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The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package might contain assessments and/or conclusions and recommendations written by individual FDA members. Such conclusions and recommendations do not necessarily represent the final position of the individual staff member, nor do they necessarily represent the final position of any FDA office or division. We have brought the agenda items to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to any subsequent regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all relevant internal activities have been finalized. Any final determination may be affected by issues not discussed at the advisory committee meeting.

Center for Drug Evaluation and Research

Advisory Committee for Pharmaceutical Science

and

Clinical Pharmacology

July 26, 2011

Food and Drug Administration

Meeting of the Advisory Committee for Pharmaceutical Science

and

Clinical Pharmacology

July 26, 2011

BRIEFING INFORMATION

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MEMORANDUM

TO: Members, ACPS-CP

FROM: Helen Winkle
Director, Office of Pharmaceutical Science, CDER, FDA

DATE: June 28, 2011

RE: ACPS-CP Meeting July 26, 2011

Dear Committee Members and Invited Guests,

We look forward to your participation in the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS-CP) meeting on July 26, 2011. There will also be a meeting of the committee on July 27th, which will be handled by a separate background package of information.

The meeting will focus on a number of important science issues currently being addressed in the Office of Pharmaceutical Science (OPS) in the Center for Drug Evaluation and Research (CDER). As you know, this office is mainly focused on the review of the quality of pharmaceutical products prior to market. This includes all pharmaceutical products – small molecule and proteins, and generic versions of these products. Through your participation and advice on the advisory committee, we are able to develop and finalize our standards for reviewing and approving products and set policy for regulatory decision-making.

Our last meeting of the advisory committee was in April 2010. We will continue our discussions with you on several topics that were discussed at that time. Additionally, since our last meeting, a number of new issues have surfaced in OPS that we will bring before the advisory committee for your awareness. Background materials for each of the proposed topics are attached.

Since our last meeting, the term for a number of members has expired and new members have been appointed. We look forward to welcoming the new members and to their scientific input into the topics being brought before the committee.

We look forward to a very productive meeting in July. We value the opportunity to solicit your assistance in defining and solidifying OPS direction in developing sound, scientific responses to the emerging issues.

At the start of the meeting on July 26, I will outline the goals and objectives for our meeting and I will also provide to you a brief update on OPS ongoing initiatives and activities.

July 26, 2011

Topic 1 – Bioequivalence (BE) Approaches for Narrow Therapeutic Index (NTI) Drugs

This topic was part of the agenda at our last meeting. Following up on Committee recommendations made at that time, we will further discuss a definition and list for NTI products, and provide various perspectives on evaluating scaling approaches for bioequivalence of NTI products. Following a presentation on the pharmaceutical quality of generic drug products, we will outline for Committee discussion and recommendation a proposal on bioequivalence limits for NTI drug products.

To supplement the material provided in the background package, additional information relative to the April 13, 2010, ACPS-CP discussions on this topic can be viewed at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm201700.htm

We will look forward to your input to address the following draft questions:

Draft Questions for the Committee:

1. Is the draft definition for NTI drugs, proposed by the FDA, reasonable and appropriate?
2. Should the following be used for bioequivalence studies of NTI drugs:
    a. The two-treatment four-period fully replicated crossover design; and
    b. The reference-scaled average bioequivalence approach?
3. Is there a need to tighten assayed potency standards and content uniformity acceptance limits for NTI drugs?

Topic 2 – Impact of Formulation and Quality on the Safety and Performance of Generic Drug Products

This is a new topic for the Advisory Committee, and it will be presented as an 'awareness' topic. Accordingly, there will be no Committee discussion or recommendations following a series of presentations. Committee members will be permitted to address the speakers during their presentations for any clarifying questions specific to the presentation.

For this awareness session, presentations will be directed to (1) an overview of possible formulation and quality design issues that could impact the safety and performance of generic drug products, including physical and organoleptic-related concerns, and postmarketing considerations for ANDAs; (2) an overview of the current product quality research being conducted within the Office of Testing Research relative to understanding and monitoring these issues; and (3) an industry perspective on the impact of quality on generic drug safety and acceptance. The topic will be concluded with a presentation on possible future considerations and activities to maintain focus on these issues.

We are looking forward to a very stimulating discussion with the committee on the selected topics. Have a safe and enjoyable journey to Silver Spring, MD. The meeting will be held at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Room 1503), 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002.

