



Advisory Committee for Reproductive Health Drugs

General Meeting
January 23 and 24, 2007

FDA Briefing Document

FDA Advisory Committee Briefing Document

**Prepared by the Division of Reproductive and Urologic Products
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General Meeting on Contraceptives

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Introduction

The Division of Reproductive and Urologic Products welcomes and appreciates the participation of the members of the Advisory Committee for Reproductive Health Drugs and other Special Government Employees at the upcoming Advisory Committee Meeting scheduled for January 23 and 24, 2007.

This general meeting will focus on hormonal contraception – specifically: oral, transdermal, and vaginal contraceptive products. Although longer acting injectable and implantable contraceptives share a number of the same safety and efficacy issues as the shorter acting products, they will not be discussed in any detail at this meeting.

The primary purpose of this general meeting is to seek advice from the Committee on a number of issues related to hormonal contraception. The Division of Reproductive and Urologic Products (also referred to as the “Division” in the document) intends to take this advice into consideration in its development of a Guidance document for the clinical investigation of hormonal contraceptives. Currently there is no FDA clinical trial Guidance document for hormonal contraceptive products.

The following issues are those that either (1) need to be satisfactorily addressed in the regulatory review of these products prior to approval for marketing or (2) require a commitment by the drug company prior to approval to investigate further post-approval (a phase 4 commitment) because the issue(s) cannot be fully addressed in preapproval clinical trials. While the actual course of the meeting may follow an order different from that in this document, based on speaker availability and other consideration, all of the topics for this two-day general meeting are introduced in this background document. These topics include:

- (1) clinical trial design issues,
- (2) contraceptive efficacy and risk/benefit assessment,
- (3) cycle control (scheduled and unscheduled bleeding and spotting) and other measures of product acceptability to the user,
- (4) translation of clinical trial findings of efficacy and safety into “real world” effectiveness and safety,
- (5) extended dosing regimens,
- (6) phase 4 commitments by Applicants for further investigation, generally of uncommon but serious safety issues, and
- (7) role and impact of labeling for communication of clinical trial findings including product efficacy, risk, and other benefits.

Where the Division has been able to obtain relevant, timely, and evidence-based publications related to these topics, the publications have been provided in this background package. In other instances, background information for the discussion topics will be provided by invited experts who will make brief background presentations at the meeting prior to discussion of a particular topic.

1. Clinical Trial Design Issues

Clinical trial design issues that are of particular interest to the Division include:

- number of subjects that should be enrolled to assess safety and efficacy adequately prior to approval for marketing
- entry criteria
- historically controlled versus active controlled trial designs
- improved quality of clinical trial data through the use of new technologies such as electronic diaries
- study participant satisfaction data (e.g., use of patient reported outcome instruments)

Number of Subjects Enrolled to Assess Safety and Efficacy Adequately

The Division has typically asked Sponsors to provide clinical data for at least 10,000 28-day treatment cycles and to have at least 200 women complete 13 cycles of use as a minimum for approval of a New Drug Application (NDA). For a hormonal contraceptive product that includes a new molecular entity (e.g., a progestin not approved for marketing in the U.S.), the Division is currently requesting that companies (referred to as “Sponsors” in the document) submit data from approximately 20,000 28-day cycles of exposure that include at least 400 women who have used the product for at least one year.

The Division will likely be recommending in the future that the 10,000 and 20,000 28-day cycles of exposure occur in the first year of use of the product.

The World Health Organization (WHO) sponsored a symposium in 1987 for the purpose of improving safety requirements for contraceptive steroids. The guidelines that were developed were updated by the Committee for Proprietary Medicinal Products (CPMP) for the European Agency for the Evaluation of Medicinal Products (EMA) in February 2000 and then again in July 2005. Many of the FDA recommendations to Sponsors are similar to these European guidances.

