

Scientific and Regulatory Aspects of Quality Control for Chiral Drugs



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Presentation Outline

1) Overview of Chiral Quality Issues

- Quality by Design (QbD); Critical Quality Attributes
- Efficacy & Safety
- Specifications; Process Capability

2) FDA Recommendations on Control of Chirality for Pharmaceuticals

- Variety of Chiral Control Strategies
- Chiral Methods
- Generic Applications
- Upcoming Meetings; References

Begin Drug Development with Quality by Design (QbD) Approach

- Design Drug Product (DP) to achieve performance (safety and efficacy)
 - Identify Critical Quality Attributes (CQA)
 - CQAs=Aspects of Drug Substance (DS) and Drug Product (DP) affecting safety and efficacy
 - Some CQAs for DS are based on DP requirements (e.g., particle size, polymorphism)
 - Other CQAs for DS linked to safety (e.g., impurities)
 - Design DS & DP processes and control strategies to assure that product meets CQAs

What are typical CQAs for Chiral Drugs?

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1. Selection of candidate isomer to develop
 - E.g., racemic vs single enantiomer
 - Link to clinical performance
 - Which isomer(s) has desired activity?
 - Preclinical data; early clinical data?
 - What are safety issues for isomers?
 - In vitro; hepatocyte; animal
2. Levels of stereoisomeric impurities
 - Safety (Tox. Qualification)

Selecting the Stereoisomer to Develop

Choice of Racemate versus Single Enantiomer

- Knowledge of activity and safety of enantiomers
- Does active racemize in vivo?
- FDA's Policy Statement for the Development of New Stereoisomeric Drugs (1992)
- <http://www.fda.gov/cder/guidance/stereo.htm>

1992 FDA Policy Statement

- Develop quantitative assays for individual enantiomers in biological samples early
- Determine main pharmacologic activities of enantiomers (in vitro, animals, or humans)
- Relatively benign tox profile of racemate would ordinarily support development without separate tox evaluation of the individual enantiomers
- In other words, identify DS CQAs that are related to safety and efficacy

Appropriate Quality Controls for New Drug Applications

Where are Chiral Test Methods Important?

- Proof of Structure
- Drug Substance Specification
 - Tests for release of each batch of active substance (E.g., Identity and Purity)
 - Test method and acceptance criteria (limit)
 - Negotiated agreement during NDA review
- Drug Product Specification

General Overview of Drug Substance Quality

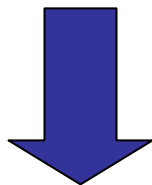
- All Critical Quality Attributes Controlled by
 - In-process Controls; **Design Space**
 - Specifications for Starting Materials
 - Specifications for Intermediates
 - Drug Substance Specification
 - Current Good Manuf. Practices (cGMP)

May provide additional design options

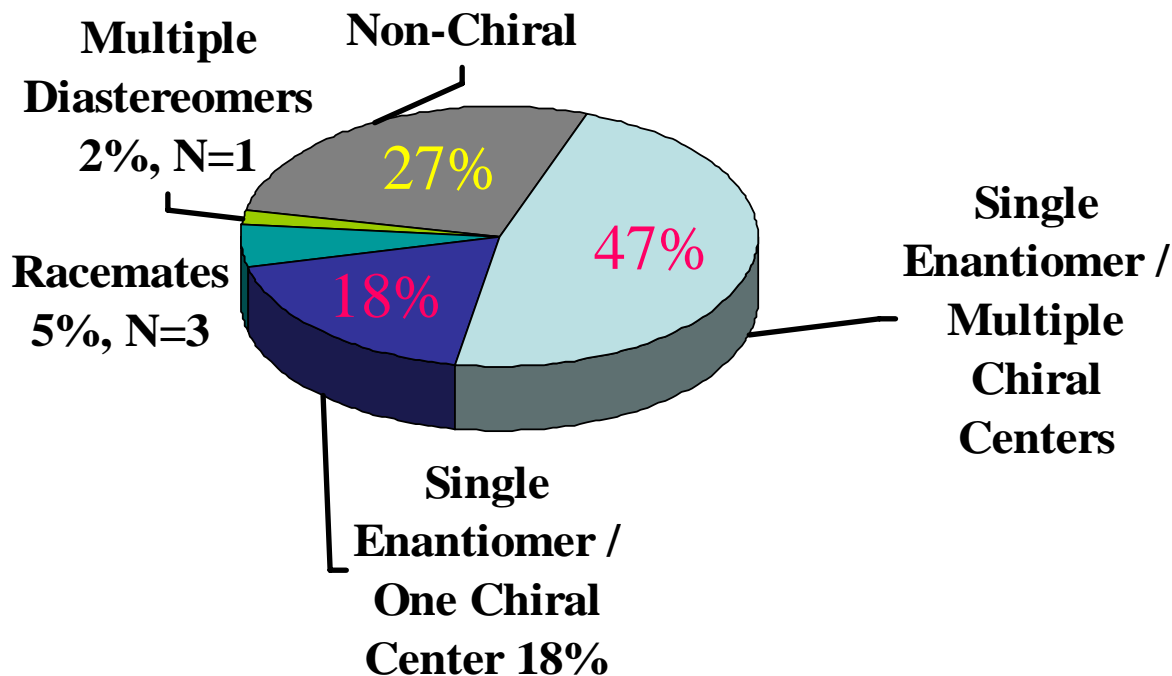


FDA practice and ICH Q6A encourage scientifically justified process control options