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS-CP)

Food and Drug Administration Campus, White Oak Conference Center
The Great Room, (Building 31, Room 1503)
Silver Spring, MD

JULY 26, 2011

TENTATIVE AGENDA
(SUBJECT TO CHANGE)
(Scheduled Presentation Times May Change Due to Open Public Hearing Requirements)

Tuesday, July 26, 2011

8:00 a.m.	**Call to Order and Opening Remarks**	**To Be Determined**
	Introduction of Committee	
	Conflict of Interest Statement	**Yvette Waples, Pharm.D.** Designated Federal Official
8:15 a.m.	**Welcome and Introductory Remarks**	**Helen N. Winkle** Director, Office of Pharmaceutical Science (OPS) Center for Drug Evaluation and Research (CDER), FDA
8:30 a.m.	***Topic 1: Bioequivalence (BE) and Quality Standards for Narrow Therapeutic Index (NTI) Drug Products***	
10:15 a.m.	**BREAK**	
10:15 a.m.	(Continued Presentations)	
11:00 a.m.	**Open Public Hearing**	
12:00 p.m.	**LUNCH**	
1:00 p.m.	***Committee discussions and recommendations***	
2:00 p.m.	***Topic 2: Impact of Formulation and Quality on the Safety and Performance of Generic Drug Products*** **[This is an awareness topic – there will be no Advisory Committee discussion of this topic]**	
3:15 p.m.	**BREAK**	
3:30 p.m.	(Continued Presentations)	
4:30 p.m.	**Open Public Hearing**	
5:00 p.m.	**ADJOURNMENT**	

July 26, 2011
TOPIC 1:

Bioequivalence (BE) and Quality Standards for Narrow Therapeutic Index (NTI) Drug Products

Background Information for the FDA Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology

July 26, 2011

Topic 1: ***Bioequivalence and Quality Standards for Narrow Therapeutic Index Drug Products***

1. Introduction

Generic drugs constitute 78% of total prescriptions dispensed in the United States in 2010[1]. Increased use and availability of generic drugs have provided significant cost savings and improved patient compliance, but also illustrate the importance of ensuring these generic products are of high quality

A generic drug is approved based on its pharmaceutical equivalence and bioequivalence, and therefore therapeutic equivalence, to the reference listed drug (RLD). Concerns have been expressed whether the current pharmaceutical quality standards and bioequivalence criteria are sufficient to ensure therapeutic equivalence of narrow therapeutic index (NTI) drugs[2] to the RLD. At the conclusion of the April 2010 ACPS meeting on NTI drugs, the Committee recommended, 13-0, that the FDA develop a list of NTI drugs with clear, specialized criteria for including drugs on the list. In addition, they voted 11-2 that the current bioequivalence standards are not sufficient for critical dose or NTI drugs. They commented:

- "Replicate studies are important.
- The Agency should look at manufacturing data on excipients from existing of formularies.
- The requirements for confidence intervals should perhaps be narrower (90-111%) and should include 100% (or 1.0)."

The ACPS Committee recommended future research, including pharmacodynamic (PD) modeling and therapeutic failure causes.

The FDA has evaluated various approaches to bioequivalence of NTI drugs including scaled average bioequivalence. In addition, the FDA conducted a survey of pharmaceutical quality of potentially NTI drug products. The following provides a brief

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1 *The Use of Medicines in the United States: Review of 2010.* IMS Institute for Healthcare Informatics, 2011.

2 A variety of terms are used to describe those drugs in which comparatively small differences in dose or concentration may lead to serious therapeutic failures and or serious adverse drug reactions. These terms include narrow therapeutic index, narrow therapeutic range, narrow therapeutic ratio, narrow therapeutic window, and critical-dose drugs. In 2010 ACPS meeting, Advisory committee members, including the industry representatives, preferred to call this group of products Narrow Therapeutic Index (NTI) Drugs as opposed to Critical Dose Drugs. NTI drugs will be used in this document.

summary about the regulatory issues, FDA research efforts and proposed approaches for NTI drugs.

2. Background

2.1 NTI definition

The Code of Federal Regulations, defined Narrow Therapeutic Ratio as following:

> "a. There is less than a 2-fold difference in median lethal dose (LD50) and median effective dose (ED50) values,
>
> or b. There is less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood, and
>
> c. Safe and effective use of the drug products require careful titration and patient monitoring."

