

Strategies for Controlling and Qualifying Impurities in Drug Substances and Drug Products

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Joint CVG/TPD International Convention and Exhibition
October 6, 2006

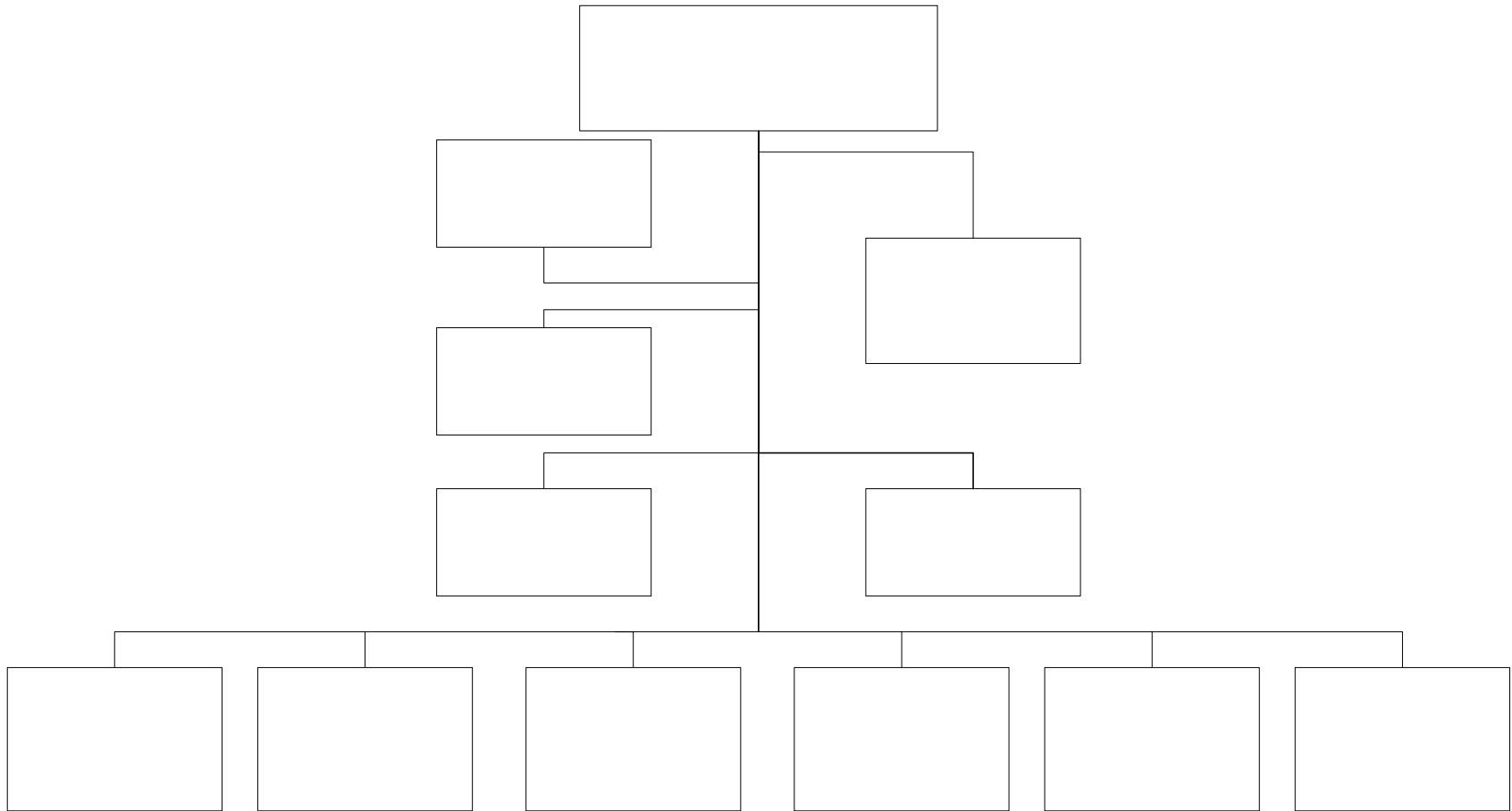
Health Products and Food Branch
Direction générale des produits de santé et des aliments

Overview

- **Highlights of ICH's Q3A and Q3B guidelines;**
- **Health Canada's "Impurities in Existing Drug Substances and Products";**
- **Sample Deficiency Comments;**
- **Future Considerations / Conclusions.**



