

# **M, Validity and Diagnostic Relevance**

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## **Is There Evidence for Outdating Antibodies? A Critical Examination of the Current Conundrum**

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- I. Course Objectives
  - A. To understand the current state of antibody outdating and how we arrived at this point
  - B. To critically evaluate the evidence basis for the current situation
  - C. To develop potential action plans to elicit change if necessary
  
- II. Outline
  - A. The situation: How did we get there?
  - B. Is there an evidence basis for the current situation?
  - C. If not, how can we amend the situation to better reflect the evidence basis as we understand it?
  
- III. The Current Situation
  - A. College of American Pathologists Survey Checklist: ANP22432
  - B. Are all immunohistochemical reagents used within their indicated expiration dates?
  - C. Derived from CLIA '88 Final Rule
  - D. *"reagents must not be used when they have exceeded their expiration date"* (42CFR493.1252(d))
  - E. *"the manufacturer has the responsibility for establishing expiration dates.."* (Federal Register 2003)
  - F. Application to IHC reagents an unintended consequence of the granting of anylate specific reagent status by the FDA
  - G. Neglects other components of CLIA '88 investing responsibility for insuring quality of ASR's to individual medical directors and their laboratories
  - H. Also may reflect fundamental misconception of the differences regarding the utilization of reagents in, for example, a Chemistry laboratory and those applied to Anatomic Pathology Practice
  - I. Bottom Line: CAP is obligated to follow guidelines as accrediting agency deemed by CMS

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- IV. Is There an Evidence Basis for This Rationale???
- A. Only two manuscripts in literature based on PubMed Search
  - B. Tubbs RR, Nagle R, Leslie K, et al. Extension of useful reagent shelf life beyond manufacturers' recommendations. Cell Markers Committee of the College of American Pathologists *Arch Path Lab Med* 1998;Dec;122(12):1051-1052
  - C. 221 laboratories immunostained 3 neoplasms with two antibodies each, both before and after the expiration date; little difference in %'s of positive and negative immunostaining before and after the expiration dates
  - D. Vigliani R, Babache N. Primary antisera before and after the expiration date. *Pathologica* 2002 Jun;94(3):121-129
  - E. Evaluated 78 primary antibodies before and after expiration dates (mean 26.3 mos after date) and found no significant immunostaining differences in 58; minor differences in 19; major differences in 1
- V. Other Evidence
- A. No other large systematic studies to date
  - B. Need for a systematic, perhaps multi-institutional evaluation to address issue
- VI. Other Evidence – Iowa Experience
- A. Utilization of “on slide” positive controls for all cases
  - B. Enables staff pathologists to compare both positive and negative control results
  - C. Enables pathologist responsible for IHC testing to longitudinally track antibody performance
  - D. Long time participation in CAP IHC Proficiency Testing Program
  - E. Only two discrepant antibodies over the last five years of testing (roughly 60 individual antibody tests per year) excluding Her2-neu/EGFR testing; neither had bearing on achieving the “correct answer”
- VII. Results of Initial Survey Prompted by CAP Inspection
- A. Approximately 40% of antibody menu beyond expiration date at any one time in a “revolving” type manner (clinical IHC laboratory has menu of approximately 150 antibodies)
  - B. Antibodies stored at 4°C
  - C. Most are concentrates; some predilutes
  - D. Antibodies most likely to be out of date are those not routinely utilized as one might expect
  - E. Some more commonly utilized are also occasionally extended secondary to dilution characteristics
  - F. Performance characteristics monitored each time antibody is utilized as indicated previously
  - G. Absolutely essential to any good IHC practice

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VIII. Current Situation Revisited

- A. CLIA '88 states you cannot utilize reagents beyond their manufacturer's supplied outdate
- B. CAP, as a vested accrediting body, must recognize and work to insure compliance with the promulgations of CLIA '88
- C. There appears to be data/evidence to support the appropriate and monitored utilization of antibodies beyond their expiration dates
  - 1. Internal inconsistency with other parts of CLIA '88 vesting in laboratory/medical director responsibility for insuring quality of ASRs
  - 2. Literature citations, although number is exceedingly small
  - 3. Anecdotal evidence from laboratories of high quality and good reputation
  - 4. University of Iowa Experience

IX. Ways out of the Conundrum?

- A. Bury Head in Sand (aka Ostrich Approach)
  - 1. Ignore everything, including your CAP inspection deficiency, for the purpose of proving a point
    - a. Not a recommended approach as it puts entire laboratory accreditation at risk
- B. Continue to engage in passive dissent, getting your laboratory cited, and then writing an explanation in an effort to focus attention to the issue
  - 1. Would urge this, with the understanding that this is an indirect approach as the responsible party is not CAP
- C. Collect appropriate data and provide such to CAP, either directly or through publications, with the intent that they can lobby CMS/Federal Govt. to amend the appropriate passages in CLIA '88 that deal with anylate specific reagents
  - 1. Efforts must be initiated along these lines; ultimate effectiveness somewhat questionable given current political environment and strong push for patient safety; ? some traction if resource utilization is considered
  - 2. Continue to point out internal inconsistency between outdated language and the language covering ASRs
- D. Will likely take combination of the latter two approaches to see any significant change

X. Summary

- A. The utilization of reagents beyond their manufacturer's outdates is prohibited by CLIA '88
- B. CAP is vested as an accreditation agency and therefore must insure that laboratories practices reflect these mandates

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- C. There appears to be little evidence to date supporting the implied underpinning to the mandate; i.e. using outdated reagents leads to inaccurate testing or adversely affects patient care
    - 1. In fact, current evidence would suggest the contrary
  - D. In order to effectively address the issue, additional evidence needs to be accumulated and the CAP must lobby on behalf of laboratories to have the appropriate passages in CLIA '88 amended to reflect the actual state
    - 1. This should always be done in the context of good general IHC practice
- XI. Pearls of Pathology
- A. Some quotes through the years
    - 1. “Never put anything into the diagnostic line that will result in a phone call from a clinician”
    - 2. “Did you look at that slide? <pause> With a microscope?”
    - 3. “A fool with a tool, is still a fool”
    - 4. “If the immuno does not fit, you must ignore it”

XII. References

- 1) The Federal Register
- 2) Final Rule, CLIA '88
- 3) Tubbs RR, Nagle R, Leslie K, Pettigrew NM, Said JW, Corwin DJ, Rickert RR, Roche PC. Extension of useful reagent shelf life beyond manufacturers' recommendations. *Cell Markers Committee of the College of American Pathologists Arch Pathol and Lab Med*, 1998;122(12):1051-1052
- 4) Vigliani R, Babache N. Primary antisera before and after the expiration date. Comparative immunohistochemical observations and analysis of data sheets and labels. *Pathologica*, 2002;94(3):121-129