REVIEW OF 73 Consecutive NDA-Method Validation Package EVALUATIONS 1997
MVPs Which Required Revisions 43
Nothing Worked -- Package Returned 1

ON IMPURITIES

- Certificate of Analysis Reported Impurity Which Exceeded NDA Limit
- Reported Ethyl Ether and Acetone Residual Solvents -- Found Acetonitrile and Acetic Acid
- Unknown/Unreported Impurity in Samples (four cases)
- Large Unreported Impurity in Bulk Drug Substance
- Two Unreported Impurities in Reference Material

ON HPLC COLUMNS

- Specified Column No Longer Commercially Available
- Seven Columns Tried (including two submitted by firm)-- None Met Requirements
- Column Operated Outside Recommended pH Range

ON STANDARDS AND SOLUTIONS

- Standard Solution Was Saturated (Precipitate Formed on Cooling -- (three cases)
- Standard and Test Solutions Prepared In Different Media (Six Cases)
- Sample Concentration 100 Times the Standard Concentration
- Standard Concentration 16 Times the Sample Concentration
- Concentration of Internal Standard in Standard Solution Twice That in the Sample Solution

OBVIOUS TYPOGRAPHICAL ERRORS

- TLC Plate Does Not Exist -- Company Name and Trademark Conflict
- Stated 2 g -- Should Be 2 Kg
- Reagent Gas Specified as 1.04% -- Should Be 0.104%
- Wrong Column Type
- Factor Calculation Wrong

TRANSLATION ERROR

- microliter to milliliter

HPLC METHODOLOGY

- No System Suitability Test Criteria (14 cases)
    - Resolution Factors, Tailing Factors, Acceptable RSD
- Sample Not Filtered Prior to Injection
- No Description on How to Prepare Mixed Mobile Phase
- Injection Volume Too Small for Good Detection (five cases)
- Light Absorption by Mobile Phase Caused Ragged Baseline

OTHER

- Unclear Method Operation (GLC split not reported)
- Wrong Column Temperature

- Detector Temperature Not Specified
- Drug Decomposed in Dissolution Medium
- Capsule Shells Absorbed at Determinative Wavelength -- Dissolution
- Specified to Weigh Out 0.43971 g

OTHER

- Recovery low and not reproducible
- Inconsistent specifications (two different % cited)
- IR Spectrum of Working Standard Different From Those of Bulk Material and Standard
- Preparation of IR Sample Not Described
- No Specifications on Optical Rotation Test
- No Specification for Drying Material
- No Time Specified for LOD Determination
- Water Specified as "Polished" and "Purified" Without a Definition of Either
- Sampling at Top, Middle and Bottom of a Suspension Without Any Acceptance Specifications

SUGGESTIONS FOR SMOOTHER VALIDATIONS

Perform ruggedness testing

- vary components of the mobile phase, try a new column.
- state what mobile phase changes will increase resolution, decrease tailing, etc.

Send portions of all impurities, internal standards, and system suitability compounds required for performing the method.

Never specify both a retention time and a flow rate.
Give approximate retention times and flow rates.

Include copies of chromatograms of standards (including impurity standards) and sample runs.

System suitability tests should specify a resolution requirement between a "critical pair," e.g.,the drug and the closest eluting impurity.

Impurity standards are required for limit tests if they have different response factors than the API.

Retention times are equivocal identifications.

The standard concentration for a limit test should be prepared approximately at the limit level.

Points on the standard curve should bracket the anticipated sample level. Recommend minimum of four data points

Include a copy of a chromatogram which shows all of the impurities.

Don't make system suitability calculations with solutions which give a very large response for one compound and a very small response for the other. (too hard to draw tangents on small peaks)

Try to use the same method for assay and chromatographic impurity tests. (Change detector sensitivity/gain, or injection volume/concentration)