Atypical Actives

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IPEC’s unofficial “Atypical Active” definition

An “excipient, food additive or personal care ingredient” that is being used as an “active ingredient” in a formulation.

generally accepted by industry and regulators
Characteristics of Atypical Actives

- Predominately produced for non-medicinal markets and applications (food, cosmetics, industrial) or as pharmaceutical excipients.
- The manufacturing equipment and design, packaging and supply chain were not designed with the API market in mind.
- Unlike traditional APIs, these materials typically have a physical effect rather than pharmacological activity but are defined as an active ingredient by regulators.
- Typically, prices and margins are low compared to standard APIs.
Manufacturers focused on primary market; unaware of API registration requirements or GMP implications

Seen as a liability by suppliers with little business benefit. Greater level of exposure and risk for users.

Compendial compliance on a label does not distinguish active or excipient use; could be misleading

Quality Agreements make avoiding the issue difficult

End use not communicated by drug product manufacturer

Concerns
Regulatory Concerns

- Regulations not designed for these
  - Self-identification and registration of APIs/facilities
  - Facility GMP inspections/audits – what standards?
  - Unclear liability concerns over mislabeling and misbranding

- Regulatory status is not defined in the U.S.
  - EU, UK and Canada have regulatory guidelines; Brazil is developing regulation
EMA/196292/2014 Guideline, Part C
• QP declaration concerning GMP compliance of active substance manufacture

MHRA
• Specifications, suitable controls for process quality, change control, audits, documented risk assessment, full testing on receipt

Health Canada DEL Bulletin #4, 11/4/16
• Must understand how product is used
• Relief from API GMP requirements - Table A “exception”
• Quality agreement between importer and manufacturer
Atypical Actives - Challenges
Manufacturers Challenges

Manufacturing
- Typically a bulk chemical environment
- Often continuous, not batch processes
- Usually produce different grade products for multiple markets

GMPs
- GMP standards for primary business may be different (excipient, food, cosmetic, industrial)
- Likely not manufactured to ICH Q7 guidelines like more traditional APIs

Controls
- Biggest gaps are usually in documentation, validation and process control
- Stability program – usually stated as “Re-evaluation” vs. Expiry dating

Risk/Cost
- Seen by most suppliers as a liability risk with little benefit
- Cost to apply ICH Q7 API GMPs would rarely be justified from a business perspective (profit margins, market size)
User Challenges

Potential risks for users such as:

- Assumption when labeled USP or USP/NF it is API grade manufactured using ICH Q7 GMPs
- Makers stop selling for use in the API, parenteral, ophthalmic, sterile, etc. markets
- Costs (auditing, fees, etc.)
- Regulatory scrutiny
- Need for risk-based decision making
Viable approaches to controlling Atypical Actives quality and appropriate GMPs are needed.

There is no ‘one size fits all’ solution.

Acknowledgement of the unique nature of Atypical Actives in regulatory structure.

GMP controls should consider a risk-based approach for the manufacture, storage, distribution and use of the ingredients.
Many safe and effective, commonly used drugs would no longer be available for the consumer

More expensive drugs would have to be used for the same functionality

Increased cost with only equal or diminished safety

Increased health risk due to potential loss of commonly available and needed drugs
What is the REAL risk?

Long history of patient/consumer safety

Many Rx, Gx and OTC drugs depend on Atypical Actives which may not have any suppliers of material made to ICH Q7 API GMPs.

Have issues been found with current marketed products?
- If so, did they result from the manufacture, GMPs or GDPs of the “Atypical Active”?
- A continuum of GMPs are currently being used for these materials

A realistic balanced regulatory approach based on risk must be developed to provide flexibility.
Managing Risk

What are Appropriate GMPs and Controls for Atypical Actives?
Risks considerations

- Most Atypical Actives present low patient safety risk as a result of GMP issues
  - Safe for excipient (or food) use at relatively high levels
  - Many are considered GRAS (Generally Recognized as Safe)
  - Usually used for treating less serious conditions
  - Well known chemical properties
  - Low toxicity
Manufacturers – Risk Management

- Clearly indicate the grade and intended use for the product on the label, COA and product literature
  - “For Excipient Use Only”; “manufactured in accordance with excipient GMPs”
- Educate marketing and sales organizations
  - Review product literature
- Whenever possible, find out how products that may be used as Atypical Actives or that have monographs in the USP are being used by customers and/or sold by distributors
  - Communicate what can/can not be supported
## Users – Risk Management

### Supplier Qualification

- Conduct a risk assessment to determine acceptability of the material as an API or in a particular application
- Determine and verify the GMP applied by the supplier is suitable for your use
- Demonstrate no compliant alternative supplier
- [EU] Document the supplier approval acknowledging compliance to the QP declaration and claim the material is an Atypical Active
- Continually assess supplier(s) – openness and transparency are key to success

