Guidance for Industry and FDA Reviewers/Staff

Guidance for Over-the-Counter (OTC) Human Chorionic Gonadotropin (hCG) 510(k)s

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U.S. Department Of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Clinical Chemistry and Clinical Toxicology Branch
Division of Clinical Laboratory Devices
Office of Device Evaluation

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Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to, Veronica Calvin, Division of Clinical Laboratory Devices, HFZ-440, 9200 Corporate Blvd, Rockville, MD 20850. Comments may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance contact Veronica Calvin at 301-594-1243, extension 151.

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Guidance[1] for Over-the-Counter (OTC) Human Chorionic Gonadotropin (hCG) 510(k)s

This document presents current approaches and concerns regarding over-the-counter hCG devices. It is based on: 1) current science; 2) clinical experience; 3) previous submissions by manufacturers to the Food and Drug Administration (FDA); 4) the FDA Modernization Act of 1997 (FDAMA); and 5) FDA regulations in the Code of Federal Regulations (CFR). As advances are made in science and technology, and as changes in implementation of legislation occur, these Review Criteria will be re-evaluated and revised as appropriate. So that the draft may be revised as necessary, please send comments as instructed in the Preface.

DEFINITION: This generic type device is intended for home use as an in vitro diagnostic (IVD) test for the qualitative measurement of hCG.

PRODUCT CODE: LCX

PANEL: 75 - Clinical Chemistry

REGULATION NUMBER: 21 CFR §862.1155

(a) Identification. An hCG test system is a device intended for the early detection of pregnancy. It is intended to measure hCG, a placental hormone, in serum, plasma or urine.

(b) Classification. Class II

REVIEW REQUIRED: 510(k)

Refer to 21 CFR §807.87 for information to be provided in a 510(k).

PURPOSE: The purpose of this document is to provide guidance on information to be submitted in 510(k) submissions. It is anticipated that this document will assist the Center for Devices and Radiological Health (CDRH) in rendering consistent decisions based on reliable, reproducible and standardized commercial tests.

[1]This document is intended to provide guidance. It represents the Agency's current thinking on the above. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

I. Background

Pregnancy tests are based on the detection of the hormone hCG primarily in urine or serum. HCG, which is thought to be produced by trophoblastic tissue, appears around the 8-9th day after ovulation where fertilization has occurred, or around the 4th day after conception. In a 28 day cycle with ovulation occurring at day 14, hCG can be detected in urine or serum in minute quantities around day 23, or 5 days before the expected menstruation. Its function includes facilitation of implantation as well as maintenance and development of the corpus luteum. HCG levels rise rapidly, doubling approximately every two days, and peak around 100,000-200,000 mIU/mL in the latter part of the first trimester of pregnancy. In normal subjects, hCG in urine provides an early indication of pregnancy. Since elevated hCG levels are also associated with trophoblastic disease and certain nontrophoblastic neoplasms, the possibility of having these diseases must be eliminated before a diagnosis of pregnancy can be made.(1)(2)

HCG is a glycoprotein composed of an alpha subunit and a beta subunit. HCG is closely related to two other gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), as well as thyroid stimulating hormone (TSH), all three of which are glycoprotein hormones. The alpha subunits of these various glycoprotein hormones are structurally very similar, but the beta subunits differ in amino acid sequences. These differences are responsible for their biological and immunological specificity.(3)

HCG circulates as the intact molecule in the serum of women who have an uncomplicated pregnancy. Subunits are cleaved rapidly and cleared promptly by the kidney. As a result, the urine contains intact hCG, and alpha and beta subunits; however, only intact hCG and beta subunits retain immunologic specificity in urine. The relative concentrations of intact and subunit hCG in serum and urine vary a great deal in patients with trophoblastic disease because of unbalanced synthesis of subunits.(4)

