What Does Having a FDA Cleared Pregnancy Test Mean?

Clinical Trials Transformation Initiative (CTTI)

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Presentation Outline

- Overview of FDA Device Regulation
- Overview of Pregnancy Device Regulation
- Types of Pregnancy Devices
- Evaluation of Pregnancy Devices for Regulatory Clearance
- Post-market evaluation of Pregnancy Devices
- Summary

FDA Regulation of Medical Devices

- Federal Food, Drug, and Cosmetic Act (The Act)
- Medical Device Amendments of May 28, 1976
  - Risk based regulation by intended use
    - Class I - low risk, usually exempt from Premarket review
    - Class II - moderate risk, requires "substantial equivalence" to predicate device (510(k) clearance)
    - Class III – high risk and novel intended uses, require premarket approval (PMA)

FDA Regulation of Pregnancy Devices

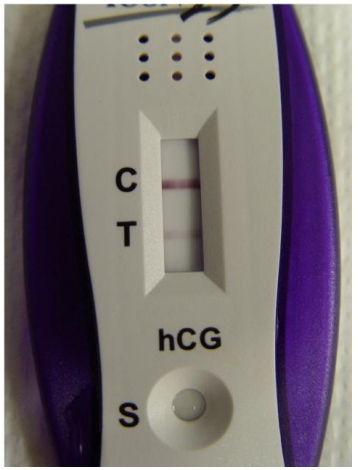
- Classified as a human chorionic gonadotropin (hCG) test system under 21 CFR 862.1155(a).
- (1) *Identification:* A human chorionic gonadotropin (hCG) test system is a device intended for the early detection of pregnancy [and] is intended to measure hCG, a placental hormone in plasma or urine.
- (2) *Classification:* Class II
- An intended use other than early detection of pregnancy is classified under 21 CFR 862.1155(b), as Class III and would need regulatory approval prior to marketing.

FDA Regulation of Pregnancy Devices

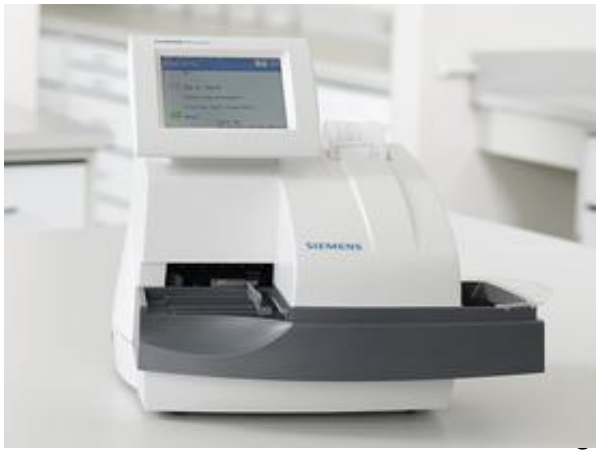
- Class II device (moderate risk)
- Requires 510(k) (regulatory clearance)
- Substantial equivalence to predicate device
- FDA (CDRH) evaluates intended use, performance, and labeling for clearance determinations

Types of Pregnancy Devices

- **Qualitative**
  - Urine (home or point-of-care)
  - Serum (central lab or point-of-care)



- **Quantitative**
  - Serum (central lab or point-of-care)



- **Application and Test Methods**
  - Midstream
  - Dip
  - Droplet (Cassette)
  - Urine/Serum Analyzer

Evaluation of Pregnancy Devices for Regulatory Clearance

- Performance near Assay Cutoff or Lower Limits of Assay
- Precision
- Recovery and Linearity for Quantitative Tests
- Stability
- Interference and Specificity
- Accuracy (Method Comparison and User-Accuracy)
- Labeling

Assay Cutoff or Lower Limit of Assay

Cutoff = concentration that yields a positive result 50% of the time and a negative result 50% of the time

- Spiked test samples or pools in the intended use matrix (serum, urine)
- Purified intact hCG traceable to a recognized standard
- Small increases and decreases in hCG concentration relative to cut-off (e.g., 20-25% increments)
- For quantitative, determine precision and bias relative to a reference material at the Limit of Quantitation (LoQ)

Precision

- Can be combined with assay-cutoff studies
- Test samples should contain hCG concentrations that span assay range and include decision levels
- Challenge the assay:
  - Multiple lots
  - Multiple operators
  - Multiple sites (POC)
  - Multiple days
  - Multiple instruments

