"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

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

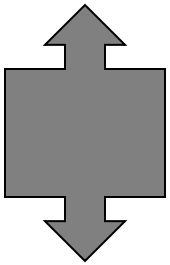
- Basis for FDA Approval
- 2 Purposes
  - Safety and Effectiveness
  - Workload Study

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 **once**; whether FOV review only or screened manually after FOV review

- This method is correct **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:

6.15*X + 1.35*Y = 480 minutes

Or

1.28*X + 0.28*Y = 100 slides

Upper limit for the total number of slides is **X+Y**

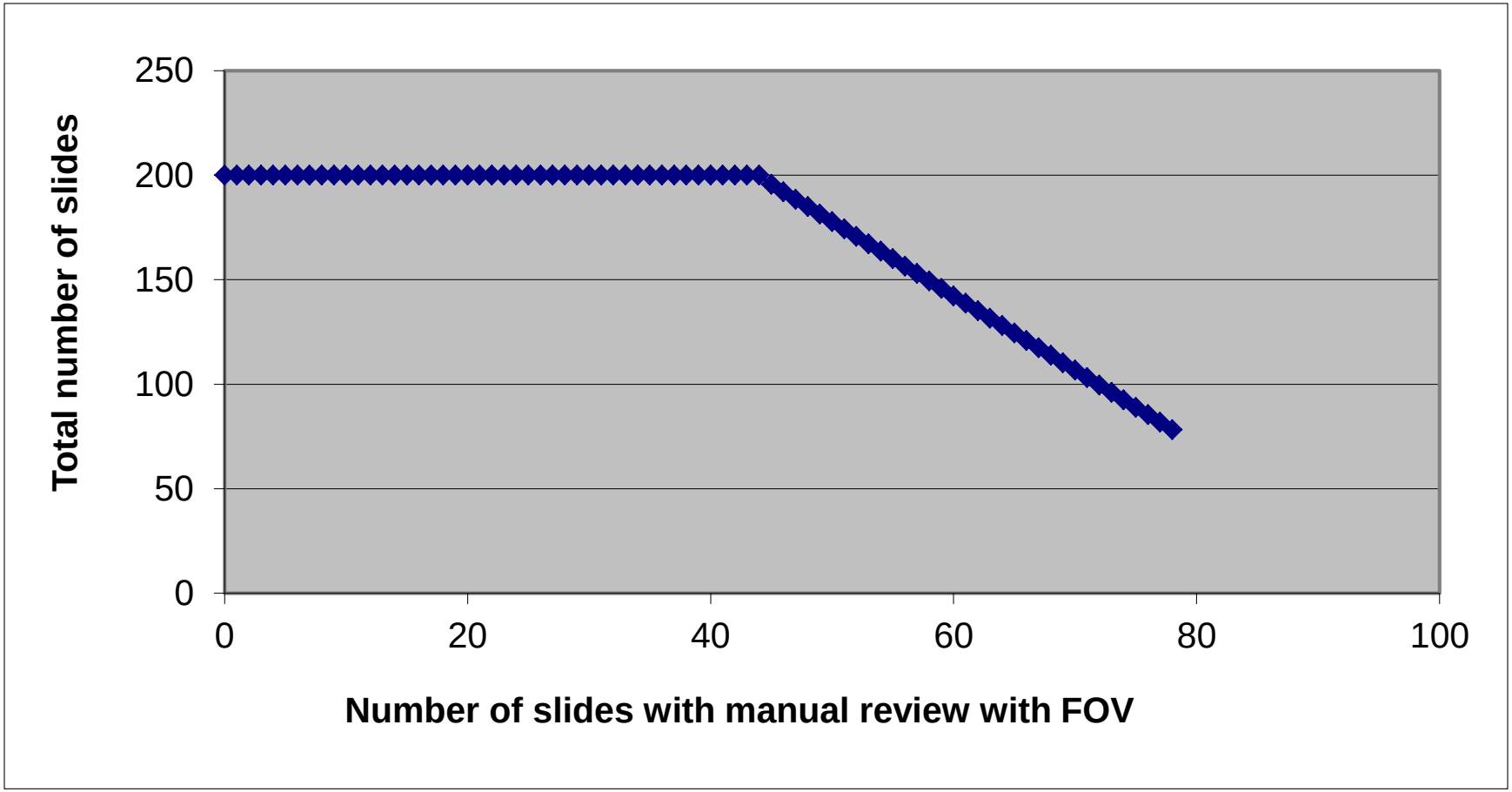
Example:

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

1.28*60 + 0.28*Y = 100 slides

- Then using the formula, Y=82 – 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*X+1.35*Y=480 for two independent clinical studies (TIS and BD)!

- Provides some additional validity for these calculations

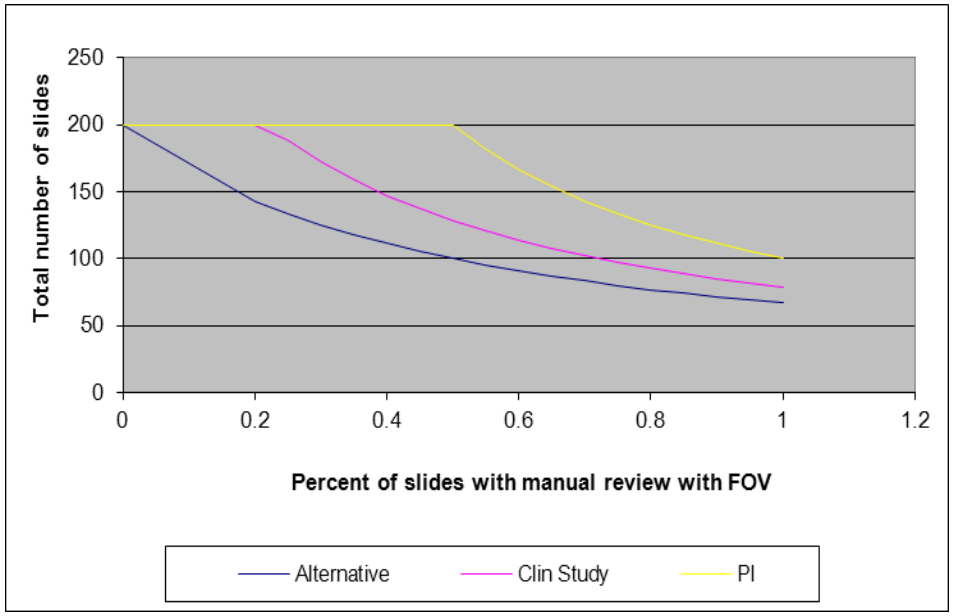
Challenge

- These weights are not easy to use in real-life laboratory settings
- Formula for calculating upper limit from clinical study is ~ 1.3*X+0.3*Y=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



Percent of slides which require manual review with FOV in average	Upper limit for total number of slides Safer Alternative	Upper limit for total number of slides Clinical Study	Upper limit for total number of slides Product Insert
20%	142	200	200
25%	133	188	200
30%	125	172	200
40%	111	147	200
50%	100	128	200
60%	90	113	166
70%	83	102	142
80%	76	92	125
90%	71	84	111
100%	66	78	100

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