CLIA Waiver
Processes and Submissions Update

FDA-Industry IVD Roundtable Meeting
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Outline:

- Overview of Current CLIA Processes for
  - Waivers by Application
  - Dual 510(k) and CLIA Waiver by Application
- MDUFA Performance
- Recent CW Approvals
- Questions

The Clinical Laboratory Improvement Amendments of 1988 (CLIA)

- CLIA requires that clinical laboratories obtain a certificate before accepting materials derived from the human body for laboratory tests. 42 U.S.C. § 263a(b).
  - CLIA Certificates are graded in 3 levels according to the complexity of the tests performed by the laboratory:

    Waived, Moderate or High

- The Centers for Medicare & and Medicaid Services (CMS) is responsible for oversight of clinical laboratories
- FDA CLIA categorizes In Vitro Diagnostic tests

Traditional Pathways to a CLIA Waived Test System

- Manufacturer submits a marketing notification/application (510(k), PMA) for a POC test system
- If cleared/approved, the test system is automatically CLIA Categorized by FDA with 10 days
- If the test system falls into the 9 generic test types waived by regulation or is cleared/approved for home/OTC use
    - Categorized as Waived
- Otherwise categorized as Moderate or High
- If categorized as Moderate, Manufacturer may apply for CLIA Waiver

CLIA Categorization Criteria for moderate or high complexity

- IVDs evaluated against 7 criteria using a 3-point scoring system for each criterion (42 CFR 493.17)
- Total score ≤ 12: moderate complexity
- Total score ≥ 13: high complexity

1. **Knowledge**
2. **Training and experience**
3. **Reagents and materials preparation**
4. **Characteristics of operational steps**
5. **Calibration, QC, PT materials**
6. **Troubleshooting and maintenance**
7. **Interpretation and judgment**

Changes to Administrative Tracking Mechanisms

Type of CLIA Categorization	Previously CLIA Categorizations tracked under:	Today CLIA Categorizations filed as:	Parent Document
Devices Approved / Cleared by CDRH/OIR	510(k), PMA, HDE, De Novo	CRxxxxxx	Kxxxxxx, Pxxxxxx, Hxxxxxx
Devices Approved / Cleared / Licensed by CBER	BP, BL, BK	CRxxxxxx	BPxxxxxx, BLxxxxxx, BKxxxxxx
Pre-Market Review Exempt Devices	X-file (Xxxxxxx)	CRxxxxxx	CRxxxxxx
Name Changes (e.g., name, distributor)	510(k) Add-to-File or PMA supplement	CRxxxxxx	Kxxxxxx, Pxxxxxx, Hxxxxxx,

Changes to Administrative Tracking Mechanisms

Type of CLIA Waiver by Application	Previously CLIA Waiver by Application tracked under:	Today CLIA Waiver by Application filed as:	Parent Document
Devices Approved / Cleared by CDRH/OIR	510(k), PMA, HDE, De Novo	CWxxxxxx	Kxxxxxx, Pxxxxxx, Hxxxxxx
Devices Approved / Cleared / Licensed by CBER	BP, BL, BK	CWxxxxxx	BPxxxxxx, BLxxxxxx, BKxxxxxx
Pre-Market Review Exempt Devices	X-file (Xxxxxxx)	CWxxxxxx	CWxxxxxx
Dual 510(k) and CLIA Waiver by Application	Manually	CWxxxxxx	Kxxxxxx

2014 CLIA Administrative Procedures Guidance

- Categorizations
  - Explains when a “CR” number will be assigned
  - Includes target categorization timeframes
  - Includes instructions for submitting requests for multiple categorizations due to name/distributor changes across multiple IVDs in spreadsheet format

2014 CLIA Administrative Procedures Guidance

- Waivers by Application
  - Explains when a “CW” number will be assigned
  - Includes review and management expectations throughout the entire submission process
  - References 2008 CLIA Waiver Guidance for details regarding data to submit for a waiver application
  - Briefly describes the Dual 510(k) and CLIA Waiver by Application Pathway

Categorization Process
for IVD marketing submissions sent to CDRH

- Sponsors will receive a pre-market tracking number (e.g., K150055, P150003) AND a CLIA categorization record tracking number (e.g., CR150032)
  - Sponsors will receive acknowledgement letters for each
- If categorization not needed (i.e., for calibrators and controls or NSE), sponsors will receive an email closing out the CR file without a categorization
- If categorization is needed, sponsors will receive a categorization letter via e-mail attachment within 10 days of marketing decision
- Categorization will appear in public database with a CR "Document" Number and a K/P/H or CR "Parent" Number

Statutory Criteria for a Waived Test

"laboratory examinations and procedures that have been approved by the FDA for home use or that…are simple laboratory examinations and procedures that have an insignificant risk of an erroneous result, including those that —

(A) employ methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible, or

(B) …pose no unreasonable risk of harm to the patient if performed incorrectly"

42 U.S.C. Section 263a(d)(3)

2008 CLIA Waiver Guidance

- describes recommendations for device manufacturers seeking to submit information through a CLIA waiver application to FDA to support a determination whether the device meets CLIA statutory criteria for waiver.

How does a test system meet the 2008 CLIA Waiver Guidance criteria?