The present European Guidance document recommends that:

“The key studies, carried out in a sufficiently representative population, should normally be at least large enough to give the overall Pearl Index (number of pregnancies per 100 woman years) with a two-sided 95% confidence interval such that the difference between the upper limit of the confidence interval and the point estimate does not exceed 1 (pregnancies per 100 woman years).” -**EMA Guideline on Clinical Investigation of Steroid Contraceptives in Women - 27 July 2005**

To achieve this precision, up to 20,000 28-day cycles of subject exposure may be required. For a new contraceptive, EMA requires that 400 women complete one year of use.

Entry Criteria

Although most entry criteria have become fairly standard and accepted, there are some exclusionary criteria that are used in contraceptive trials that may limit the Division's ability to evaluate safety of a product adequately prior to approval. Exclusionary criteria in clinical trials do not necessarily match what happens in clinical practice (e.g., women with BMI > 35, smokers over the age of 30 but less than 35, and women with a relative who has a history of a thrombotic or thromboembolic event may be excluded by the Sponsor of the clinical trial). These exclusionary criteria also are not reflected in the contraindications in the label for the product.

The exclusion of obese women in clinical trials is also of concern, particularly for low dose oral products because of possible reduced effectiveness in "real world" usage.

Study participants may be "fresh starts" (women who have never taken a hormonal contraceptive) or "switchers" (women switching from another hormonal product). Depending on a subject's prior use of a contraceptive product, her response to the product under investigation (e.g., frequency of unplanned bleeding and acceptance of hormonal contraception in general) may vary. The educational and socioeconomic level of the subjects across studies also may vary widely. These and other demographic issues are critical in studying populations who are likely to be "representative" of anticipated users.

Some clinical trials that are used to support marketing approval of new hormonal contraceptive products in the U.S. may include data almost entirely from foreign study sites and include few data from U.S. sites. There may be significant differences between U.S. and non-U.S. populations in regard to BMI, general compliance, and representation of non-Caucasian participants. Although the diagnosis of pregnancy is fairly consistent across all countries, accuracy of dating the time of conception (e.g. ultrasonographic estimates of date of conception) also may vary at non-U.S. sites.

Possible Discussion Items

- Should entry criteria be more reflective of actual clinical prescribing regarding BMI, smoking, and family history of thrombosis or thromboembolism?
- Should a certain minimum percentage of the subjects in phase 3 studies be studied at U.S. sites? The Division has seen different efficacy results in foreign studies compared to U.S. studies (often better efficacy results in Europe).
- Should a certain percentage of the study population represent "fresh starts" as opposed to "switchers?"
- Are there cultural or physical attributes in foreign populations that would render contraceptive study data from such populations less applicable to the U.S. population?

Historically Controlled vs. Active Controlled Trial Designs

Traditionally, hormonal contraceptive products have been approved in the U.S. based upon historically controlled trials.

Possible Discussion Item

- Is there a role for active controlled trials; if so, under what circumstances?

Improved Quality of Clinical Trial Data through Use of New Technologies

Electronic diaries are increasingly used throughout all areas of drug development in an effort to improve the quality of data collection. In contrast to traditional paper diaries, electronic diaries allow accurate time dating of entries and reduce recall bias. In contraceptive studies, this technology could potentially improve collection of data to help in the analysis of user failure vs. method failure rates, incidence of unscheduled bleeding and spotting, etc.

Possible Discussion Item

- Should electronic diaries be recommended for all pivotal contraceptive clinical trials?

Study Participant Satisfaction Data

Although patient satisfaction questionnaires have been used in clinical contraceptive trials in the past, these questionnaires have not been adequately validated. For this and other reasons, the Division has not permitted the information obtained from these questionnaires to be included as secondary claims in product labeling. The FDA has recently issued a draft Guidance that allows for potential inclusion of health related patient reported outcomes (PROs) in labeling.

Possible Discussion Items

- The Division has typically used premature termination rates as an assessment of patient acceptability and satisfaction in clinical trials. Would information obtained from validated PRO instruments be useful in contraceptive trials?
- Could a validated PRO instrument, either alone or in conjunction with other measures, be used to obtain a secondary labeling claim of superiority (e.g., better cycle control)?

