

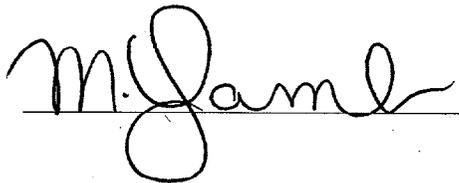
M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: February 8, 2000  
To: Dockets Management Branch (HFA-305)  
From: Melissa Lamb  
Office of Generic Drugs  
Subject: Guidances for Industry

This memorandum forwards overheads of a presentation to the Dockets Management Branch for inclusion in Docket 90S-0308. The following is information on the presentation for the Docket records:

Title of Presentation: Impurities in Drug Substances & Products  
Presented for: Generic Pharmaceutical Industry/FDA Fall Technical  
Date Presented: 10/19/99  
Presented by: Robert W. Trimmer, Ph.D  
Number of Pages: 15



Attachment

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90S-0308

M660

***Generic Pharmaceutical Industry/FDA Fall Technical***

***WORKSHOP***

**Bethesda, Maryland**

**October 19, 1999**

**Guidances for Industry**

**ANDAs:**

***Impurities in Drug Substances & Products***

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***Expert Regulatory Review Scientist***  
**Office of Generic Drugs**

## Introduction

- ☺ **We will give a brief recapitulation of the *ICH Q3A* and *Q3B* processes.**

**(Q3A is applicable only for *new* drug applications dealing with previously unregistered synthetic drug substances).**

- ☺ **Comparison of the two systems, ICH vs. OGD, for the qualification and identification of Drug Substance and Drug Product impurities.**
- ☺ **The Development of the OGD Guidances for Industry *ANDAs: Impurities in Drug Substances & Drug Products*.**
- ☺ **Discussion of the qualification process for generic bulk drug substances and drug products.**

## **Seven Areas Addressed by the ICH & OGD Guidances on Impurities:**

- **Classification of impurities\***
- **Rationale for the reporting and control of impurities**
- **Analytical procedures**
- **Reporting impurity content of batches**
- **Limits for impurities\***
- **Qualification of impurities\***
- **New impurities\***

## **Classification of Impurities**

- ***Organic Impurities* (Process & Drug Related)**

**Starting materials**

**By-products**

**Intermediates**

**Degradation Products (at BDS & DP levels)**

**Reagents, Catalysts and Ligands**

**[excluded: Enantiomeric impurities]**

- ***Inorganic* (from the manufacturing process)**

**Reagents, Catalysts, & Ligands**

**Heavy Metals**

**Inorganic Salts**

**Other materials (*e.g.* Filter Aids & Charcoal)**

## **New Impurities Observed in Drug Substances**

- **A change in qualitative impurity profile due to a Drug Substance process change may necessitate qualification of any newly arisen impurities.**
- **A new qualification would be necessary if the impurity exceeds the limit provided in the earlier qualification.**