The FDA Guidance for Industry "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations" provided a definition of narrow therapeutic range drug products as follows: "This guidance defines narrow therapeutic range drug products as those containing certain drug substances that are subject to therapeutic drug concentration or pharmacodynamic monitoring, and/or where product labeling indicates a narrow therapeutic range designation. Examples include digoxin, lithium, phenytoin, theophylline, and warfarin."

At the April 2010 ACPS meeting, Advisory committee members, including the industry representatives, preferred to call this group of products Narrow Therapeutic Index (NTI) Drugs as opposed to Critical Dose Drugs. A proposed definition of NTI drugs presented before the ACPS April 2010 meeting is as follows:

- Those drugs where small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions. Serious events are those which are persistent, irreversible, slowly reversible, or life-threatening,
- NTI drugs generally have the following characteristics:
  - Steep dose-response curves for both safety and efficacy in the usual dosing interval or close effective concentrations and concentrations associated with serious toxicity
  - Subject to therapeutic drug monitoring based on pharmacokinetic (PK) or pharmacodynamic (PD) measures
  - Small within subject variability.

2.2 Current bioequivalence criteria for NTI drugs

Bioequivalence studies are generally conducted by comparing the in vivo rate and extent of drug absorption of a test and a reference drug product in healthy subjects. In the U.S., a test product is considered to be bioequivalent to a reference product if the 90% confidence interval of the geometric mean ratio of AUC and C_{max} between the test and reference fall within limits of 80-125%. This approach is based on the premise that a 20% difference between test and reference product is not clinically significant. The same BE limit acceptance criteria are applied to NTI drugs. Health Canada tightened the limits of AUC for critical dose drugs to 90-112%, while EMEA expressed that the usual 80-125% acceptance interval "may need to be tightened".

Most NTI drugs have small within-subject variability. Table 1 summarizes the residual variability of 7 drugs from ANDA BE studies, with mean ranging from 5.7% to 21.7%. Based on NTI features described in previous section, these 7 drugs are potentially considered as NTI drugs. Please note that these are the residual variability of test and reference products. The actual variability may be smaller.

Table 1. Summary of residual variability (%CV)[3] from ANDAs

	AUC0-t		**Cmax**	
Drugs	**Mean**	**Range**	**Mean**	**Range**
Wafarin (n=29)	5.7	3.3, 11.0	12.7	7.7, 20.1
Levothyroxine (n=9)	9.3	3.8, 15.5	9.6	5.2, 18.6
Carbmazepine (n=15)	8.0	4.4, 19.4	8.7	5.2, 17.6
Lithium Carbonate (n=16)	7.8	4.5, 14.0	13.5	6.4, 24.4
Digoxin (n=5)	21.7	13.1, 32.2	21.0	14.3, 26.1
Phenytoin (n=12)	9.2	4.1, 18.6	14.9	7.4, 20.0
Theophylline (n=3)	17.9	12.8, 24.2	18.2	11.8, 25.8

2.3 Current pharmaceutical quality requirements for generic NTIs

A generic product should have the same pharmaceutical quality as the RLD. A generic product meets the same requirements for identity, purity, assay, and other quality attributes, and complies with the same rigid standards of GMP regulations for manufacturing as the innovator product. As with other drugs, most NTI drugs are required to meet 90-110% for assay limits and USP <905> for content uniformity. Table 2 lists the USP and BP pharmacopeia standards for the seven drugs. The assay limits

3 The residual variability is derived the ANOVA Root Mean Square Error (RMSE) from two-way crossover BE studies, comparing test and reference product. The RMSE, as it is calculated from combined test and reference data, is an estimate of the residual variability in the pharmacokinetic measures of each individual drug substance.

varied among different drug products, different pharmacopeia and different dosage forms of the same drug, ranging from 95.0-105.0% to 90.0-110.0%.

Table 2. Comparison of assay limits in USP and BP of Summary of residual variability (%CV) from ANDAs

Drug products	Assay USP limits	Assay BP limits
Carbamazepine IR	92.0-108.0%	95.0-105.0%
Carbamazepine chewable tablet	93.0-108.0%	-
Carbamazepine ER tablet	90.0-110.0%	-
Carbamazepine ER capsule	90.0-110.0%	-
Carbamazepine suspension	90.0-110.0%	-
Digoxin IR tablet	90-105%	90.0-110.0%
Levothyroxine IR tablet	95.0-105.0%	90.0-105.0%
Lithium carbonate IR tablet	95-105 %	-
Lithium carbonate ER tablet	90.0-110.0%	-
Theophylline ER tablet	No USP	95.0-105.0%
Warfarin IR tablet	95.0-105.0%	

3. FDA research efforts to address NTI issues

3.1 FDA simulation efforts to evaluate scaled average bioequivalence approach for NTI drugs

In contrast to NTIs, drugs with high within-subject variability (within-subject variability of 30% or greater in the pharmacokinetic measures AUC and/or Cmax) generally have a wide therapeutic window which means they have been demonstrated to be both safe and effective despite high variability. US FDA employs a scaled average bioequivalence approach to evaluate highly variable drugs (HVD)[4, 5, 6].

