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
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