Included Articles Related to Clinical Trial Design

Guideline on Clinical Investigation of Steroid Contraceptives in Women. EMEA, Adopted in July 2005

Draft Guidance for Industry - Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims, FDA, February 2006

Helmerhorst FM et al. The Cochrane Fertility Regulation Group: synthesizing the best evidence about family planning. Contraception 2006 Oct; 74(4): 280-6

2. Contraceptive Efficacy and Risk/Benefit Assessment

This section covers the issues of:

- contraceptive efficacy and analysis
- risk-benefit assessment

Contraceptive Efficacy and Analysis

Contraceptive efficacy is assessed by the rate of unplanned pregnancies during a specified time of exposure. The two methods that are currently used to measure efficacy are the Pearl Index and life table analysis. The Pearl Index, defined as the number of contraceptive failures per 100 women-years of exposure, uses as the denominator the total months or cycles of exposure from the initiation of product use to the end of the study, occurrence of unintended pregnancy, or discontinuation of the product. Life table analysis provides the contraceptive failure rate for each month of use, and can provide a cumulative failure rate for any specific length of exposure.

Pregnancy rates in clinical trials submitted to the Division in support of approval for new contraceptive products appear to have increased through the years, particularly in the past decade. This apparent increase could be due to a number of factors including:

- increased method failures (i.e., a failure that occurs when a product is used perfectly in accordance with the recommended dosing regimen) that may be attributable to lower dosages of estrogens and progestins, heavier subjects, or other factors
- user failure (i.e., a failure that occurs when the subject does not completely follow the recommended dosing regimen, such as failure to take one or more doses)
- other factors, such as improvement of pregnancy detection (e.g., more frequent and more sensitive pregnancy testing).

Possible Discussion Items

- At the present time, the primary efficacy assessment to support approval for a new contraceptive product is based on the Pearl Index. Life table analyses for pregnancy rates are also reviewed.
 - What are the relative merits of each approach?
 - Are there situations where one approach should be favored over the other? If so, what are they?
 - How should divergent pregnancy rates, calculated by the Pearl Index versus those calculated by life table methods, be considered in the approval process and in labeling?
- How should divergent pregnancy rates, obtained in U.S. and non-U.S. populations, be considered in the approval process and in labeling?

- Should “on-study pregnancies” be defined to include only those pregnancies that occur while subjects are within the treatment cycle or also include those pregnancies with an estimated date of conception that may have occurred within a certain number of days after the end of the last treatment cycle (e.g., 2, 5, 14 days – where the treatment cycle is defined to include the pill-free interval following active treatment)? If yes, where should the cut-off be established or should it vary according to how reliably a drug inhibits ovulation?
- How can the life table analysis of pregnancy rates be adjusted for the use of back-up contraception midway through the exposure period, for example, only during treatment Cycle 6 in a 13-cycle treatment period?
- How should the analysis of pregnancy rates be adjusted for the use of back-up contraception in extended cycle contraceptive trials? For example, in an 84/7 dosing regimen, should an entire 91 day cycle be considered nonevaluable if a single use of backup-contraception occurs, or should only a 28 day portion of the cycle be excluded from consideration of at-risk cycles?

Risk/Benefit Assessment

The approval of any drug product is based upon the balance of its benefit and its risks. The risk/benefit assessment of hormonal contraceptives has historically tried to balance not only the safety and efficacy demonstrated in the clinical trials but also the safety implications of an unplanned pregnancy. Therefore, the serious adverse events related to thrombosis and thromboembolic complications need to be balanced against similar risks associated with an unplanned pregnancy, including the postpartum period.

The primary clinical trials used to support approval of all oral contraceptives from 1960 to 1970 had contraceptive failure rates of < 1 as judged by an overall Pearl Index. In 1975, the issue of efficacy for Ovcon® 35 (35µg ethinyl estradiol [EE] and 400 µg norethindrone) was brought before the Obstetrics and Gynecology Advisory Committee (predecessor of the Reproductive Health Advisory Committee). Subsequent to this Advisory Committee meeting, the Division recommended a Pearl Index cut-off limit of 1.5 as establishing an acceptable level of efficacy. The Division has observed that as the dosage of the estrogen and progestin components have decreased to that seen in products contemporarily being presented to the Agency, the number of method failures has increased; this is consistent with less sustained ovulation suppression in newer products as compared to the earlier higher dose regimens ($EE \geq 30 \mu\text{g}$ and generally higher progestin doses).