For NTI drugs, we also applied simulation methods to investigate different BE approaches including 1) direct tightening of BE limits; 2) tightening BE limits based on reference variability. The power of a given study design when using average scaled BE and average BE were compared. Variables evaluated in the simulations included: impact of study design, within subject variability; sample size (24-48), and point estimate limit.

4 S. Haidar et al. Bioequivalence approaches for highly variable drugs and drug products. *Pharm. Res.* 25:237-241 (2008).

5 B. M. Davit et al. Highly variable drugs: Observations from bioequivalence data submitted to the FDA for new generic drug applications. *The AAPS Journal*. 10:148-156 (2008).

6 S. Haidar et al. Evaluation of a scaling approach for the bioequivalence of highly variable drugs. *The AAPS Journal*. 10:450-454 (2008).

Preliminary results suggest that a four-way cross over replicate design is a reasonable approach for the BE evaluation of NTI drugs. Compared to direct tightening of BE limits, a replicate design has the advantage of comparing test and reference product variability and having the BE limit varied based on reference variability.

3.2 FDA survey of pharmaceutical quality of NTI drugs

For NTI drugs, small changes in the dose could cause serious or life-threatening adverse results. The 90-110% assay limits from Table 2 allow a potential 20% difference in drug dose between lots or the same lot at different times during the product shelf life. To provide additional data beyond the specifications, we conducted a pharmaceutical quality survey of NTI drugs to evaluate the actual test results relative to these specifications as well as limits on content uniformity and dissolution. This survey also estimated which products would pass the current USP <905> content uniformity standard.

Besides the NDA/ANDA review process, the FDA utilizes a variety of information gathering strategies to monitor the quality of prescription and non-prescription drug products in commercial U.S. distribution, including MedWatch, Adverse Event Reporting System (AERS), and Drug Quality Reporting System (DQRS). A comprehensive pharmaceutical quality survey, including drug formulation, manufacturing process, drug assay, content uniformity, stability, product recall, and field alerts, was conducted on the seven NTI drugs products. Annual reports between 2005 and 2011 were accessed to examine post-approval product quality. Recalls submitted to DMPQ/RSB January 1st 2000 thru May 3rd 2011 were analyzed and the total number of recall events for seven selected potential NTI products in the past 12 years were collected and categorized.

4. FDA proposed approaches for NTIs

Based on FDA's simulation efforts, it is proposed that sponsors for ANDAs of NTI drugs should conduct a replicate design study to quantify the variability of both the test and reference products and use a scaling approach for determination of BE. The BE limits would change as a function of within subject variability of the reference product. FDA proposes for NTI drugs that the default BE limits be 90-111% and that they be scaled using a regulatory constant of $sigma_0 = 0.1$ (which corresponds to a CV of 10.03 %).

When reference variability is less than 10%, the BE limits would narrow as a function of within subject variability of the reference product. When reference variability is greater than 10%, the BE limits would expand but the expansion would be capped at 80-125% (the current limit). The limits would expand to 80-125% for drug products with a variability of approximately 21% CV.

The FDA is also investigating the impact of adding additional bioequivalence acceptance criteria to the above proposal. These additional proposed criteria are point estimate limits for C_{max} and AUC and a requirement that the 90% confidence interval of test/reference C_{max} and AUC ratios includes 100%.

4.2 FDA proposed approaches for pharmaceutical quality evaluation of NTIs

Corresponding to the tightening of BE limits, the FDA proposes to tighten the assayed potency limit to 95.0-105.0% for NTI drug products. In addition, each NTI drug should meet tighter acceptance limits of content uniformity to ensure higher probability of NTI drug products meeting current USP 905. The NDA/ANDA applicants are advised to report detailed content uniformity data in the annul report. In addition, for NTI drug tablets with a score, content uniformity and dissolution of the split tablets should also be provided. Trends in stability data such as consistent use of stage 3 dissolution testing should be routinely investigated as part of the manufactures' overall product quality system. The risk assessments that underlie these quality systems should account for the greater severity of a product quality failure and treat such observations differently for NTI drugs.