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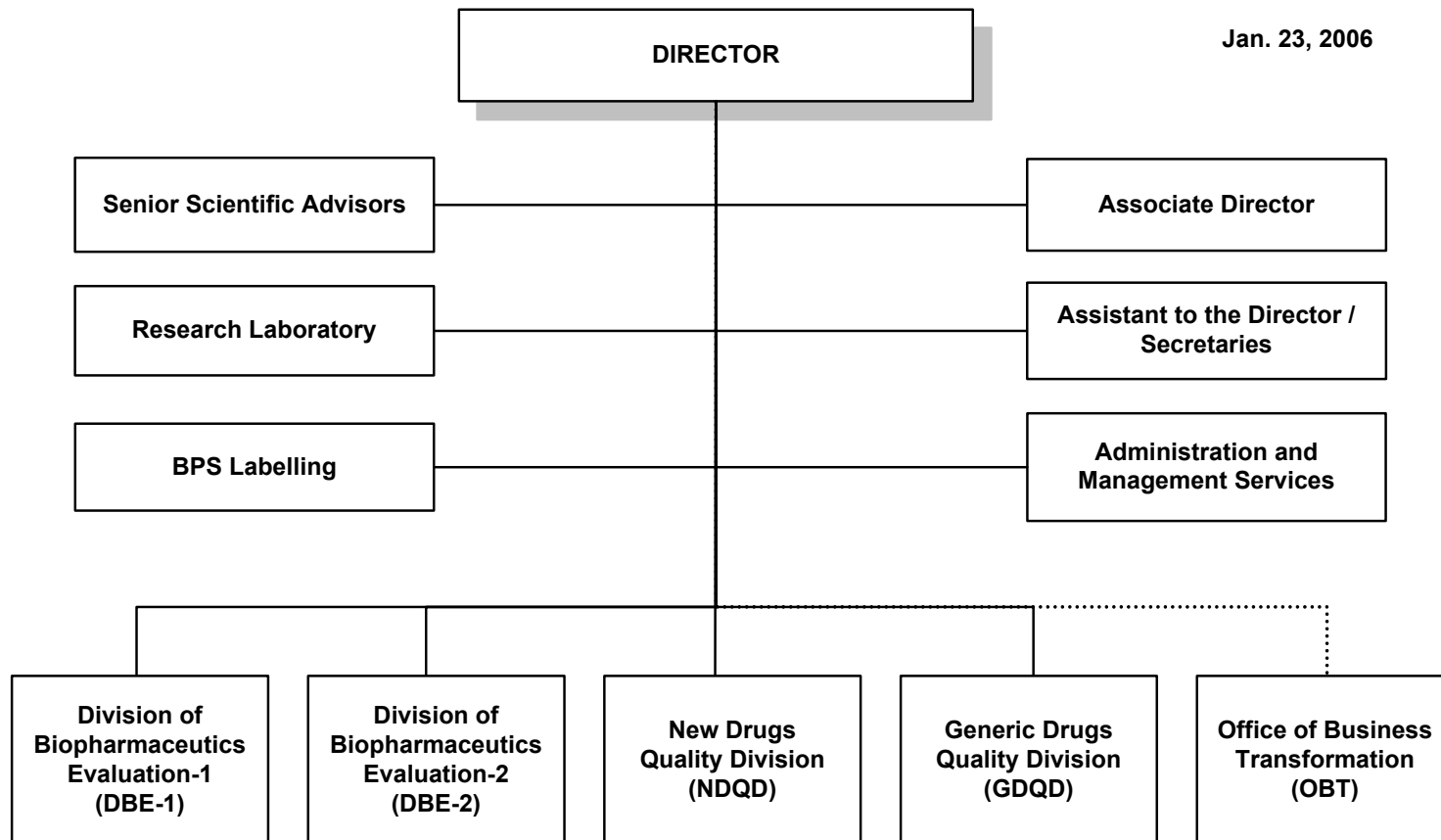
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Jan. 23, 2006



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Q3A and Q3B Maintenance

➤ **Like ICH's Q1A Stability guideline, the Q3A and Q3B guidelines have been the subject of the ICH "maintenance process" to:**

- promote consistencies within the documents;
- promote consistencies with other ICH guidelines (e.g., Q6A);
- provide clarity and to develop further guidance;
- promote consistency across Regions (e.g., application of Thresholds, rounding of analytical results).