In the past decade, some oral contraceptive products have been approved with overall Pearl Indices above 2.0. There currently is divergence of opinion in the Division as to whether or not efficacy in the clinical trial should be defined by a set limit on the overall Pearl Index (e.g., efficacy established by a Pearl Index ≤ 2.0) and, if so, just what that set limit should be (1.0, 1.5, 2.0, 2.5, or higher?). Should acceptable efficacy be defined by a set limit on the method failure rate or overall failure rate as assessed by the Pearl Index? If so, what should this limit be? Indeed, there are some who would suggest that there

should be no upper limit to the acceptable Pearl Index as long as the prescriber and the patient are informed as to the failure rate and the observed safety profile.

Also, as hormonal contraceptive dosages have decreased and pregnancy rates appear to have increased in clinical trials, the true balance of risk vs. efficacy has become more difficult to assess because rare, but serious complications are unlikely to be detected in clinical trials. This is further compounded by the difficulty of predicting effectiveness in the real world from trial data.

There may be better efficacy and a greater margin for user non-compliance in higher dose pills, but a theoretically better safety profile in a lower dose estrogen product. However, the relationships of efficacy and risk of serious adverse events may also be associated with the progestin dose and the estrogen/progestin balance, and not simply with estrogen dose. In addition, while clinical trials are likely to be able to demonstrate a difference in efficacy between dose levels, a differential risk of serious thromboembolic events between dose levels can generally only be detected in large, phase 4 (post-approval) studies because of the rare occurrence of such events.

Possible Discussion Items

- For historically controlled trials, should evaluation of pregnancy rate be based only upon the point estimate, the upper bound of the 95% confidence interval around that point estimate, or both?
- Is there a pregnancy rate that would be unacceptably high, regardless of the risk/benefit balance of the product? If so, what would that rate be?
- Should we accept a possible decrease in effectiveness balanced by an even less-well documented decrease in the risk of serious adverse events with lower dose products as compared to higher dose products (e.g., the risk of venous thromboembolic events with 20 µg estrogen vs. 30-35 µg estrogen contraceptive products)?

Included Articles Related to Contraceptive Efficacy and Risk/Benefit Assessment

Trussell J. Contraceptive failure in the United States. Contraception 2004 Aug; 70(2): 89-96

Gallo MF et al. Twenty micrograms vs. >20 microgram estrogen oral contraceptives for contraception: systematic review of randomized controlled trials. Contraception 2005 Mar; 71(3): 162-9

Gerlinger C et al. Recommendation for confidence interval and sample size calculation for the Pearl Index. Eur J Contracept Reprod Health Care 2003 Jun; 8(2): 87-92

3. Cycle Control (Scheduled vs. Unscheduled Bleeding and Spotting) and Other Measures of Product Acceptability to the User

Cycle Control (Scheduled and Unscheduled Bleeding and Spotting)

Although the term cycle control could be used in a broad sense to include all facets of a woman's menstrual cycle that are affected by exogenous hormones, it typically refers to bleeding and spotting issues. Hormonal contraceptives, based on their overall dosage, relative proportion of estrogen to progestin, and dosing schedule, can affect bleeding/spotting in many ways. Effects can range from no bleeding or spotting to frequent bleeding and/or spotting episodes throughout the treatment cycle. The traditional dosing regimen has allowed for scheduled bleeding during hormone-free periods; some newer methods have attempted to reduce or eliminate the number of scheduled bleeding episodes or reduce the magnitude of scheduled bleeding. Of most concern to users is likely to be the unscheduled bleeding or spotting that may occur during periods of active drug treatment.

Many clinical studies have been performed to analyze a single product or to compare products to determine the degree to which the product favorably influences the cycle and keeps the unscheduled bleeding and/or spotting to a minimum. The studies that have been performed to assess cycle control have varied greatly in the protocol data assessment and even in definitions of what constitutes bleeding and spotting. Two new journal articles (by Mishell et al.) which appear in the January 2007 issue of *Contraception* address clinical study inconsistencies and provide an approach to a unified trial design for the collection and evaluation of bleeding/spotting data. These articles are included in the bibliography section of the background document.

