A Modern Approach to Excipient Quality Assurance

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Outline

- The crux of the matter
- High priority monographs
- Modernizing the approach

Excipients Need to be Safe and Provide Consistent Quality including Performance

- Generally regarded as safe when used in a manner consistent with precedent use
- Excipients must be manufactured in accordance with CGMP
- USP grade excipients meet both of the above criteria
- Drugs are approved with the premise that excipients used in exhibit batches are going to remain consistent while the drug is on the market
- Variations outside of approved “space” can result in a supplemental application (SUPAC provides general guidelines)

Concerns about Excipient Purity

- The amount of excipients quite often exceeds the amount of API in any given drug
- Excipient purity is difficult to determine for many excipients
  - Heterogeneity of the chemical composition is common for many excipients whereby the excipient is still considered to be a “pure drug substance”
  - Test methods often fail to account for anywhere near 98%, whereas we generally regard 2.0% to be the upper limit for substances regarded as unnecessary if not deleterious to safety or efficacy of a drug.

Globalization and Cost Pressures Have Changed the Playing Field

- Greater uncertainty about integrity of supply chain
- Confirmed incidents involving intentional adulteration suggesting the risk, as far as the US supply chain, has increased
- Pressure leading to shortcuts and risk taking which might not be in best interest of patient safety

Shortcomings in Testing Have Been Exploited and Opportunities Might Still Exist

- DEG, OSCS and Melamine adulteration incidents come to light in past decade
- On review of excipient monographs it is apparent that even if performing all tests in the specification it might not be possible to detect undesirable substances present at significant levels.
  - Non-specific ID and assay methods
  - Questionable acceptance criteria
- Certain common excipients are used in many drug products and often present at significant level/dose. Thus a single contaminated excipient;
  - can be at least as harmful as a contaminated API
  - can have more far reaching implications for the US drug supply

CGMP Requirements for Acceptance of Incoming Batches of Excipients

- The acceptor is not required to perform all specified tests provided
  - for any test which is waived there is an adequate level of confidence
    - includes periodic verification
  - the acceptor performs a set of ID tests which are specific

- Reliance upon ID testing and CoA ….is it justifiable? What is the residual risk? What might be the shortcomings?

Monograph Modernization – DEG in Polyols

Past examples of FDA and USP collaborative efforts to modernize monographs include:

- USP Glycerin Monograph
  - **May 2007**: FDA issued a guidance on *Testing of Glycerin for Diethylene Glycol* (DEG) that referenced USP Glycerin monograph tests
  - **April 2007**: FDA requested USP to place tests/limits for DEG into monograph's *Identification* test
  - **May 2009**: USP monograph official with revised *Identification* tests/limits for DEG/EG (ethylene glycol)

Monograph Modernization – Examples

USP monographs for similar articles were also revised to include DEG/EG tests/limits in ID test:

- **February 2010**:
  - Propylene Glycol,
  - Sorbitol Solution,
  - Sorbitol-Sorbitan Solution,
  - Noncrystallizing Sorbitol Solution
- **August 2010**:
  - Maltitol Solution

FDA Committed Significant Resources to USP Monograph Modernization as Part of Strategy to Defend Against EMA

At its convention in April 2010 (2010 -2015 cycle), USP Resolved to:

- "Strengthen USP's focus on core compendial activities to ensure relevant, timely, accurate public standards."
- "Strengthen the USP-FDA Relationship…to better provide and maintain up-to-date national standards for legally marketed drugs…."

- FDA commits support to the modernization of USP-NF Monographs, aiming to:
  - Help prevent adulteration/contamination incidents
  - Promote use of modern spectrographic methods in monograph *Identification* tests
  - Assure tests and limits for impurities are appropriate and consistent

FDA's Role In Compendial Excipient Modernization

- CDER established a Monograph Modernization Task Group (MMTG) to manage complexity of overall task, oversee progress and communicate with USP
- CDER prioritized excipients for modernization based on public health risks (combination of factors) and identifying weakness in ID and assay testing in certain monographs
- FDA provided liaisons who play an advisory role to the Excipient Expert Committee and supporting *ad hoc* expert panels
  - Regulatory
  - Technical

The Most Recent High Priority Excipient List (Estimated % Drug Products Containing Excipient

1. Butylated Hydroxyanisole (1.1%)
2. . Butylated Hydroxytoluene (2.6%)
3. . Calcium Stearate (0.6%)
4. . Crosslinked Sodium Carboxymethylcellulose (Croscarmellose Sodium, Sodium CMC) (7.5%)
5. . Dextrose (1% but many more as atypical active)
6. . Gelatin (6.5%)
7. . Guar Gum (0.1%)
8. . Microcrystalline Cellulose (MCC) (22%)
9. . Pregelatinized Starch (0.8%)
10. . Shellac (2-3%)
11. . Silicon Dioxide (Colloidal) (20%)
12. . Titanium Dioxide (22%)

Major Accomplishments and Initiatives

- All batches of glycols and sugar alcohols vulnerable to DEG as an adulterant are now tested prior to use through ID test requirement
- Identification of a variety of alternative modifications to existing methods for gelatin and povidone to deter melamine adulteration risk associated with nonspecific N assay
- A revised test protocol to assure absence of asbestos in talc to be proposed in a stimulus article soon to appear in PF

Dealing with Excipient Variation

- Excipient composition is loosely specified or based on the monograph sponsor's specification
- Specification might not be correlated to or indicative of certain important aspects of excipient quality
- Uncertain outcome if and when an excipient property falls within the range of the specification but outside of historical ranges
- Are there good supplier controls in place?
  - certainty about where the excipient is and will always be manufactured unless otherwise stated
  - customer notification in advance of any significant changes

Striving Toward a Higher Level of Assurance of Consistency and Predictability

- Supplier qualification
- Controls related to intended use
  - Purity and composition
  - Use of appropriate grade
  - Physical attributes- measurement and control
- Verification of incoming excipient
  - ID testing
  - Visual checks
  - Testing for critical attributes

Overall Multi-Tiered Approach

- Robust excipient supplier qualification program, control strategy and mutually workable quality agreement which assure excipients are appropriate for intended use and continuity of supply
- Knowledge of each excipient supply chain back to prime excipient manufacturer
- Modernized test methods eliminating enticement to substitute or falsify ingredients

Managing and Mitigating Risk

- As we continue to look at excipient standards we should be aiming to manage quality risks
  - Information gathering and sharing
  - Robust standards and PREVENTIVE controls
  - Mitigating uncertainty and dealing with residual risk