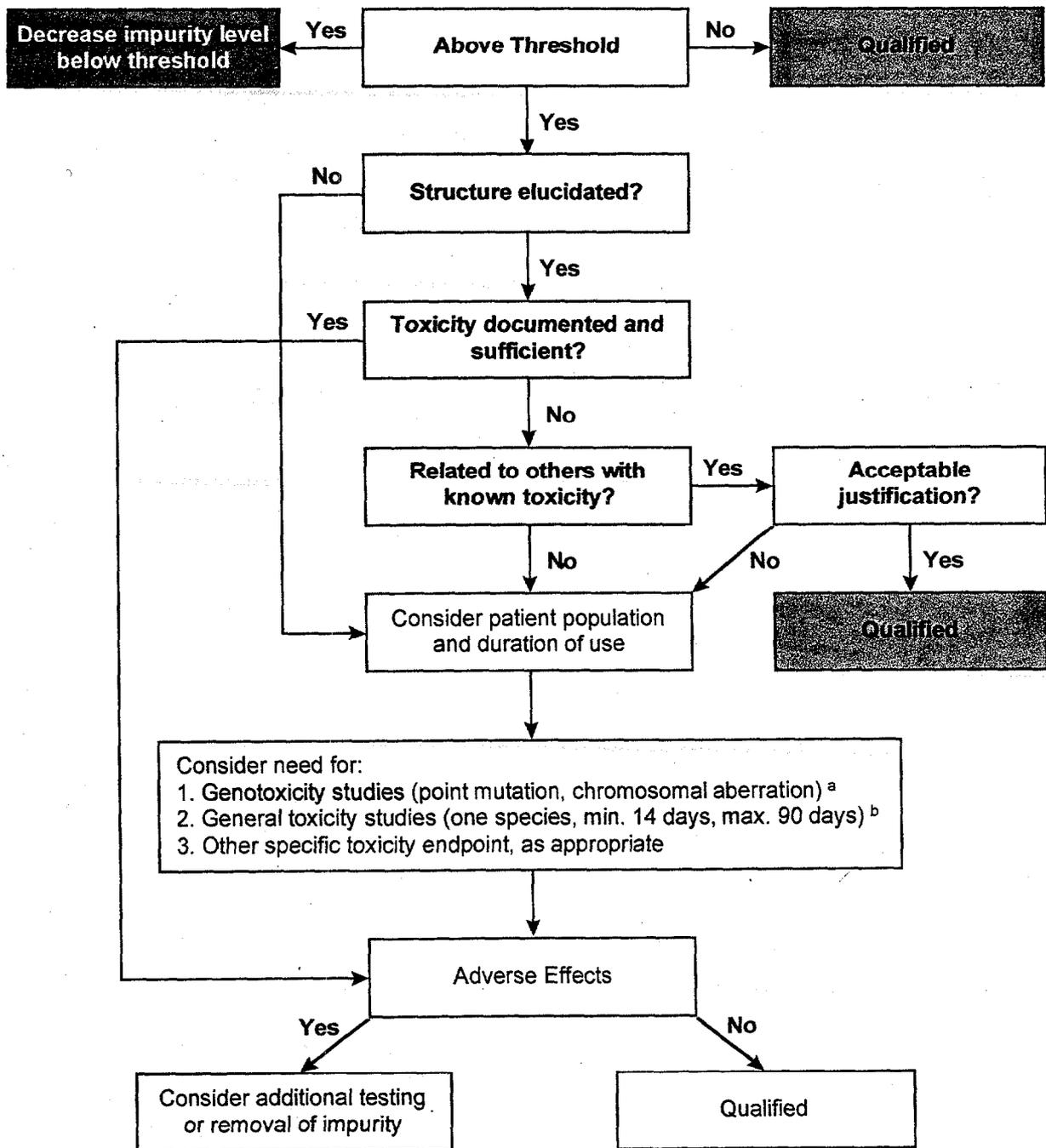
## Qualification of Drug Substance Impurities

- **High Dose Drugs\*:** An impurity at  $< 0.1\%$  may need to be qualified *if* the drug substance exceeds a certain amount:

<b><u>Maximum Daily Dose</u></b>	<b><u>Qualification Threshold</u></b>
<b><math>\leq 1</math> gm/day</b>	<b>0.1%</b>
<b>1 to 2 gm/day</b>	<b>1 mg/day</b>
<b><math>&gt; 2</math> gm/day*</b>	<b>0.05%</b>

- Qualification of an impurity is generally made unnecessary by decreasing its level below the threshold.

# ICH Decision Tree for Safety Studies



<sup>a</sup> If considered desirable, a minimum screen for genotoxic potential should be conducted. A study to detect point mutations and one to detect chromosomal aberrations, both in vitro, are seen as an acceptable minimum screen.

<sup>b</sup> For NDAs, general toxicity studies are desirable, study(ies) should be designed to allow comparison of unqualified to qualified material. The study duration should be based on available relevant information and performed in the species most likely to maximize the potential to detect the toxicity of an impurity. In general, a minimum duration of 14 days and a maximum duration of 90 days will be acceptable.