Possible Discussion Items

- Do the members of the Advisory Committee agree with the recommendations for standardization of data collection and analysis of bleeding in combined hormone contraceptive trials proposed in the articles by Mishell et al.?
- How should the Division take into account the degree of unscheduled bleeding in reviewing new hormonal contraceptive products?
- What objective measures beyond hemoglobin and hematocrit values, if any, should be employed to assess significant change in hematologic status?

Included Articles Related to Cycle Control

Mishell DR et al. Combined hormonal contraceptive trials: variable data collection and bleeding assessment methodologies influence study outcomes and physician perception. Contraception 2007 Jan 75(1)4-10

Mishell DR et al. Recommendations for standardization of data collection and analysis of bleeding in combined hormone contraceptive trials. Contraception 2007 Jan; 75(1): 11-5

4. Translation of Clinical Trial Findings of Efficacy and Safety into “Real World” Effectiveness and Safety

Translating the results of controlled clinical trials into the expected outcome when contraceptive products are used in the general population is a complex issue, illustrating the distinction between the terms “efficacy” (how well the product works in a clinical trial) and “effectiveness” (how well the product works in actual practice). The clinical trial environment, where subjects may have frequent contact with investigators, may be paid to attend clinic visits, and may even keep daily diaries of their use of the product, is unlikely to generalize fully to the actual conditions under which women use contraceptive products. For this, among other reasons, the pregnancy rates obtained from clinical trials may be markedly better than the actual pregnancy rates observed when women in the general population use the product, often in a less consistent and reliable manner. Also, data obtained in non-U.S. trials may not generalize well to the heterogeneous U.S. population.

While other “real world” limitations, such as formulary access to specific contraceptives and provision of only one month’s supply at a time, may also impact actual use effectiveness, it is important that trials identify, to the extent possible, subpopulation representation, subject satisfaction with the product, and reasons for trial discontinuation that may be relevant to non-compliant use and discontinuation-of-use by the broader population. In addition to information about “perfect use” (always using the product exactly as prescribed or labeled) and “typical use” (not always using the product exactly as prescribed or labeled) failure rates, data must be available to inform prescribers and potential users to determine how difficult it is to use a particular product correctly and consistently.

Possible Discussion Items

- Can trial designs be modified so as to provide results that are more reflective of actual effectiveness in the “real world”?
- Can trial designs be modified so as to provide results that are more generalizable to U.S. subpopulations (e.g., enrolling more minorities and/or subjects from lower socioeconomic groups) who may have more real or perceived barriers that may impact on effectiveness, compliance, and safety?
- Should clinical trials investigate new technologies that may facilitate compliance in “real world” use?

**Included Articles Related to Translation of Clinical Trial Findings to the
“Real World”**

Moos M-K et al. Counseling in the clinical setting to prevent unintended pregnancy: an evidence-based research agenda. Contraception 2003 Feb; 67(2): 115-32

Rosenberg, MJ et al. Compliance and oral contraceptives: A review. Contraception 1995; 52: 137-41

Clark, LR. Will the pill make me sterile? Addressing reproductive health concerns and strategies to improve adherence to hormonal contraceptive regimens in adolescent girls. J Pediatr Adolesc Gynecol 2001, 14: 153-62

5. Extended Dosing Regimens

There are now a number of oral contraceptive products that have varied dosing regimens that differ from the traditional “21 days on and 7 days off” of the older products. Some of the alterations occur in the 7 day window (adding combination pills [24/4 dosing regimens] or small amounts of ethinyl estradiol only). Other regimens have utilized 84 active pills followed by either 7 inactive pills (84/7 dosing regimens) or 7 pills containing a lower dose of ethinyl estradiol. The most extreme modification is to take an active combination tablet daily without any discontinuation, a dosing regimen that currently is not available for an approved product in the U.S.

