Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the
Advisory Committee for Pharmaceutical Science and Clinical Pharmacology Meeting
September 25, 2013

Location: Bethesda North Marriott Hotel and Conference Center, Bethesda, Maryland

Topic: The committee discussed optimal strategies for the evaluation, interpretation, and communication of drug-drug interaction (DDI) information. FDA sought input on: (1) best practices in DDI communication through prescription drug product labels (i.e., "package inserts"), namely: a) appropriate format for presentation (e.g. tables, graphs, text) of DDI information; b) level of detail of DDI study results; and c) appropriate wording for clinical recommendations based on empirical data vs. anticipated interactions; (2) appropriate criteria for determining whether or not to describe DDI information derived from the literature in product labels; and (3) how package insert information on DDIs is used by various end-users (e.g., prescribers, dispensers, DDI database curators) in decision making and/or communication.

These summary minutes for September 25, 2013, Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology of the Food and Drug Administration were approved on December 17, 2013.

I certify that I attended the September 25, 2013, meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
Yvette Waples, PharmD
Designated Federal Officer, ACPS-CP

/s/
Jeffrey S. Barrett, PhD, FCP
Acting Chairperson, ACPS-CP

Summary Minutes of the
Advisory Committee for Pharmaceutical Science and Clinical Pharmacology Meeting
September 25, 2013

The following is the final report of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology meeting held on September 25, 2013. A verbatim transcript will be available in approximately four weeks, sent to the Office of Clinical Pharmacology and posted on the FDA website at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm361585.htm

All external requests for the meeting transcripts should be submitted to the CDER Freedom of Information Office.

The Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS-CP) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on September 25, 2013 at the Bethesda North Marriott Hotel and Conference Center, White Oak Room, Bethesda, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA. The meeting was called to order by Jeffrey S. Barrett, PhD, FCP (Acting Chairperson). The conflict of interest statement was read into the record by Yvette Waples, PharmD (Designated Federal Officer). There were approximately 150 people in attendance. There were no Open Public Hearing speakers.

Issue:
The committee discussed optimal strategies for the evaluation, interpretation, and communication of drug-drug interaction (DDI) information. FDA sought input on: (1) best practices in DDI communication through prescription drug product labels (i.e., "package inserts"), namely: a) appropriate format for presentation (e.g. tables, graphs, text) of DDI information; b) level of detail of DDI study results; and c) appropriate wording for clinical recommendations based on empirical data vs. anticipated interactions; (2) appropriate criteria for determining whether or not to describe DDI information derived from the literature in product labels; and (3) how package insert information on DDIs is used by various end-users (e.g., prescribers, dispensers, DDI database curators) in decision making and/or communication.

Attendance:
ACPS-CP Members Present (Voting): Jessie L-S Au, PhD; Rose Marie Caballero, MSN, RN (Consumer Representative); Fernando J. Muzzio, PhD; James E. Polli, PhD

ACPS-CP Members Not Present (Voting): Prabir K. Basu, PhD, MBA; Harriet B. Nembhard, PhD; Fadia T. Shaya, PhD, MPH; Elizabeth M. Topp, PhD

ACPS-CP Members Present (Non-Voting): Jack Cook, PhD (Industry Representative); James J. Keirns, PhD (Industry Representative)

ACPS-CP Members Not Present (Non-Voting): Edwin Hemwall, PhD (Industry Representative); Peter Honig, MD, MPH (Industry Representative)

Temporary Members (Voting): Jeffrey S. Barrett, PhD, FCP (Acting Chairperson); Ruth S. Day, PhD; David Flockhart, MD, PhD; John R. Horn, PharmD; Daniel Malone, RPh, PhD; Michael J. Miller, RPh, DrPH, FAPhA; Marilyn E. Morris, PhD; Kathleen A. Neville, MD, MS; Alice Pau, PharmD; Jürgen Venitz, MD, PhD

Guest Speakers: David W. Bates, MD, MSc; David Juurlink, BPharm, MD, PhD; Karl Matuszewski, MS, PharmD

Speaker: Tricia Lee Wilkins, PharmD, PhD

FDA Participants (Non-Voting): Issam Zineh, PharmD, MPH; Shiew-Mei Huang, PhD; Kellie Schoolar Reynolds, PharmD; Darrell Abernethy, MD, PhD; Lei Zhang, PhD