The International Reference Preparation for Chorionic Gonadotropin (1st IRP for CG), officially designated the 3rd International Standard (3rd IS), contains only pure intact hCG. The 2nd IS contains a mixture of intact hCG and its beta subunit. The 1st IRP is also available as pure beta subunit and pure alpha subunit. It is now possible for manufacturers to characterize and define the specificity of their assays for intact hCG and/or its subunits. It is not possible to obtain uniformity in the reporting of results solely through the use of a common standard, since hCG is a complex molecule. Different immunoassays may use different antibodies that recognize different components (epitopes) of the molecule.(5)

II. Historical Background and Description

Clinically useful bioassays were introduced by Ascheim (1927), Zondek (1931), the Friedman test (1931), and the Xenopus laevis test (Shapiro, 1934). The first tests could confirm pregnancy approximately two months after a missed period.(6) In addition to the fact that they were not very sensitive, bioassays had other problems limiting their usefulness as routine pregnancy tests. Because of this, they were replaced by immunoassays with the first being reported in 1960. Sensitive radioimmunoassay (RIA), immunoradiometric (IRMA), and enzyme immunoassay (EIA) techniques now available allow an accurate and precise quantitation of hCG through the use of highly specific antibodies.

Presently, all of the home pregnancy tests available use monoclonal or polyclonal antibodies in an enzyme-linked immunoassay format. Monoclonal antibodies are highly sensitive to one specific site along the hCG molecule. If hCG is present in urine, it will be trapped by the anti-hCG antibody that is bound to a solid surface. A second antibody is utilized in the device; it is linked to an enzyme that reacts with the anti-hCG complex to cause a color change, producing a positive result. These tests can detect pregnancy by the first day of the missed menstrual period. The development of monoclonal antibodies to hCG provides a supply of homogeneous antibodies and improves the specificity of the assay. (7)(8) Consequently, commercially available pregnancy tests are much less susceptible to interference from other substances than were the earlier immunoassays.

III. Performance Characteristics/Laboratory Evaluation

A. Comparison Study/OTC Study

1. Study Design

FDA recommends that at least 100 fresh, human urine specimens be used. Each specimen should be split between the subject and the professional, who should perform testing on the predicate device (for professional use or OTC use) and the new device. In addition to comparing the new device to a predicate device, the new device can also be used to compare the subject's results to the professional user's results.

The portion of the comparison study performed by the subject should mimic actual use. FDA recommends that the subject collect the sample and perform the test without assistance. We recommend using freshly voided first-morning urine specimens because the hCG concentration is highest at this time. If specimens cannot be tested immediately, they should be stored at 2-8°C for up to 48 hours.(9) If claims are being made to "use any time of day", then samples collected any time of day should be used in the study.

Alternatively, the home users may be provided with coded positive and negative specimens. For spiked (urines with hCG added) specimens, FDA recommends including specimens around (e.g., 10-20% above and below) the sensitivity level. Also, the FDA requests that the concentrations of spiked specimens be provided in the 510(k) submission.

For devices utilizing more than one testing procedure, e.g., urine stream and dip procedure, we strongly recommend that data be provided to validate the equivalency of both procedures. Fifty or more OTC users (subjects) should perform the urine stream method.

OTC users (subjects) can be selected on a random basis as they present themselves at clinics and/or physicians' offices or via advertisements. They should represent diversity of age, background, and education. When the testing is complete, users should complete a questionnaire. The questionnaire is to generate information such as, feedback on the test and ease of use, and clarity and readability of the package insert. FDA requests that a summary of the responses to the questions be provided in the 510(k) submission.

Include a summary of the OTC study protocol in the 510(k) submission.

2. Data Analysis

FDA recommends expressing the data in terms of percent accuracy, which should never exceed >99%. Accuracy, per the NCCLS labeling guideline, is based on test efficiency, i.e., true positive plus true negative results divided by the total number of samples tested.

This performance can be described in text or tabular form. In addition, misleading statements such as, virtually 100% accurate, nearly 100% accurate, 100% accurate, etc., should be avoided.

