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Cloud Over FDA Advisory Panel Meeting From 'Over-Reporting' In Birth Control OTC Switch Study

by Malcolm Spicer

> While HRA consultant says its study "meets or exceeds standards of most other studies assessing adherence, including an oral contraceptives," FDA ONPD director says particpants' over-reporting "is not something we see in a typical actual use study."

The US Food and Drug Administration is holding the line on requiring reliable data supporting an OTC switch application no matter how much and how often the sponsor describes the numerous public health benefits of expanding access to a daily oral contraceptive.

Agency officials, on 9 May during the first day of a two-day advisory panel meeting conducted online, also heard almost unanimously from consumers and representatives of medical and advocacy groups recommending approval of HRA Pharma's supplemental new drug application to allow OTC sales of Opill (0.75-mg norgestrel). Of the 37 people speaking during the public comment portion, 35 supported OTC sales of the progestin-only formulation, most imploring the FDA to expand access to birth control for females under 18 years old.

But part of the FDA's concerns stem from HRA's study data about adolescents' self-selection of Opill.

Also prompting FDA questions are the *Perrigo Company PLC* subsidiary's actual use trial showing "improbable dosing in approximately 1/3 of participants" recorded in online diaries provided in the study, the cause of which HRA concluded "is incompletely understood." The agency, as explained in its *briefing material*, also has questions about the numbers of adolescents and persons with limited literacy levels the firm recruited for the actual use trial and the self-selection study preceding it.

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Other than an hour and 45 minutes for public comment at the end of the day, the meeting was used for HRA to present results from the multiple studies it conducted in support of its sNDA and convince the agency's Nonprescription Drug and Obstetrics, Reproductive and Urologic Drugs advisory committees to recommend approval, and for FDA officials to explain their concerns about whether some of the firm's data could be trusted to show accurate self-selection and safe use of Opill.

'Over-Reporting' An 'Inherent Risk' In Self-Report Study – Oral Contraceptive OTC Switch Sponsor

By Malcolm Spicer

08 May 2023
HRA says its research in support of its sNDA for its 0.75-mg norgestrel tablet branded Opill shows accurate OTC self-selection and safe use of the progestin-only drug by females of reproductive age.

Read the full article here

The *FDA's agenda* for the second day of the meeting includes four questions: three discussion points, including recommendations for design changes if it asks HRA for another actual use study, and one yes/no vote:

- VOTE: Is there adequate information to conclude that consumers will be likely to properly use norgestrel tablet such that the benefits of making this available for nonprescription use (access without needing to interact with a healthcare professional), exceed the risks (contraceptive failure due to inadequate adherence, using this medication when they have a contraindication to its use, failure to see a health care professional when appropriate)?

- a. If you voted NO: Explain why you believe the risks outweigh the benefits for nonprescription use, and what additional data would be necessary to support approval.

- b. If you voted YES: Explain why you believe the benefits outweigh the risks for nonprescription use.

HRA Study 'Meets Or Exceeds Standards Of Most Other' Adherence Studies

During their presentations, HRA executives and consultants working with them said, as the firm stated in its *briefing material* provided to the committees in advance of the meeting, that "over-reporting" by some participants, which FDA officials call improbable dosing, is an inherent risk in any trial relying on participants' self-reporting.

The over-reporting, which FDA reviewers found in HRA's data before the agency asked the firm to explain – leading to postponing the advisory panel from the originally scheduled November date, didn't affect the results showing accurate self-selection and safe use, HRA and its consultants say.

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The actual use study "meets or exceeds the standards of most other studies assessing adherence, including an oral contraceptive," said Arthur Stone, a professor of psychology, economics and public policy at the University of Southern California and director Center for Self-Report Science there.

Time-stamped electronic diaries are "a form of self-report that's known to increase the accuracy of self-reporting compared to more commonly used methods, such as retrospective questionnaires or paper diaries," Stone said.