Designated Federal Officer (Non-Voting): Yvette Waples, PharmD

Open Public Hearing Speakers: None

The agenda proceeded as follows:

Call to Order and Introduction of Committee	**Jeffrey Barrett, PhD, FCP** Acting Chairperson, ACPS-CP
Conflict of Interest Statement	**Yvette Waples, PharmD** Designated Federal Officer, ACPS-CP
Introduction and Background	**Issam Zineh, PharmD, MPH** Director, Office of Clinical Pharmacology (OCP) Office of Translational Sciences (OTS), CDER, FDA
GUEST SPEAKER PRESENTATION	
Drug Labels and Interactions on the Front Lines	**David Juurlink, MD, PhD** Associate Professor Department of Medicine, University of Toronto Attending Physician, Division of General Internal Medicine Sunnybrook Health Sciences Centre Scientist, Institute for Clinical Evaluative Sciences Toronto, Ontario

FDA PRESENTATIONS

Communicating Drug Interaction Information: Drug Labeling	**Kellie Schoolar Reynolds, PharmD** Deputy Director, Division of Clinical Pharmacology IV OCP, OTS, CDER, FDA
Inclusion of Literature-Based Drug Interaction Information into FDA Drug Labeling	**Lei Zhang, PhD** Special Assistant to the Office Director OCP, OTS, CDER, FDA

Clarifying Questions

BREAK

SPEAKER PRESENTATION

Update- Health IT Initiative on Drug Interactions	**Tricia Wilkins, PharmD, PhD** Project Officer, Beacon Community Program Office of the National Coordinator for Health IT (ONC) Washington, District of Columbia

GUEST SPEAKER PRESENTATIONS

Best Practices in DDI - Related Content and Management	**David W. Bates, MD, MSc** Medical Director of Clinical and Quality Analysis, Partners Healthcare Chief Quality Officer, and Chief, Division of General Medicine Brigham and Women's Hospital Boston, Massachusetts
Strategies for Improving Drug Interaction Alerts for Clinical Decision Support (CDS)	**Karl Matuszewski, PharmD, MS** Vice President, Clinical Editorial First Databank, Inc. (FDB) South San Francisco, California

Clarifying Questions

LUNCH

Open Public Hearing Session

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Please discuss the following with regard to format of drug interaction study results presentation in prescription drug labeling:

   a) The level of detail on study design and study results

   b) The advantages and disadvantages of presenting the drug interaction study results in a forest plot versus a table versus a narrative

   Committee Discussion: *There was a general consensus that all drug-drug interaction (DDI) information should be placed together in one section of the prescription drug labeling. Many of the committee members stated the study results should include actionable information explaining what to do with a specific type of DDI (i.e., change in dose). In addition, some committee members suggested that the information should be in the simplest language and to include a link in the labeling to easily access more detailed information.*

   Some of the committee members made the following comments regarding the advantages and disadvantages of presenting the drug interaction study results in a forest plot versus a table versus a narrative:
   - *Some committee members stated that forest plots are valuable and can be interpreted easily while others disagreed, stating that forest plots are difficult to interpret and lack pertinent information (i.e. therapeutic window and dosing data)*
   - *Tables are easy to interpret; however, a recommendation was made to alphabetize the listing of drugs in the table and include dosing*
   - *Tables are more informative than forest plots*
   - *Narratives provide more detail; however, the narrative should be simple and straightforward*
   - *Narratives are less valuable than having data in tables*
   - *Narratives can be too lengthy*

   A key point was made that any of the above mechanisms for communication could be valuable and complementary as long as 1) they are non-redundant; and 2) they are clear. A suggestion was made to focus on what would make a useful table, forest plot, and narrative, rather than deciding on a general preference for one over the others.

   There was a general consensus that identifying the audience is a key factor in determining which tool(s) to use to deliver DDI information. Please see the transcript for details of the Committee discussion.