B. Specificity

Specificity studies should be performed on specimens with high physiological concentrations of luteinizing hormone (LH), follicle stimulating hormone (FSH), and thyroid stimulating hormone (TSH). Ideally, high levels of LH will not significantly cross-react with the hCG antibody used. Spiking samples with LH, FSH or TSH is useful in demonstrating the absence of cross-reactivity at high LH, FSH or TSH levels.

C. Interfering Substances

Interference studies should be performed on urine containing prescription/OTC drugs, elevated levels of chemical analytes (e.g., caffeine, ascorbic acid), and elevated levels of

biological analytes (e.g., glucose, protein, albumin, bilirubin, hemoglobin). It is also useful to evaluate the effects pH may have on the results.

D. Sensitivity/Detection Limit

For qualitative assays, the sensitivity/detection limit is the analyte concentration at which 95% of the test results are positive. Assay sensitivity should be such that small quantities of hCG will be detected while false-positive results due to the presence of LH will be minimized.(2) Additionally, it is expected that all positive results will have reacted within the specified time frame.

Sensitivity can be evaluated by spiking at least 30 clinical samples from normal, nonpregnant females or males with six different concentrations of hCG below (including one at –50% of the sensitivity and one at –25% of the sensitivity), at and above the stated sensitivity. For example, for a test with a detection limit of 25 mIU/mL, concentrations of approximately 0, 12.5, 18.75, 25, 50, and 100 mIU/mL may be used. FDA requests that the concentrations tested be provided in the 510(k) submission.

E. Imprecision or Reproducibility Studies

These studies may be performed if desired. FDA recommends following a scientifically valid protocol when evaluating imprecision.

F. Expected Values

A section entitled as such need not appear in an OTC insert. However, within the text the manufacturer may state that the test is capable of detecting pregnancy by the first day of the missed period and no sooner, unless validated by clinical data. (Note: We recommend discussing clinical study proposals with Division representatives before performing studies.)

G. Calibration

The source of reference material that the standards or test are calibrated against (1st IRP, 2nd IS, or 3rd IS) for hCG should be stated in the submission only.

H. Quality Control

If a device contains a procedural or design control, the function of the control should be described in detail. Examples of descriptions are listed below.

- The control determines if chemicals are working properly.
- The control determines if an adequate amount of sample was added.
- The control determines if the proper procedure was followed.

FDA also requests that you identify the components of the internal control and state where applicable, the sensitivity (detection limit) of the reference line.

I. Stability Data

The data showing stability of the reagents need not be submitted to the FDA, but may be kept on file by the manufacturer in accordance with Good Manufacturing Practices (GMP).

A summary of data to support the stability of the results (i.e., maximum time for interpreting result after it first appears) should be provided in the 510(k) submission.

J. Antibody Information

Information on characterization and purification of the monoclonal antibody(ies) in the device is usually provided in the 510(k) submission. If these procedures are performed by another manufacturer, a copy of the Certificate of Analysis from that manufacturer may be included in the 510(k) file.

K. Limitations

The list presented here is not all-inclusive. Include limitations in the labeling (i.e., package insert) as needed.

1. The test cannot be reused.
2. Do not use this test past the expiration date.
3. Pain relievers, oral contraceptives, antibiotics, and other commonly used medications (for example) should not interfere with the test. (Studies should be performed to validate this claim.)
4. Certain health conditions, such as an ovarian cyst or ectopic pregnancy (pregnancy outside the uterus), can cause a false or irregular result.
5. The procedures should be followed precisely for accurate results.
6. A false negative result (negative when pregnancy exists) may occur if the urine is too dilute or with a very early stage pregnancy. If pregnancy is still suspected, retest using a first-morning urine.
7. For in vitro diagnostic use (not for internal use).

IV. Labeling

The package insert should be concise, easy to understand, and contain clear illustrations and drawings. The labeling format should conform to the 21 CFR 809.10 labeling regulations. However, for OTC products, sections such as,

- Intended Use
- Summary and Explanation of the test

- Principle of the Procedure
- Reagents
- Quality Control
- Expected Values
- Performance Characteristics

need not be presented with the formality of professional use labeling. Information relative to these sections can be simplified and contained within the text without such subheadings. This is to eliminate "technical" or incomprehensible language.