## HARMONIZATION ISSUES APPLICABLE to GENERIC DRUGS

### ANDAs: IMPURITIES in DRUG SUBSTANCES

	<u>Current ANDAs</u>	<u>New ANDA Guidance</u>	<u>ICH Q3A (NDA's)</u>
Identification:	where possible; no thresholds given. 1987 DS Guideline	follow ICH threshold	ICH threshold
Qualification:	none	ICH/OGD Decision Tree: qualification is consistent with ICH and within the <i>Hatch-Waxman Act</i> ; generic impurities evaluated per our OGD Decision Tree, e.g., scientific literature base including use of QSAR, and using simple (only) <i>in-vitro</i> genotox studies.	ICH Decision Tree. Levels used in safety studies are deemed qualified.
Setting of Limits:	generally "low". limits set case-by- case per 1987 DS Guideline.	Based on ICH/OGD Decision Tree qualification.	Based on ICH qualification

Where differences appear from the ICH *Decision Tree* they are redlined.

[file #97-05-14.ogd]

## Draft Guidance Development

- The initial draft was prepared by the OGD Project Leader, then later evaluated by the CDER Drug Substance Technical Committee and CDER Pharmacology/Toxicology personnel.
- Before publication there were evaluations and comments from the OGD and ONDC Chemistry Team Leaders and from our Office Management.
- Endorsement had been secured from the *Chemistry Manufacturing Controls Coordinating Committee (CMC CC)* and our *General Counsel (GC)*.

# **Draft Guidance Development**

## **ANDAs: Impurities in Drug Substances**

- **This draft Guidance was published for comment in the *Federal Register* (FR) in 1998. The comment period officially ended November 23, 1998.**
- **During this time we received 9 communications from the NDA & ANDA Industry, the Generic Trades; all 116 specific comments were evaluated by myself and three other senior OGD scientists.**
- **This final ANDA guidance is expected to be published November 1999 in the *FR*. The corresponding ICH Q3A guideline had been published January 4, 1996.**

# **Draft Guidance Development**

## **ANDAs: Impurities in Drug Products**

- **This draft Guidance was published for comment in the *Federal Register* (FR) in January 1999. The comment period officially ended May 1999.**
- **During this time OGD received 14 communications from the NDA & ANDA Industry, and the Generic Trades; all 88 specific comments are currently being evaluated by senior OGD scientists.**
- **This ANDA guidance is expected to be published early next year in the *Federal Register*.**

## **Qualification of the GENERIC DRUG SUBSTANCE**

**Qualification of impurities is accomplished by the bulk drug substance manufacturer or applicant (for degradants in DP's).**

**L1&2 Is the Impurity above Threshold? Structure Elucidated?**

**L3a Compliance with a USP specification for a specified individual impurity constitutes qualification. If not...**

**L3b Comparison with the innovator's drug (*e.g.*, isolated from the drug product); if the impurity profile is present at similar level, then it is qualified, but NMT 2X and not to exceed 1.0%. If not, go to the next level.**

**L3c When a new impurity is detected, it may qualified if the open literature can substantiate that it is a non-toxic impurity at the levels used. If not, go to the next level.**