Wide Variety of Drug Types



Variety of Chiral Control Strategies



Approximate Proportion of the New Molecular Entities
approved Jan 2004-June 2006 (<http://www.fda.gov/cder/rdmt/>)



Single Enantiomer Drugs

Drug Substance (DS) Issues

- Chiral identity is part of the DS specification
 - e.g., Optical Rotation
- Minor enantiomer controlled during synthesis and/or measured in DS (many different ways!)

Drug Product (DP) Issues

- Chiral Identity generally NOT in DP specification
 - part of acceptance testing of drug substance?
- Generally, one-time studies to determine if racemization occurs during DP manufacture and storage

Racemic Drugs



Drug Substance (DS) Issues

- Consider the need for chiral identity testing for batch release of DS
 - Is an enantiomer of the DS also made in the facility?
 - Any unintended non-racemic development batches?

Drug Product (DP) Issues

- Chiral Identity testing generally NOT needed in DP release specification
- Chiral identity in *DS acceptance* testing?
 - Is an enantiomer of the DS also available in quantity?
 - Is chiral identity part of release testing for DS?

Single Enantiomer Drugs



- One chiral center in drug substance
 - Control or monitor the level of the minor enantiomer for each batch of drug substance synthesized
- Multiple chiral centers in drug substance
 - Controlling or monitoring diastereomers generally more important

Single Enantiomer Drugs

How to Control Minor Enantiomer?

Options to consider – choose based on your DS and your manufacturing process

1. determine process parameter(s) that control level of enantiomer
 - EE of chiral aux; temp; crystallization parameters; etc
2. measure in earlier intermediate
 - correlate with levels in finished drug substance
3. measure in drug substance

Minor Enantiomer in Drug Product

One chiral center in drug substance

- minor enantiomer is routinely measured in drug substance
- control minor enantiomer in drug product
“unless racemization has been shown to be insignificant during manufacture of the dosage form and on storage” (ICH Q6A)
- what is reasonable level of evidence at time of approval?

Minor Enantiomer in Drug Product

One chiral center in drug substance

- “Insignificant during manufacture and on storage”
- One approach: racemization not observed in
 - registration batches at release
 - stability batches at recommended storage condition (e.g., 25deg/60%RH) in data available at time of approval
 - accelerated stability data (or intermediate accelerated)
 - continue to assess racemization in registration stability batch(es) out to maximum expiration dating period

How to Control Minor Enantiomer?