Questions.

Does the committee agree with the following:

1. Is the draft definition for NTI drugs, proposed by the FDA, reasonable and appropriate?
2. Should the following be used for bioequivalence studies of NTI drugs:
    a. The two-treatment four-period fully replicated crossover design; and
    b. The reference-scaled average bioequivalence approach?
3. Is there a need to tighten assayed potency standards and content uniformity acceptance limits for NTI drugs?

July 26, 2011
TOPIC 2:

Impact of Formulation and Quality on the Safety and Performance of Generic Drug Products

Background Information for the FDA Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology

July 26, 2011

Topic 2: ***Impact of Formulation and Quality on the Safety and Performance of Generic Drug Products***

Generic drug product availability provides significant cost savings on pharmaceuticals, and the use of generic drug products continues to rise. It is estimated that generic drugs now account for approximately 78% of all retail prescriptions dispensed in the US, but represent less than 20% of total drug spending (1). Given the potential for even greater market share and cost savings for generic drugs in the future, it is of no surprise that considerable attention has been focused on the safety and quality of generic drugs.

Generic drug products must be therapeutically equivalent to their reference listed product, and, are thus expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. (2) Recognizing the additional requirements of generic drug products, the Office of Generic Drugs continues to closely evaluate the quality and equivalence of generic drug products in the premarketing setting and is working to formalize internal postmarketing surveillance processes specifically focused on the unique needs and challenges of generic drug products.

The passage of FDAAA in 2007 brought forth an increasing CDER-wide emphasis on postmarketing surveillance. OGD is focused on evaluating postmarketing safety and quality reports for generic drug products, with an emphasis on manufacturer-specific quality, safety, and equivalence issues. Not only is the Office concerned about safety signals that may indicate serious, unlabeled adverse events, but OGD must also look critically at reports to determine if issues of therapeutic inequivalence or manufacturer-specific quality issues exist that may either increase the incidence of nonserious, labeled adverse events, or contribute to a lack of efficacy with a specific manufacturer's drug product. Generic drug products contain the same active ingredient as the reference listed drug. However, failures in quality assurance during manufacturing or unexpected differences in bioequivalence due to formulation design could lead to two AB-rated drug products having different safety and/or efficacy profiles for specific lots of product or in specific subsets of the patient population.

Pharmaceutical quality can be defined as a product that is free of contamination and that reproducibly delivers the therapeutic benefit promised in the label to the consumer (3). In the case of a generic drug product, this definition can go a step further and incorporate the requirement for therapeutic equivalence to its reference listed drug product. In order for pharmaceutical quality to increase, the Agency recognizes it must be built into the product through quality by design and other tools. Sponsors of ANDAs should begin with a thorough understanding of the NDA target product profile (TPP) and the translation of the TPP into a quality target product profile (QTPP) specific for the ANDA product. The QTPP should include quantitative targets relevant to product specific

performance requirements. (4) Examples may include adhesion for a transdermal system, particle size for products which include beads labeled for sprinkling administration, and tablet size for solid oral dosage forms intended for patient populations with known swallowing difficulties.

OGD is working closely with the Office of Testing and Research in evaluating generic drug products. Through postmarketing surveillance activities and complementary scientific and laboratory support, OGD continues to focus on the development of new scientific methods and regulatory testing paradigms to further assure the identity, quality, safety, and equivalence of generic drug products.

1. Report by the IMS Institute for Healthcare Informatics. *The Use of Medicines in the United States: Review of 2010.* http://www.imshealth.com/deployedfiles/imshealth/Global/Content/IMS%20Institute/Static%20File/IHII_UseOfMed_report.pdf. Accessed 23May11.

2. Approved products with therapeutic equivalence evaluations. 29th ed. Washington, DC: US Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Sciences, Office of Generic Drugs, 2009. www.fda.gov/Drugs/Development/ApprovalProcess/ucm079068.htm. Accessed 23May11.

3. Woodcock, J. The concept of pharmaceutical quality. *Am Pharm Rev* 2004:1-3.

4. Lionberger, RA, Lee SL, Lee L, Raw A, Yu, LX. Quality by Design: Concepts for ANDAs. *The AAPS Journal* 2008;10(2):268-276.