## **Generic Qualification**

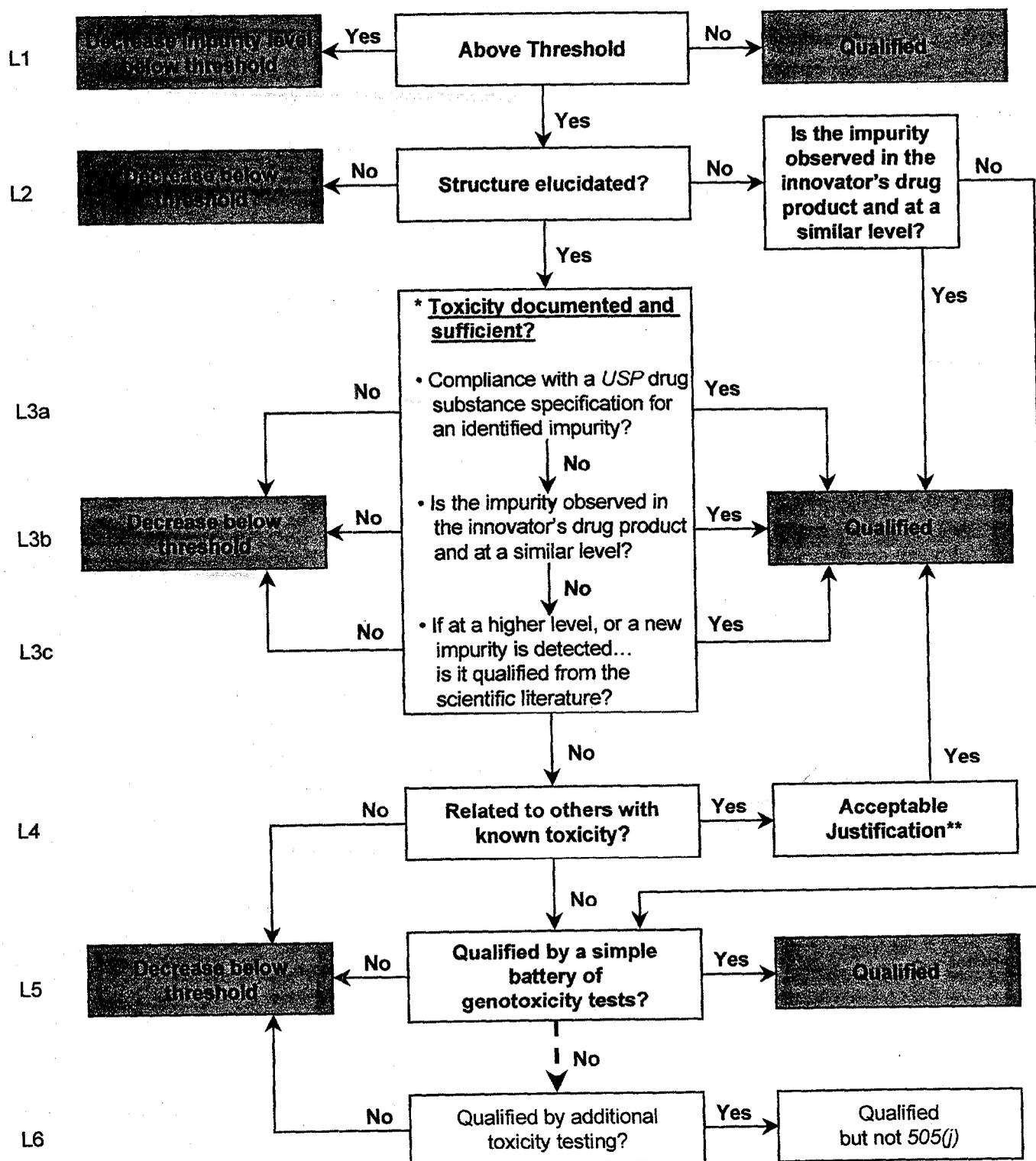
**L4. Qualify by an established *Quantitative Structure Activity Relationship* (QSAR) database program.**

**Not to exceed a level of 0.5% or 500 mcg/day.**

**If not qualified at this level then go to next L5.**

**L5. Qualify by a simple battery of *in vitro* genotox tests, or avoid by lowering impurity level below the threshold (0.1% or 0.05%).**

# Impurities Decision Tree (Generic Drug Substance)



\* Generic Drug Pathway  
 \*\* e.g., qualified by QSAR

## Summary

- ☺ The *ICH Q3A Guideline* was intended to harmonize the review of new drug applications dealing with previously unregistered (*i.e.* NME's) synthetic drug substances. Q3B applicable to new DP's.
- ☺ The OGD Guidances for Industry *ANDAs: Impurities in Drug Substances & Products* seek to clarify and to harmonize the ICH Guideline to Generics with allowances made to the *Hatch-Waxman Act*.
- ☺ The qualification of impurities in generic bulk drug substances is generally expected to be conducted by the drug substance manufacturers; in DP's the degradation products are qualified by the applicants.
- ☺ The date of publication of the DS Guidance is expected to be in early November 1999; OGD's actual implementation of this guidance will begin one year thereafter.  
The publication of the DP Guidance is expected to be in 2000.