- **Is the test system simple?**
  - Simple test characteristics
  - Labeling at 7th grade level
- **Does the test system have an insignificant risk of erroneous result?**
  - Risk Analysis and Flex Studies
  - Validated Fail-Safe and Failure Alert Mechanisms
  - Accuracy Studies

CLIA Waiver by Application Process

- Sponsors encouraged to submit Pre-Submissions to request feedback on planned protocols or study designs to support CLIA waiver
- After submission, sponsors receive acknowledgement letter with CW #
- If additional information is needed, sponsors will receive an email by day 90 which puts the file on hold pending submission of additional information
  - Sponsors should submit additional information to DCC as a supplement to the CW number
- Within 180* total FDA days, sponsors will receive either an waiver granted or denial letter via e-mail attachment

**330 if advisory panel review is required*

- If waiver granted, categorization will appear in public database with a CW “Document” Number and a marketing application “Parent” Number

The Dual Pathway (510(k) and CLIA Waiver by Application)

- The Dual pathway, established as part of MDUFA III, offers the opportunity for a simultaneous approval of a CLIA Waiver along with a 510(k) clearance, with potentially **significant time and cost savings due to combined study designs**
- A Pre-submission during which agreement was reached on a Dual strategy is required
- Interest in Duals is increasing…

	# of Pre-Submissions where Dual discussed	# Submitted	# Approved	# Under Review
FY13	8	0	0	0
FY14	7	1	1	0
FY15	19	3	0	3

Dual Submission Study Basic Idea

510(k) – POC, non-waived Candidate in hands of POC operators	CLIA waiver clinical study Candidate in hands of CLIA waived operators
Analytical studies as analytical sensitivity, analytical specificity, linearity, reagent stability, sample stability, and so on	Simple, Flex studies
Precision (POC sites)	
Comparison (POC sites) Candidate vs Predicate	Comparison (CLIA waived sites) Candidate vs CM

Combined for Dual:

A) 3 CLIA waived sites, 9 CLIA waived operators
Comparison of Candidate vs CM

B) Precision (CLIA waived sites)

Dual 510(k) & CLIA Waiver by Application Process

- Sponsor should ensure the following criteria are met:
  - Must be preceded by a Pre-Submission during which the dual pathway was discussed
  - Must be a single submission containing all 510(k) and Waiver by Application required elements
    - may not be staged or modular
    - 510(k) user fee applies
    - Mandatory eCopy per 510(k) requirements

- If the above criteria are met, sponsors will receive two acknowledgement letters (CW and K)
- FDA will proceed with *one review* under *one review clock*

Dual 510(k) & CLIA Waiver by Application Process

- Sponsors will receive either an acceptance or rejection notification via e-mail by day 15 (per 510(k) RTA criteria)
  - If rejected, sponsor must submit additional information to DCC as a supplement referencing both CW and K numbers
  - Single review clock resets to day 0 when a supplement that is ultimately accepted is received by DCC
- If after substantive review of the entire submission FDA determines additional information is needed, sponsors will receive an email by day 90 which puts the CW and K on hold pending submission of additional information
  - Sponsors should submit additional information to DCC as a supplement referencing both the CW and K numbers

Dual 510(k) & CLIA Waiver by Application Process

- Within 210 total FDA days, sponsors will receive one of the following results:
  - 510(k) SE and CLIA Waiver Approval letters via e-mail attachment
  - 510(k) SE and CLIA Waiver Denial letters via e-mail attachment
  - 510(k) NSE and CLIA Waiver Denial letters via e-mail attachment

- If SE/Approved, categorization will appear in public database with a CW “Document” Number and a K “Parent” Number

MDUFA III Commitments

- Performance goals for CLIA Waivers by Application:
  - FDA will engage in a substantive interaction within 90 days
  - FDA will issue a decision for 95% within 180* FDA days

**330 if advisory panel review is required*

- Performance goals for Duals:
  - FDA will engage in a substantive interaction within 90 days
  - FDA will issue a decision for 90% within 210 FDA days

MDUFA III Performance Update

- All CLIA Waiver and Dual MDUFA Performance Goals met for FY14
  - 100% SI within 90 days
  - 100% MDUFA Decision within 180 days for CWs, within 201 days for Duals
- On target to meet all goals for FY15

CLIA Waiver (without Panel Review) MDUFA Decision Performance Goals

Performance Metric	FY 2013	FY 2014	FY 2015
CLIA Waiver Applications accepted	3	14	11
MDUFA III Decisions within 180 FDA Days	3	14	5
CLIA Waiver Applications pending MDUFA III Decision	0	0	6
Current Performance Percent within 180 FDA Days	100%	100%	100%

MDUFA III Performance Update: Duals

DUAL (501(k) and CLIA Waiver) (without Panel Review) MDUFA Decision Performance Goals

Performance Metric	FY 2013	FY 2014	FY 2015
CLIA Waiver Applications accepted	0	1	3
MDUFA III Decisions within 210 FDA Days	0	1	0
CLIA Waiver Applications pending MDUFA III Decision	0	0	3
Current Performance Percent within 210 FDA Days	N/A	100%	100%

- First Dual Approved in December 2014
  - Quidel Sofia Strep A+ FIA (from throat swab only)

Recent CLIA Waiver Approvals

Test System / Manufacturer	Analyte	Effective Date
• Roche Molecular cobas Liat System {cobas Liat Influenza A/B Assay}	Influenza A/B	9/18/2015
• Alere i Instrument	Streptococcus group A	7/15/2015
• Theranos anti-HSV-1 IgG Assay (Fingerstick Whole Blood Only)	Herpes simplex I and/or II antibodies	7/15/2015
• Roche Molecular cobas Liat System	Streptococcus group A	5/15/2015
• Alere i Influenza A & B Test (Direct Nasal swab only)	Influenza A/B	1/5/2015

Thank you!

Questions?

- For CLIA related questions please email:

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References

- CLIA Administrative Procedures Guidance

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070762.htm

- CLIA Waiver by Application Guidance

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079632.htm

- CLIA Public Database

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/search.cfm