➤ **Timeline:**

- Q3A: 1995 → Q3A(R1): 2002 → Q3B(R2): ?
- Q3B: 1996 → Q3B(R1): 2003 → Q3B(R2): 2006



Q3A(R) and Q3B(R)

➤ Reporting:

- Any impurity at a level greater than (>) the reporting threshold (see Attachment 1) and total impurities observed in these batches of the new drug substance should be reported;
- Below 1.0%, the results should be reported to:
 - ... two decimal places (Q3A(R))
 - ... the number of decimal places in the applicable reporting threshold (Q3B(R));
- At and above 1.0%, the results should be reported to one decimal place (both Q3A(R) and Q3B(R));
- Results should be rounded using conventional rules (see Attachment 2).



Q3A(R) and Q3B(R)

➤ Identification:

- The studies conducted to characterise the structure of actual impurities present in the new drug substance at a level greater than (>) the identification threshold given in Attachment 1 should be described.
- ... In addition, any degradation product observed in stability studies at recommended storage conditions at a level greater than (>) the identification threshold should be identified.
- When identification of an impurity is not feasible, a summary of the laboratory studies demonstrating the unsuccessful effort should be included in the application.



Q3A(R) and Q3B(R)

➤ **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.

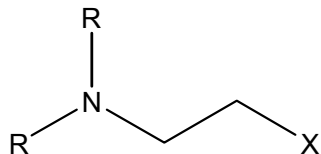
➤ **Options (if Qualification Threshold is exceeded):**

- reduce level to safe level (e.g., additional purification steps for DS, more protective container closure);
- correspond to level found in safety and/or clinical studies;
- significant metabolites present in animal and/or human studies are generally considered qualified;
- adequate data could be available in the scientific literature to qualify an impurity (e.g., USP, Ph.Eur.);
- NB: higher or lower thresholds for qualification of impurities can be appropriate for some individual drugs based on scientific rationale and level of concern.

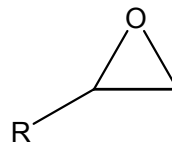


Q3A(R) and Q3B(R)

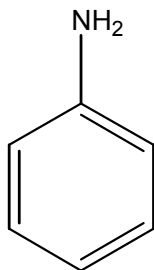
➤ Examples of possible “structural alerts”:



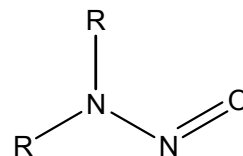
Alkylating agents



Epoxides



Anilines



Nitrosamines



Q3A(R) and Q3B(R)

- **In summary, the new drug substance specification should include, where applicable, the following list of impurities:**
 - Each specified identified impurity;
 - Each specified unidentified impurity;
 - Any unspecified impurity with an acceptance criterion of not more than (\leq) the identification threshold;
 - Total impurities.

- **Similarly, the new drug product specification:**
 - ... degradation product ...



Q3A(R) – Attachment 1

Maximum Daily Dose	Reporting Threshold	Identification Threshold	Qualification Threshold
</= 2 g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
> 2 g/day	0.03%	0.05%	0.05%



Q3B(R) – Attachment 1

Maximum daily dose

≤ 1 g

> 1 g

Reporting

Threshold

0.1 %

0.05 %

Maximum daily dose

< 1 mg

1 mg - 10 mg

>10 mg - 2 g

> 2 g

Identification

Threshold

1.0 % or 5 µg TDI (whichever is lower)

0.5 % or 20 µg TDI (whichever is lower)

0.2 % or 2 mg TDI (whichever is lower)

0.10 %

Maximum daily dose

< 10 mg

10 mg - 100 mg

>100 mg - 2 g

> 2 g

Qualification

Threshold

1.0 % or 50 µg TDI (whichever is lower)

0.5% or 200µg TDI (whichever is lower)

0.2 % or 3 mg TDI (whichever is lower)

0.15 %



Q3A(R2) and Q3B(R2)

➤ Q3B(R2):

- released as a Step 4 document in June 2006 (without the typical issuance of a Step 2 draft document);
- revised to provide consistent information for the examples in Attachment 2 as that provided in Q3A(R).

➤ Q3A(R2):

- currently under development;
- addressing minor editorial corrections in Attachment 2.



