Common Gaps in BLA Packages for QC Release and Stability Method Validations*

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**Please ignore or refute everything I'm going to say (at least until I decide to retire…)*

Disclaimers:

- My expertise is entirely based on analytical methods for biological products:
  - Therapeutics and vaccines
  - Ancient and modern product modalities
  - Novel, legacy, and biosimilar products
  - Physical and functional method technologies
  - Compendial and non-compendial methods
  - In-house and contract testing laboratories (academic and industry)
  - Pre-IND/IMPD through BLA/MAA + PAI, and subsequent GMP inspections

- My comments are derived from 30+ years of my own direct, detailed interactions with regulatory reviews and inspections of GMP-compliant method SOPs and method validation packages for BLAs/MAAs and PACs, both prospectively (avoiding train wrecks) and retrospectively (remediating train wrecks)

- I am not now, nor have I ever been, a member of a Regulatory Agency; my comments reflect my own experiences with sponsor's products plus my professional interactions with regulators in conferences, task forces, and committees

- I have worked alongside regulatory representatives long enough to clearly state that:
  - Specific strategies are evaluated on a case-by-case basis
  - Results may vary depending on how lucky you are
  - Objects in the rear-view mirror are larger than they appear

Golden Rule #1: The burden of proof is on the sponsor

- ✓ *Proof = Relevant, supportive DATA that is accurate, complete, and available to review*
- ✓ *FDA 2015 guidance clarified regulatory expectations for what reviewers need to see in BLA to conduct speedy but effective review of 3.2.S.4.2 – 4.3 and 3.2.P 5.2 – 5.3 (method procedures and method validations)*

Golden Rule #2: Just because it was fine before does not guarantee it will be fine now

- ✓ *Reviews and inspections of method SOPs / validation packages is not typically 100% of 100% at time of filing (ie not 100% of QC methods, not 100% of validation data)*
- ✓ *Routine GMP inspections have not always included thorough QC analytical laboratory inspections (though more now due to data integrity issues)*
- ✓ *Data integrity problems have triggered more in-depth reviews of old method validation packages that have also revealed numerous technical flaws and disconnects with the "validated' method*
- ✓ *FDA CDER and CBER have produced far more consistent reviews and inspections for biologic product QC SOPs and method verification/validations since 2015 (internal training?)*

Frequent BLA-MAA Regulatory Review Comments / PAI-GMP Inspection Observations

GMP Compliant QC Method SOPs

- **SOP does not clearly specify the validated method's intended use(s)**
  - *Which product material(s) will be analyzed with the method? (eg DS, DP, IPC, excipient)*
  - *What is the state of the test materials? (eg frozen, liquid, lyo, cream, patch)*
  - *What parameter(s) are being evaluated for reportable results? (eg identity, purity/impurities, concentration, content, process residual, potency)*
  - *What is the nature of the reportable results? (eg qualitative, empirically quantitative, relatively quantitative)*
  - *Is it intended to be used for both release and stability testing?*

- **SOP(s) does not contain sufficient operational detail to consistently execute the validated workflow with the intended test materials for**
  - *Preparation of materials and reagents (control of critical reagents)*
  - *Specific configuration of validated analytical instrumentation and software*
  - *Preparation of standards, assay controls, and test samples (control of Ref Stds)*
  - *Validated intra-assay replication scheme*
  - *Processing of raw data (including transfer between computerized systems)*
  - *Stepwise system suitability criteria*
  - *Utilization of intra-assay outlier assessment*
  - *Generation of reportable results*

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GMP Compliant Method Validation Packages

- **Validation experiments are deficient in that they**
  - Do not reflect the full workflow of the method SOP (esp sample preparation steps)
  - Do not reflect all levels of the intra-assay replication scheme (esp in IP runs)
  - Do not contain sufficiently rigorous the intermediate precision runs (n #)
  - Ignore operational bias in intermediate precision runs
  - Do not utilize the test materials specified for QC testing with the validated method
  - Do not use instruments, software, critical reagents equivalent to those used in the validated method
  - No/inadequate validation data across the method's working range (measurement range)
  - No/inadequate validation data across the method's reportable range (spec range)
  - Failures of the working range parameters are ignored (SST is post-validation)
  - Use of intra-assay outlier masking is not documented in validation runs

- **Validation packages are deficient in that there are no/inadequate data**
  - To support the stability-indicating capabilities of stability methods
    - Comprehensive, systematic FD for biologic product stability profile
  - To confirm the operational robustness of key method steps
    - CONFIRM is different from optimize (ICHQ1)
  - To support the platform elements of platform methods
    - CRO vs in-house platform method data