FDA May Ask HRA For Another OTC Birth Control Actual Use Study Due To 'Improbable Dosing'

By Malcolm Spicer

08 May 2023

With "improbable dosing in approximately 1/3 of participants" in HRA actual use study, FDA asks advisory committees to recommend design changes if it asks firm for another study. FDA asked HRA to explain discrepancies after it began reviewing the firm's sNDA submitted in June 2022.

Read the full article here

Additionally, the study allowed "a relatively short recall period compared with published studies in oral contraceptive work." While participants could retrospectively report for up to 11 days in HRA's study, other oral contraceptive studies typically allowed for retrospective reporting for up to three months, he added.

Stone noted these "important reasons" for finding HRA's study results reliable in addition to self-reporting being the standard and most common method for assessing medication adherence:

Over-reporting as observed in HRA's study is only detected "when extraordinary design elements are incorporated," including staff tracking participants' medication supply and allowing participants to report taking pills when they don't have pills available;

design elements in HRA's study that permitted over-reporting reflect a reasonable and frequently made compromise to balance the need to

US Oral Contraceptive OTC Switch Sponsor Says 'Challenging Target' Met For Adolescents In Study

By Malcolm Spicer

08 May 2023

HRA executives and other representatives for firm and FDA officials will make presentations about HRA's sNDA to agency's Nonprescription Drug and Obstetrics, Reproductive and Urologic Drugs advisory committees during a joint meeting on 9-10 May.

Read the full article here

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minimize interference with participant behaviors during the study with the ability to optimally collect the data in an actual use trial.

"In my view, the design of [HRA's] study did not encourage over-reporting. Instead, over reporting does appear to be a function of decisions made by individual participants," he said.

'Not Something We See In Typical Actual Use Study'

Members of the advisory committees asked multiple questions about the over-reporting data, some suggesting they agree with HRA that the discrepancies didn't make the firm's data unreliable.

More members, though, indicated with their questions that the agency's discovery of improbable dosing data in HRA's sNDA could point to broader discrepancies in its results.

"This finding of improbable dosing in this study is really quite extraordinary. This is not something we see in a typical actual use study," Teresa Michel, director of the Office of Nonprescription Drugs in the FDA's Center for Drug Evaluation and Review, told the committee members.

The over-reporting data FDA reviewers found was in large volume, but other data on additional over-reporting might be in lower volume, requiring additional analysis to find.

Adolescent Access Weighs Heavy In US FDA Decision On First OTC Daily Oral Contraceptive

By Malcolm Spicer

08 May 2023
FDA asks its Nonprescription Drug and Obstetrics, Reproductive and Urologic Drugs advisory committees during a joint meeting on 9-10 May to recommend whether to approve HRA Pharma's proposal for OTC switch of a daily oral contraceptive, its 0.075-mg norgestrel tablet branded Opill.

Read the full article here

"The results have to be incredibly extreme to show up in this kind of a study. Because we're really looking at a very blunt instrument for determining this finding. In order for us to pick up on the fact that consumers were reporting doses that they didn't take, they had to way over-report to the point where they were reporting dosing beyond the number of tablets that they received," Michel said.

Over-reporting was found by 30% of the participants.

"Almost a third of the subjects in the trial, you really have to wonder about what happened with the other two-thirds? If they also over reported, but just not to the extent where we could pick up

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on it? So that's the question that we're asking the advisory committee to ask themselves," Michel said.

If approved, Opill would be the first daily oral contraceptive available OTC in the US. (Also see "*US FDA Has 10 Months To Provide Answer On Perrigo/HRA OTC Oral Contraceptive Application*" - HBW Insight, 11 Jul, 2022.)

Dublin-based Perrigo acquired HRA in a cash deal announced in 2021 for €1.8bn ($2.1bn). That same year, Paris-based HRA received approval in the UK to reclassify 75-mcg desogestrel, a progestogen-only contraceptive branded Hana, from prescription-only to pharmacy status; British firm Maxwellia Ltd. at the same time received UK approval for pharmacy sales of its namesake brand desogestrel. (Also see "*Perrigo Continues Overhaul Adding HRA Pharma, Boosts Chances For OTC Oral Contraceptive In US*" - HBW Insight, 8 Sep, 2021.)

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