HC's guidance for "Existing Drugs"

➤ ***Impurities in Existing Drug Substances and Products (draft, 2005-09-06):***

- originally released as a draft for Stakeholder consultation in 1999 entitled *Identification, Qualification, and Control of Impurities in Existing Drugs* ;
- finalization was delayed due to maintenance activities of ICH's Q3A and Q3B guidelines;
- the release of ICH's Q3A(R) / Q3B(R) guidelines allows for the further development of this guidance document now entitled *Impurities in Existing Drug Substances and Products*;
- as a number of changes have been introduced since the original 1999 draft (e.g., Q3A(R) / Q3B(R)), this HC guidance document was re-released as a draft document.



HC's guidance for "Existing Drugs"

➤ Highlights:

- the text from the Q3A(R) and Q3B(R) guidelines has been copied verbatim and merged into a single document;
- changes necessary to reflect the recommendations for existing drugs indicated by "<text>" (consistent with the approach taken with HC's *Stability Testing of Existing Drug Substance and Products*);
- link:
 - www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/chem/index_e.html
- consultation period closed: 2005-12-01.



HC's guidance for "Existing Drugs"

➤ Examples of changes for existing drugs:

- "new drug" to "<existing drug>" throughout;
- definition of an "existing drug" (e.g., generics, changes to approved new drugs and abbreviated new drugs);
- results observed in batches used in "... <bioequivalence / bioavailability> studies";
- additional qualification options for specified impurities in existing drugs:
 - <... impurity present in the existing drug is considered qualified if the amount of the impurity in the existing drug *reflects the levels* observed in the corresponding approved human drug product> (i.e., unstressed samples of the Canadian Reference Product);
 - also reflected in Attachment 3.



HC's guidance for "Existing Drugs"

➤ Changes to reflect recommendations for existing drugs (continued):

- "<QSAR programs may be used for prediction of toxicity, ... the results are not generally considered conclusive for qualification purposes.>";
- Glossary:
 - Canadian Reference Product, Existing Drug, Schedule B Monograph;
- Attachments:
 - Attachment <1a>: Thresholds <for Impurities in Existing Drug Substances>
 - Attachment <1b>: Thresholds for Degradation Products in <Existing> Drug Products, etc.



Sample Deficiencies Noted Regarding Impurity Information

➤ Drug related impurities:

- provide ample discussion of the rationale for the proposed limits (e.g., in either Module S.3.2 or S.4.5);
- results of impurity analyses should be generated by the submission sponsor (rather than the API supplier);
- certain potential impurities were not investigated (“contact the API supplier for a list of potential impurities”);
- Identification and Qualification Thresholds were not properly calculated (i.e., should be based on maximum possible daily dose, rather than maintenance dose);
- general limit for “Unspecified Impurities” should correspond to the applicable ICH Identification Threshold (even if USP/Ph.Eur. general limit for unsp. imps. is absent or higher than ICH);



Sample Deficiencies Noted Regarding Impurity Information

➤ Drug related impurities (continued):

- adequate qualification for proposed limit has not been provided;
- if applicable, report levels of impurities found in clinical and non-clinical (toxicity) batches;
- limits listed in a draft forum (Pharmacopoeial Forum, Pharmeuropa) are not considered official/qualified;
- if a pharmacopoeial method is used for identified impurities that are not listed in the monograph, the method should be fully validated for these specified identified impurities;
- if a House analytical method is used, a discussion/justification should be provided for excluding impurities listed in a monograph (e.g., potential impurities listed in Ph.Eur. *Transparency Monographs*).



Quality by Design (QbD)

- **The fundamental principles of QbD should be applied when setting specifications, including impurity limits:**
 - should be based on knowledge and understanding of the product and process;
 - reflective of a robust manufacturing process;
 - limits should be clinically relevant;
 - specifications should not inhibit innovation or continuous improvements.



Conclusion

- **Continue our commitment to the adoption of ICH guidelines and international collaboration (e.g., potential use of EDQM's CEP);**
- **Focus in moving towards a QbD approach to the development of pharmaceuticals, recognizing the existence of products developed using the traditional model;**
- **Develop and/or update any domestic (Canadian) guidance documents, where necessary;**
- **Continue internal and external communications, including dialogue with other Regulatory Agencies, Industry, Pharmacopoeia, and Canadian Provinces.**





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www.hc-sc.gc.ca/dhp-mps/prodpharma/index_e.html

Quality Guidances:

www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/chem/index_e.html



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