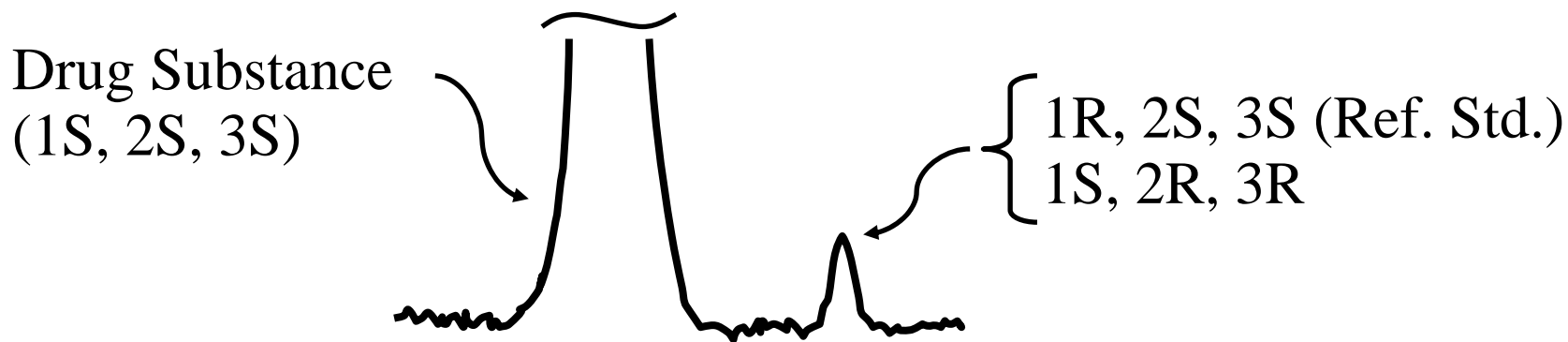
Multiple chiral centers in DS

- Control of diastereomers generally more important
 - Particularly for convergent synthesis
 - 5% minor (1 center) → 0.25% minor (2 centers) → etc.
 - Sequential chiral induction
 - 5% minor (1 center) → 5% minor (2 centers) → etc.
- 2 chiral centers - generally monitor minor enantiomer
 - standards and chiral methods will be typically be needed
 - control via intermediates or process parameters post approval?
- ≥ 3 chiral centers - what is expected level of minor enantiomer?
- Natural product or semisynthetic
 - is enantiomer a realistic impurity?

Control of Diastereomeric Impurities

Multiple chiral centers in drug substance

- One approach is to monitor as pairs of diastereomers using achiral method:



Possible Misconceptions about Chiral Methods for an NDA

- Must be described in USP ***False***
 - New drugs frequently have new methods
- Must be a chromatographic method ***False***
 - Can be any technology that is valid
- Must resolve all diastereomers ***False***
 - Focus on those produced by this synthetic process

Can be any method that makes scientific sense

- Suitable for this drug and manufacturing process

Choose Appropriate Level of Control for Each Situation

- **Moderate Risk – control or monitor each batch. E.g.:**
 - stereospecific identity of DS
 - enantiomer level in DS for single stereocenter
- **Low/Unknown Risk - one-time study to rule out racemization. E.g.:**
 - enantiomer level in DP with 1 chiral center in DS
- **For some low risk situations, scientific principles justify omission of testing. E.g.:**
 - enantiomer in DP with ≥ 3 chiral centers in DS

Controls on Minor Enantiomer in Generic Applications

Is a test scientifically appropriate?

- Same approaches as for NMEs; number of chiral centers, nature of synthesis, etc.

How to select acceptance criterion?

- Similar approach to other related substances; focus on safety
- Base on USP monograph
- If no USP monograph, can generally base on internationally recognized pharmacopoeia
- Applicant can justify with data from marketed samples of Reference Listed Drug

Desired Direction – Moving Forward

- 1) Choose control strategy that fits your product and process
 - Process parameters, Starting Material Spec; In-process Tests; Intermediate Spec; DS or DP Spec, as appropriate
- 2) Emphasis on Process Knowledge
 - Focus on critical quality attributes (CQA)
 - Identify Critical Process Parameters
 - Capability of manufacturing process to meet CQA
 - Less reliance on end product testing

Process Knowledge Contribution to Quality

- Drug-specific and process-specific regulation
- Greater emphasis on risk assessment
 - risk to patients; DP safety and performance
- Capability of critical process parameters to produce product meeting CQAs
 - more knowledge and understanding of product and process than currently disclosed in NDAs
 - more regulatory flexibility to optimize process post-approval within design space

Opportunities for Input and Discussion

- PhRMA API Workshop in Denver
Sept 25-27, 2006
- FDA-ISPE-PDA Workshop on Q8 & Q9,
Washington DC; Dec 6-7, 2006
- FDA Pharmaceutical Quality Initiative
Workshop, Washington DC
Feb 28-Mar 2, 2007

Reference Sources

1) FDA, Development of New Stereoisomeric Drugs (1992)

- <http://www.fda.gov/cder/guidance/stereo.htm>

2) October 5-7, 2005 Workshop

- AAPS Workshop on Pharmaceutical Quality Assessment A Science and Risk-based CMC Approach in the 21st Century; Co-sponsored with FDA and ISP
- <http://www.aapspharmaceutica.com/meetings/meeting.asp?id=51>

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3) ICH, Specifications in DS & DP (Q6A)

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5) Health Canada, Stereochemical Issues in Chiral Drug Development (updated Feb 2000)

–http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/stereo_e.pdf

Reference Sources

6) FDA, BA & BE Studies for Oral Drug Products (2000)

- Chiral issues in pharmacokinetic studies

- <http://www.fda.gov/cder/guidance/3615fnl.pdf>

7) FDA, Analytical Procedures and Methods Validation (Draft)

- <http://www.fda.gov/cder/guidance/2396dft.pdf>

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köszí Ďakujem dhanya-waad Дякую
Dziękuję Спасибо go raibh maith agat
bedankt ありがとう شكرًا Thank you
tesekkürle Merci tack så mycket díky
谢谢 Thank you hvala
Shukriyâ Danke Mulțumesc kiitos
takk Obrigada אודות anugurihiitosumi
Ευχαριστώ Grazie dhanya-waad nandri
Muchas gracias ačiû köszönöm
aitāh 너를 감사하십시오 tack
dēkujī vam mange tak salamat