“Workload Issues for Computer-Aided Cytology Devices”

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Background

- Joint project between CMS and FDA
- Role of Pap Smears in CLIA ‘88
- Two issues:
  - Counting slides-how do you weight?
  - Setting workload limits
- Previous versions of package inserts were not clear
- Package inserts revised to align with lab safety tip
Slide Counting:

• The product labeling regarding workload counting was difficult to interpret: variability and lack of standardization.
• Challenged with developing a counting approach that reflects clinical study performance **AND** is easy to use in real-life laboratory settings.
Maximum workload limits

• Upper limit is **NOT** for everyday productivity or a performance target

• CLIA ’88 requires *individual* maximum workload limits to be established by the technical supervisor
As a result the FDA.....

• Required manufacturers to revise their product labeling and send customer bulletins

• Published laboratorian safety tip

• [http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/TipsandArticlesonDeviceSafety/ucm220292.htm](http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/TipsandArticlesonDeviceSafety/ucm220292.htm)
Computer-aided Semi-Automated Gynecologic Cytology Screening Devices presently on the market (FDA Approved)

- Hologic ThinPrep® Imaging System (TIS)
- BD FocalPoint™ GS (Guided Screening) Imaging System
Hologic ThinPrep® Imaging System

- Imaging technology identifies microscopic fields for cytotechnologist review
- Automated stage
- 22 Fields of View (FOV)
- If no abnormalities, FOV review only
- If abnormal, Full Manual Review performed (FMR)
- Former 200 slide upper limit
BD FocalPoint™ GS Imaging System

- Imaging technology identifies and ranks microscopic fields for cytotechnologist review
- Designates slides for QC
- 10 FOV
- If no abnormalities, FOV review only
- If abnormal, Full Manual Review performed (FMR)
- Former 170 slide upper limit
Pivotal Clinical Studies

• Basis for FDA Approval
• 2 Purposes
  – Safety and Effectiveness
  – Workload Study
Basic Clinical Study Design

• Four cytology laboratories in US
• Accuracy of manual screening was compared to accuracy of screening with computer aided device
• Because an increase in productivity was anticipated, the accuracy objective was equivalence (not superiority)
• Establish an upper limit for workload
Manual screening arm
- 100% manual screening ("Manual")
- At least 10% QC rescreening

Computer-aided review arm
- Review of FOVs ("FOV only")
- If FOVs have abnormal findings, manual review of full slide ("Manual with FOV")
- At least 10% QC rescreening
In the Clinical Studies.....

• CT reviews only FOV (**NOT** allowed to do even a quick check outside of FOVs);
• If FOV does not have abnormal findings, CT is **NOT** allowed to do a manual review.

• **OTHERWISE** estimation of computer-aided device accuracy will be **BIASED** (overestimated) – it will be easy to demonstrate an equivalence of computer-aided device and manual screening.
Workload Study Design

• Each day number of slides and number of hours were recorded
• Data for days with number of hours <4 were deleted from calculations
• If CT showed a decrease in accuracy the data was deleted from the calculation of the workload data
Workload Study con’t

Using the adjusted data:

- Average rate per hour was calculated (among all days)
- Low rate per hour; high rate per hour
- 85-90% percentile was taken
- These rates were multiplied by 8 hours to obtain “extrapolated” rate per day (theoretical rate per day, breaks during the day were not considered)
Workload Study con’t

- “Extrapolation” (8 hours) is OK for the determination of upper limit of workload
- **NOT** for determination of everyday productivity
For TIS, the computer-aided review arm had **22%** of slides in average reviewed manually after FOV review

**By gold standard:**

- Prevalence of ASC-US+ = 7.3%
- Prevalence of LSIL+ = 2.4%
- Prevalence of HSIL+ = 1.5%
For BD FocalPoint GS, the computer-aided review arm had 31% of slides in average reviewed manually after FOV review*

By gold standard:
• Prevalence of ASC-US+ =14.8%

* Study included seeded samples
Workload Limit per 8 hours

- An upper limit; **NOT** a productivity level
- Breaks were not considered
- 200 slides for TIS and 170 slides for BD FocalPoint GS
- *Is an upper limit dependent on the number slides that were manually reviewed in the clinical study*
- In each laboratory, the number of slides manually reviewed varies and therefore, the workload limit could vary
Why the Product Inserts were not clear

• Count any slide screened on imager \textit{once}; whether FOV review only or screened manually after FOV review

• This method is correct \textbf{ONLY} if the percent of manual review slides with FOV is less than the rate seen in the clinical studies
Example

Suppose the percent of manual review among all slides is 50% (100/200).

X=100 slides (manual review with FOV)
Y=100 slides (FOV review only)

Since you can only screen 100 manual slides per CLIA ’88 you will exceed your maximum if you screen 100 additional FOVs
We know….

• The upper limit for 8 hours according to CLIA ’88 is 100 slides, therefore…..

• It takes approximately 4.8 minutes to manually screen one slide

Using the 200 slide limit determined in the TIS study and 22% manual review rate, we can calculate that screening:

- FOV takes ~ 1.35 minutes
- FOV + manual review takes ~ 6.15 minutes
In the TIS Clinical Study…

If we let $X$ be a number of slides with manual review with FOV and $Y$ be a number of slides with FOV review only, then for 8 hours:

$$6.15X + 1.35Y = 480 \text{ minutes}$$

Or

$$1.28X + 0.28Y = 100 \text{ slides}$$

Upper limit for the total number of slides is $X+Y$
Example:

X=60 (42.3%) number of slides with manual review with FOV;

\[1.28 \times 60 + 0.28 \times Y = 100 \text{ slides}\]

- Then using the formula, \(Y=82 - \text{number of slides with FOV review only.}\)
- Total number of slides 142 (60+82)
- **Upper limit of the total number of slides** = 142 (not 200)
Relationship of the **total number of slides** \((X+Y)\) vs number of slides with manual review with FOV \((X)\) for 8 hours (480 minutes)
Same Calculations for BD-FPGS:

170 upper workload limit with slides with full manual review = 31%

- Same formula $6.15 \times X + 1.35 \times Y = 480$ for two independent clinical studies (TIS and BD)!

- Provides some additional validity for these calculations
Challenge

• These weights are not easy to use in real-life laboratory settings
• Formula for calculating upper limit from clinical study is ~ $1.3X + 0.3Y = 100$ slides
• Prevalence varies lab to lab
• How can we develop a counting method that reflects the clinical study performance AND is realistic for use?
Simpler and Safer Approach

1.5*X + 0.5*Y = 100 slides
Relationships of the total number of slides vs percent of slides with manual review with FOV for 8 hours
Laboratory Safety Tip

- FMR = 1 slide
- FOV = 0.5 slide
- FMR + FOV = 1.5 slides
- Upper Limit = 100 slides
Thank you!

MDR:

http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/FormsandInstructions/default.htm