### GMPs

- Perform on-site audits of manufacturers
  - Mutual understanding of GMPs in place
  - Focus on key control points
- Agree and document the GMPs that will be implemented for the Atypical Active
**Users – Risk Management**

### Technical
- Use pharmacovigilance data to show patient safety from the status quo
- Agree on specifications and implement further controls either with maker or on receipt
- Conduct full testing of the incoming material
- Implement a Quality Agreement with supplier

### Business Considerations
- Maintain a close working relationship with suppliers to increase understanding
- If feasible, financial incentive (price premium if additional controls are needed)

### Regulatory Considerations
- Inform regulator proactively (do not wait for an inspection) explaining the justification and ask “Do you have any reservations about us continuing to market our product?”
Compendial Considerations
"Appropriate GMPs" is a requirement in the General Notices

There are no confirmed API grades of some of these produced by manufacturers!

- Carboxymethylcellulose Sodium, USP/NF
- Hypromellose, USP, Ph. Eur., JP
- Povidone, USP

Can you tell from the:
- Label?
- COA?
- Compendial compliance?
USP Work Relating to Atypical Actives

<table>
<thead>
<tr>
<th>USP Excipients Group:</th>
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</thead>
<tbody>
<tr>
<td>- Created list of USP official substances registered as APIs and appearing on the FDA IID (Inactive ingredient Database) list for excipient use. Current list contains 94 APIs.</td>
</tr>
<tr>
<td>- Reviewed the Excipient Expert Committee list of excipients - 38 excipients are in the USP section of the compendium. Some used in OTCs:</td>
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<thead>
<tr>
<th>DEHYDRATED ALCOHOL</th>
<th>JUNIPER TAR</th>
<th>SACCHARIN SODIUM</th>
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<tr>
<td>TOLU BALSAM</td>
<td>MANNITOL</td>
<td>SAFFLOWER OIL</td>
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<tr>
<td>ALCOHOL</td>
<td>METHYLCELLOULOSE</td>
<td>SODIUM CHLORIDE</td>
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<td>ANHYDROUS CITRIC ACID</td>
<td>MINERAL OIL</td>
<td>SORBITOL SOLUTION</td>
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<td>CALCIUM SACCHARATE</td>
<td>MINERAL OIL, RECTAL</td>
<td>SOYBEAN OIL</td>
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<tr>
<td>CARBOXYMETHYLCELLULOSE SODIUM</td>
<td>NONOXYNOL 9</td>
<td>TALC</td>
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<td>CARBOXYMETHYLCELLULOSE SODIUM PASTE</td>
<td>PECTIN</td>
<td>TITANIUM DIOXIDE</td>
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<td>CASTOR OIL</td>
<td>PETROLATUM</td>
<td>TOPICAL LIGHT MINERAL OIL</td>
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<td>CITRIC ACID MONOHYDRATE</td>
<td>PHENYLETHYL ALCOHOL</td>
<td>TOPICAL STARCH</td>
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<td>TYLOXAPOL</td>
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<td>PROPYLENE GLYCOL</td>
<td>XYLOSE</td>
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<td>ISOPROPYL ALCOHOL</td>
<td>SACCHARIN CALCIUM</td>
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Ref: Catherine Sheehan, USP Perspective on Atypical Actives, USP Excipients Stakeholder Forum, Nov. 29, 2017
Next steps for USP?

Possible considerations:

- Should there be further clarification regarding ‘appropriate GMPs’ in the General Notices?
- Should there be a General Chapter?
- Should specific applications be addressed in certain monographs, e.g. ‘for injection’ and ‘for ophthalmic use’?
  - How to determine appropriate specifications?
  - Can the parameters be measured and/or controlled?
  - Compendial vs. maker/user requirements?
IPEC-Americas’ Concepts for Atypical Actives

- Excipient or other appropriate GMPs for the type of intended use should be acceptable

- Technical considerations may need to be addressed, for example:
  - Composition and potential variability
  - Specifications
  - Continuous processing and dedicated equipment
  - Stability understanding
  - Cleaning / environmental controls
  - Change control and customer notification procedures

These are technical requirements, not a higher level of GMP
Other Considerations

- Utilize **confidentiality** and **quality agreements** to improve sharing of technical and use information.

- Use a decision tree process to define an Atypical Active and what information is available to determine appropriate control.
  - Discuss & agree upon design criteria before setting specifications.

- Develop a Risk Mitigation Plan that addresses key areas of difference between established GMPs and ICH Q7.
Conclusions

- It is unrealistic to expect all materials being used as “Atypical Actives” to comply with ICH Q7 API GMPs
  - HOWEVER, manufacturers need to demonstrate compliance to a general, realistic quality standard
- The fundamentals of Atypical Actives are the same globally
- It is important that industry and regulators agree on viable approaches to controlling Atypical Active quality and appropriate GMPs
  - Compatibility with existing regulations in EU, UK, Canada
  - Guidance for existing and new products
- Plans need to include clarity on compendial matters
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