Possible Discussion Items

- If the modified or extended dosing regimen does not expose a women to a greater daily or monthly quantity of either hormonal component of an approved and marketed otherwise identical product, does a proposed drug product need to meet any criteria other than the “standard” criteria for efficacy and safety required for a traditional 21/7 product? If so, what should these criteria be?
- If the modified or extended dosing regimen exposes a woman to a greater daily or monthly quantity of either hormonal component of an approved and marketed otherwise identical product, what are the additional criteria that a proposed drug product needs to meet to support approval for marketing?
- Products with extended dosing regimens are often intended to reduce the number of scheduled (or withdrawal) bleeding episodes. Such a reduction in scheduled bleeding may be offset by an increase in unscheduled bleeding or spotting, particularly in the first several treatment cycles. Can this information be adequately addressed in labeling so that both the prescriber and consumer will be aware of both the potential limitations and benefits of the new dosing regimen?
- What cycle length should be used when analyzing cycle control in extended cycle products?

Included Articles Related to Extended Dosing Regimens

Edelman A et al. Continuous versus cyclic use of combined oral contraceptives for contraception: systematic Cochrane review of randomized controlled trials. Hum Reprod 2006 Mar; 21(3): 573-8

Birtch RL et al. Ovarian follicular dynamics during conventional vs. continuous oral contraceptive use. Contraception 2006 Mar; 73(3): 235-43

6. Phase 4 Commitments

A phase 4 commitment is an agreement by the Sponsor of a product to conduct specified studies or activities following approval of the product in order to provide information that is not available at the time of initial review. It is typically negotiated between the Division and the Sponsor during the initial review process. Although it had not been the Division's policy to require phase 4 studies of oral contraceptives, in recent years, the Division has been requesting phase 4 studies for (1) hormonal contraceptive products that contain a new molecular entity and (2) new dosing regimens that increase the average monthly exposure to one or both hormonal components of a product beyond that of a currently approved and marketed product containing the same hormonal components. A reason for requesting further investigation of safety as a phase 4 commitment in the postmarketing period includes the difficulty of detecting or defining the rate of occurrence of rare events (e.g., those occurring in $<1/3,000$ subjects) in preapproval clinical trials. Another reason for a phase 4 commitment is to detect the emergence of unidentified or underappreciated adverse events when a product is used for greater duration and/or in more diverse patients, including those with co-morbid conditions that may have been excluded in clinical trial populations. The most serious adverse events associated with oral contraceptives, such as arterial and venous thrombotic events, occur rarely, and therefore their rate of occurrence cannot be accurately assessed in typical premarketing efficacy trials. With changes in the progestin used, as well as changes in dosing, route and frequency of administration, and estrogen/progestin ratios, the predictability of the safety profile expected from a given product may vary. This also affects the amount of data required to evaluate safety.

Phase 4 evaluation can range from simple signal detection arising via spontaneous and voluntary postmarketing safety reports submitted to the FDA's Adverse Event Reporting System (AERS) database, to case series and data-mining signals developed using the AERS database from a product or class of products, to observational studies, and finally to randomized, controlled trials conducted once a product is marketed. Using spontaneous reports in the FDA's AERS database, it is not possible to calculate accurate event rates, because both the numerator (the number of events that have truly occurred) and the denominator (the number of patients at risk for the adverse event) are unknown. While "reporting rates" based upon the numbers of prescriptions filled or other surrogates for actual nationwide exposure may be calculated, such rates are only weak proxies for actual incidence rates. In contrast, observational studies, such as pharmacoepidemiologic studies conducted in a claims database or a health maintenance organization database, can allow for actual estimates of the relative risk of an adverse event, because they can evaluate both treated and untreated control groups within the database selected and can test pre-specified hypotheses. Finally, a large, simple safety study using a randomized controlled design can be used to evaluate limited safety outcomes in a large population, avoiding the potential biases inherent in an observational design.