Recovery and Linearity

- Quantitative tests
- Spiked samples with hCG concentrations that span entire claimed measuring range
- Multiple replicates
- Line of regression and regression statistics
- For recovery, determine expected versus observed concentrations

Stability

- Shelf-life and open-vial stability of calibrator and control materials intended to be used as part of pregnancy test system
- Also review stability of unitized pregnancy test devices that do not need calibration by the end-user
- Review protocols, acceptance criteria, and summary of results
- Stability information should support all expiration date claims

Interference and Specificity Testing

- Common prescription and over-the-counter drugs,
- Endogenous compounds
- For urine assays - pH and specific gravity.
- Luteinizing hormone (LH), follicle stimulating hormone (FSH), and thyroid stimulating hormone (TSH)
- Determine whether extremely high concentrations of hCG may cause a falsely low result with the device, i.e., “hook” effect.
- ß-core fragment hCG (hCGßcf), which may be present at high concentrations in urine after the first several weeks of pregnancy.

Accuracy – Method Comparison

- Compare results obtained with new device to those obtained with a previously cleared pregnancy test device (predicate) that uses the same sample matrix and assay range or cut-off.

- Use natural, unaltered (i.e., not diluted or spiked) patient samples that cover the intended use population: *women who suspect they may be pregnant and those who are very early in pregnancy*

- Each sample matrix type and application method (e.g. dropper, dip) are tested

Accuracy – User Studies

- For prescription tests, method comparison accuracy studies are performed at intended use sites with the intended use operators (e.g., nurses, physicians, etc.)
- For home use tests, method comparison studies are performed by laboratory technicians and a separate lay-user accuracy study is also performed
- Lay-user accuracy studies compare results obtained from lay-users versus laboratory technicians using the new device; spiked samples may be used
- Testing performed using only English language labeling with no coaching or training
- A survey/questionnaire is completed by lay-users immediately after testing to assess readability of package insert.

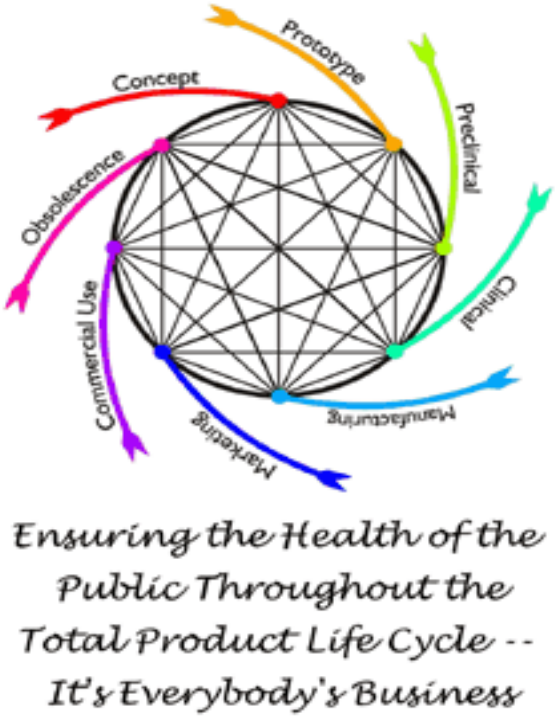
Labeling

- 21 CFR 809.10
- User manual or package insert instructions
  - Test instructions easy to understand?
  - Are pictures or diagrams included to aid end-users?
  - Calibration/quality control instructions
- Box and container labels
- OTC labeling at 8th grade reading level

Post-market Signals and Adverse Reports

FDA monitors signals for reports on false positive results, false negative results, and other adverse device reports

- FDA MedWatch Program
- MedSun Program
- Medical Device Reports
- Other signals



Total Product Life Cycle

Summary

- Devices intended for the early detection of pregnancy are FDA regulated as Class II devices (moderate risk) and require 510(k) clearance prior to marketing.
- Adequate performance and substantial equivalence to predicate devices must be demonstrated to support clearance.
- FDA reviews a number of performance factors during 510(k) review – including precision, cut-off performance, linearity, interference, accuracy, and stability.

Summary – cont'd

❖ FDA also evaluates device labeling – including manuals, inserts, and box labeling during 510(k) review.

❖ FDA monitors post-market adverse event signals after clearance. Pre-market and post-market review of devices is part of the CDRH Total Product Life Cycle approach to medical device review.

❖ Monitoring to date indicates pregnancy test devices are accurate, with few false positive and/or false negative results generally reported.

Thank you!

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