For example, include in the beginning of the package insert:
- the analyte being measured
- type of specimen used
- a description of how the test works

When listing materials provided, the test device could be described as a test strip containing chemicals, a test strip containing antibodies, etc, and not identify the specific biological and chemical components.

As a part of quality control, describe in detail the function of the internal control. This is often included under Interpretation of the Results or in the Question and Answer section.

We also recommend that a maximum time for interpreting results or how long the results are stable be included in the insert, particularly for negative results, which may become positive over time. A sentence relative to the sensitivity of the test, i.e., how early pregnancy can be detected, should be included as well as the accuracy of the device determined by laboratory studies and in the hands of OTC users. For additional guidance, refer to the NCCLS labeling guideline GP14-P (10), DCLD's Points to Consider for Home Use IVDs (11), and CDRH's Write It Right guidance (12).

V. Bibliography

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3. Ross GT. Clinical relevance of research on the structure of human chorionic gonadotropin. American Journal of Obstetrics and Gynecology 1977; 129:795.

4. Lab Report for Physicians. Standardization of human chorionic gonadotropin. December 1985; 7:12.

5. Jeffcoat, SL. Standardisation of hCG immunoassays and pregnancy kits. Lancet 1982; 1:803.

6. Chayen J, Daly JR, Loveridge N. The cytochemical bioassay of hormones. Recent Prog. Horm. Res. 1976; 32:33-72.

7. Henry JB. Clinical Diagnosis and Management by Laboratory Methods, 18th edition, 1991, WB Saunders and Co.

8. Wide L, Gemzell CA. An immunological pregnancy test. Acta Endocrinology 1960; 35:261.

9. Krieg AF. Pregnancy tests and evaluation of placental function. Clinical Diagnosis and Management by Laboratory Methods, 18th edition, Henry JB, editor, 1979; 680.

10. National Committee for Clinical Laboratory Standards. Labeling of Home-Use In Vitro Testing Products. NCCLS Document GP14-P, Vol. 9, No. 8, 1989.

11. Report of the CDRH Home-Use IVD Working Group Assessing the Safety and Effectiveness of Home-Use IVDs: Guidance Regarding Premarket Submissions.

12. Write It Right. Recommendations for Developing User Instruction Manuals for Medical Devices Used in Home Health Care.

ABBREVIATIONS

CDRH	Center for Devices and Radiological Health
DCLD	Division of Clinical Laboratory Devices
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
HCG	Human Chorionic Gonadotropin
IRP	International Reference Preparation
IS	International Standard
IVD	In Vitro Diagnostic
LH	Luteinizing Hormone
NCCLS	National Committee for Clinical Laboratory Standards
OTC	Over-the-Counter
QC	Quality Control
TSH	Thyroid Stimulating Hormone

CHECKLIST

Instructions: Use this checklist for premarket submissions for human chorionic gonadotropin (hCG)/pregnancy tests intended for over-the-counter use. Please check the box next to the items below that you have included in the premarket notification.

☐ CDRH Premarket Submission Cover Sheet

☐ Truthful and Accurate Statement verbatim as required by 21 CFR 807.87(j). Additions and deletions are not permitted.

☐ 510(k) Summary **or** Statement as required by 21 CFR 807.92 or 21 CFR 807.93 respectively.

☐ Indications for Use Form

☐ Sensitivity/Detection Limit Data

☐ Specificity Data including LH, FSH, and TSH

☐ Interfering Substances Data

☐ Comparative Study Data including the following: summary of study protocol, concentrations of spiked specimens used, data to validate all testing procedures (e.g., urine stream and cup method), summary of responses to OTC study questionnaire.

☐ Antibody Characterization/Purification Information

☐ Components and Function of Internal Control

☐ Predicate Device Labeling