Possible Discussion Items

- What designs should be considered for phase 4 studies of hormonal contraceptives and what are the strengths and limitations of each type of design? What are the most important cost/benefit considerations and limitations of each design (e.g., a more rigorous design but a delay in obtaining outcome data)?
- Phase 4 studies have generally been confined to obtaining information primarily or entirely related to safety issues. Can such studies be designed to obtain a better estimate of true “actual use” product effectiveness? If so, how best can this information be obtained?
- To what extent are phase 4 studies of effectiveness likely to provide overestimates of effectiveness due to decreased ascertainment of contraceptive failures (e.g., abortions may not be captured in claims databases)?
- In addition to thrombotic and thromboembolic risk, are there other safety issues that should be addressed within long-term or large phase 4 studies?

Included Articles Related to Phase 4 Commitments

Guidance for Industry, Good Pharmacovigilance Practices and Pharmacoepidemiology Assessment, FDA, March 2005

Sidney, S et al. Venous thromboembolic disease in users of low-estrogen combined estrogen-progestin oral contraceptives. Contraception 2004; 70: 3-10

Skegg DC. Evaluating the safety of medicines, with particular reference to contraception. Stat Med 2001; 20 (23): 3557-69

Burkman R et al. Safety concerns and health benefits associated with oral contraception. Am J Obstet Gynecol 2004 Apr; 190 (4 Suppl): S5-22

7. Role and Impact of Labeling for Communication of Clinical Trial Findings including Product Efficacy, Risk, and Other Benefits

Product labeling should optimize communication to patients and prescribers, clearly articulate topics including perfect use and overall effectiveness, and provide clear risk communication. For example, different hormonal contraceptives vary in the extent to which they suppress ovulation, the degree to which other mechanisms of action assist in the prevention of pregnancy, and may differ in their margin of “forgiveness” without reducing effectiveness when pills are missed.

A typical hormonal contraceptive label runs to 40 or more pages as a pdf file, and contains both information for prescribers (the Package Insert or PI) and for patients (the Patient Package Insert or PPI).

In January 2006, the FDA published new requirements on the content and format of labeling (the Physician Labeling Rule), based upon research findings that prescribers primarily use labeling to answer a specific question or find a specific piece of information, find the existing format difficult to use, and would use labeling more if it included a short synopsis of the contents. That same month, the Agency published the draft Guidance on Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements. Changes in the labeling format are intended to streamline and focus the label, and include the addition of an introductory summary of information (“Highlights”) designed to encompass the information from the full label that prescribers most commonly reference and consider the most important information.

The new labeling format will be implemented for all approved marketing applications submitted on or after June 30, 2006. The Division anticipates that when the first eligible application is submitted, substantial revision of all current hormonal contraceptive labels will have to be undertaken, due to the large amount of class labeling included in hormonal contraceptive labels.

Possible Discussion Items

- Can labeling information be made more useful for counseling patients, in order to better inform patients about the likely effectiveness, safety, and other “acceptability considerations” (e.g., expected bleeding patterns, secondary benefits of using contraceptives, such as cycle control)? Would such information likely reduce discontinuation rates and improve actual product effectiveness?
- Should product labeling be modified to include pregnancy rates or safety data for specific subgroups when available?
- How do we communicate the risk of an unplanned pregnancy in the days or weeks immediately following discontinuation of a product?
- How can we best communicate how to handle a situation where a patient misses pills?

- Should potential secondary, non-contraceptive benefits of hormonal contraceptives be discussed in labeling?

Included Articles Related to Labeling

Draft Guidance on Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements. FDA, January 2006

Steiner MJ et al. Communicating contraceptive effectiveness: A randomized controlled trial to inform a World Health Organization family planning handbook. Am J Obstet Gynecol 2006 Jul; 195(1): 85-91

Curtis, K et al. Effective use of hormonal contraceptives, Part 1: Combined oral contraceptive pills Contraception 2006; 73(2): 115-24

Other References

If the advisory committee member is interested in additional text reading the following sources may provide additional information:

- Hatcher RA et al. editors. Contraceptive technology - 18th Ed. New York: Ardent Media Inc; 2004
- Speroff L, Darney PD. A Clinical Guide for Contraception – 4th Ed. Philadelphia. Lippincott Williams & Wilkins; 2005