2. **DISCUSSION:** How do you recommend that complex drug-drug interaction (DDI) information be presented in prescription drug labeling? Examples of complex DDI information include:

   a) DDIs that differ between poor metabolizers and extensive metabolizers if the drug is metabolized by a polymorphic enzyme

b) DDIs that change over time

c) DDIs that differ depending on organ impairment (kidney or liver)

d) DDIs in patients who take three or more drugs, but DDIs were evaluated in pairs

Committee Discussion: *The committee reiterated that all drug-drug interaction (DDI) information should be easy to find and placed together in one section of the prescription drug labeling.*

Some of the committee members made the following recommendations regarding how complex drug-drug interaction (DDI) information should be presented in prescription drug labeling:

- *Information should be clearly stated and easily understood*
- *Include clinical relevance of DDI*
- *Include actionable information explaining what to do with a specific type of DDI; provide specific recommendations*
- *Focus on what occurs at steady state*
- *Indicate which populations are most vulnerable to DDIs*
- *Include quantitative measurement*
- *Categorize severity and frequency of occurrence (i.e., histogram)*
- *Clearly state that DDIs are unknown in patients who take three or more drugs because three drugs together were not studied*

Please see the transcript for details of the Committee discussion.

3. **DISCUSSION:** Some DDIs can be predicted based on *in vitro* studies, other *in vivo* studies, and *in silico* analyses. In those situations, what information about predicted DDIs should be included in prescription drug labeling? Should the labeling list all potential interactions or a subset (based on drug class, likelihood of co-administration, or severity of interaction)?

Committee Discussion: *Some committee members stated the following regarding what information about predicted DDIs should be included in the prescription drug labeling (these do not reflect consensus points):*

- *Clearly state if DDI information is extrapolated from non-human studies and separate this information from actual empirical studies*
- *The source should be included in the prescription drug labeling to indicate which model was used (i.e., in vitro, in vivo, or in silco)*
- *Consider that some stakeholders want details while others want simplified information*
- *Using historical DDI data to formulate modeling is a reasonable approach in making dosing recommendations*
- *The information should not be static and labeling should be updated as more information becomes available*

Please see the transcript for details of the Committee discussion.

4. **DISCUSSION:** What statements about the management of drug interactions are most useful? Least useful?

   Committee Discussion: *Some of the committee members stated the following regarding what statements about the management of drug interactions are most and least useful:*
   - *There was a recommendation to define and differentiate the terms "contraindication", "should be avoided", and "should not be given together" to make it easy for the clinicians and consumers to understand. It was also recommended to avoid using these terms interchangeably.*
   - *Use actionable terms and avoid using soft terms such as "should be avoided" or "should not co-administer"*
   - *Most useful are statements that are specific about what should be taken into account; least useful are the general statements such as "monitor the patient" and "exercise caution"*
   - *Statements explaining how to maintain drug therapy with the medications prescribed and stay within the therapeutic window would be useful*
   - *Specific dosing recommendations and contraindications are the most useful*
   - *Specific and detailed monitoring information is useful and an important risk management tool*
   - *Taking the end user into consideration, the information needs to be conveyed to the health care provider in a way that is easy to understand so that he/she can optimally manage patients' drug therapy*

   Please see the transcript for details of the Committee discussion.

5. **DISCUSSION:** Under what circumstances should DDI results from the literature be included in the prescription drug labeling? Please discuss the factors that should be considered to determine whether literature reported DDI results are included in the labeling qualitatively (general description of the DDI) or quantitatively (the quantitative information may be used for dosage adjustment).

   Committee Discussion: *There was a general consensus that the proposed decision framework is a good approach for looking at DDI results from the literature and may set a standard for investigators to provide higher quality data. The committee was pleased that OCP was trying to bring some formality to the evidence assessment process.*

   Some of the committee members made the following recommendations:
   - *Consider adding the expectedness and mechanistic plausibility to the algorithm*
   - *Engage the sponsors by providing them reports on the safety issues*
   - *Consider early in the framework whether the study result is consistent with other literature that has been published or anticipated based on what is known about each drug*
   - *Recommendation: formally state that the literature article must report a trial founded in good science relative to the attributes of the drug molecules in question*
   - *Recommendation: include data in the target population*

- *For 2c of the proposed framework, consider presenting the DDI results that are expected or unexpected in the same manner in labels (i.e., either both quantitatively or both qualitatively)*

Please see the transcript for details of the Committee discussion.

The meeting was adjourned at approximately 4:00 p.m.