  
Chlorophyllin copper complex sodium (USP)  
Colloidal oatmeal (USP)  
Copovidone (USP/NF)  
Crospovidone (USP/NF)  
Dihydroxyaluminum aminoacetate (USP)  
Gelatin (IID)  
Glucagon (USP)

Guar gum (USP/NF)  
Hyaluronidase (USP)  
Imidurea (USP/NF)  
Lactose (USP/NF, IID)  
Melphalan (USP)  
Povidone (USP/NF)  
Povidone-Iodine (USP)  
Protamine sulfate (USP)  
Protein hydrolysate (powder) for injection (USP)  
Taurine (USP)  
Thioguanine (USP)  
Urea (USP)  
Wheat bran (USP)  
Zein (USP/NF)

# Chemometrics to check for “sameness”

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## Potential screening program

- Build model with representative samples capturing expected variability
- Screen new samples for differences from training set
- Flag “different” samples for further investigation

# Issues for Chemometric Screening

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Will model capture normal variability?

Maintenance of model as new sources of variability are introduced?

System suitability and controls on quality of input data?

Will frequent unnecessary investigations be triggered?

Will contaminants be missed?

# Undeclared actives

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Steroids in OTC topicals

Weight loss supplements containing bumetanide, cetilistat, fenproporex, fluoxetine, furosemide, phenytoin, rimonabant, sibutramine

Erectile dysfunction drugs or analogs in dietary supplements

# Ion Mobility for Screening

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Analyte must have some volatility below 200 deg C  
Analyte extracted from sample for introduction to IMS

Sibutramine in dietary supplements\*

- 2 ng limit of detection, dilution into range
- caffeine and vitamin B6 did not interfere
- portable IMS shown to be feasible

ED drugs (sildenafil citrate, tadalafil, vardenafil) and analogs in herbal supplements\*\*

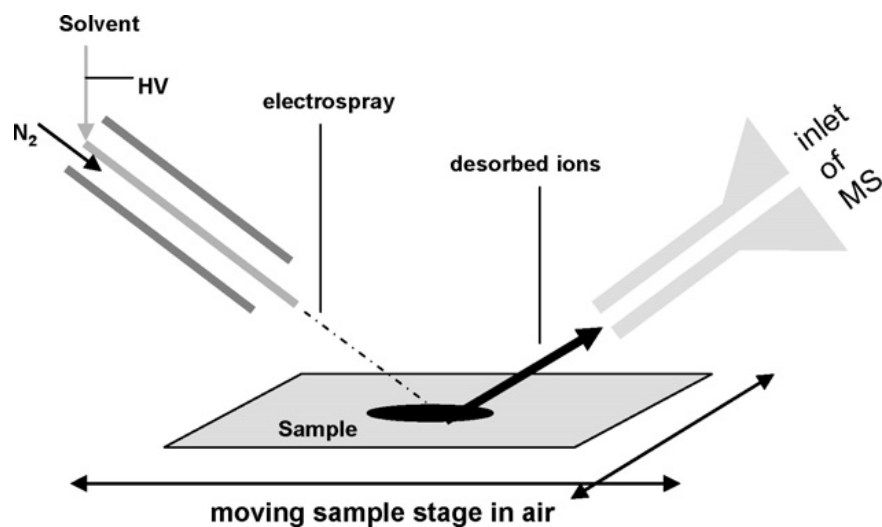
- qualitative identification based on reduced ion mobilities

\*J.D. Dunn et al., *J.Pharm. Biomed. Anal.*, 54 (2011) 469–474

\*\*C.M. Gryniewicz et al., *J. Pharm. Biomed. Anal.*, 49 (2009) 601–606

# Other screening techniques for undeclared actives

DESI – desorption electrospray ionization



Screening for hormones in veterinary products

M.W.F. Nielen, et al., *Analytica Chimica Acta* 637 (2009 ) 92–100

# Other screening techniques for specific contaminants or undeclared actives

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DART – Direct Analysis in Real Time

NIR

Raman

Immunoassay

Isotope ratio MS

Approaches similar to screening for counterfeits

# Anticipating the next threat

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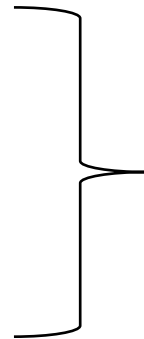
Cost or volume of material, i.e., level of economic motivation

Complexity of supply chain

Detectability of adulterants

Level of monitoring

Penalties



Probability of getting caught?

# Combined Approaches

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Regulatory, Compendia, Industry, Policy-maker cooperation

Supply chain control

- quality agreements
- supplier audit
- supplier inspection

Risk-based testing

- material specifications
- material screening programs