Atypical Actives – Industry Perspective

USP Excipients Stakeholder Forum
November 29, 2017

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Multiple stakeholders; **one objective.**

International Pharmaceutical Excipients Council

Collaborative solutions for excipient industry stakeholders

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

Historical perspective

These have a long history of SAFE use!

- Commonly used in Rx, Gx and OTCs, including parenterals and ophthalmics
- Use of these as actives in drugs was established long before ICH Q7 API GMPs were developed

Why is this a concern now?

Manufacturers are focused on primary market and are unaware of API registration requirements or associated GMP implications.

End use is not communicated by drug product manufacturers.

Compendial compliance on a label does not distinguish between active or excipient use and could be misleading.

Recent proliferation of Quality Agreements makes avoiding the issue difficult.

Many suppliers see Atypical Actives as a liability risk with little business benefit. Greater level of exposure & risk for users.

Regulatory Concerns

- Regulations were not designed for these types of products
  - 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

Regulatory Landscape Challenges

- Potential risks to makers such as:
  - Increased GMP expectations (ICH Q7)
  - Increased regulatory scrutiny
  - Increased compliance costs (site & DMF registrations, GMPs)

- 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
  - Increased costs (auditing, fees, etc.)
  - Increased regulatory scrutiny
  - Increased need for risk-based decision making

Compendial Issues - Excipient or API?

Carboxymethylcellulose Sodium, USP/NF

Hypromellose, USP, Ph. Eur., JP

Povidone, USP

Can you tell from the:

- Label?
- COA?
- Compendial compliance?

”Appropriate GMPs” is a requirement in the General Notices

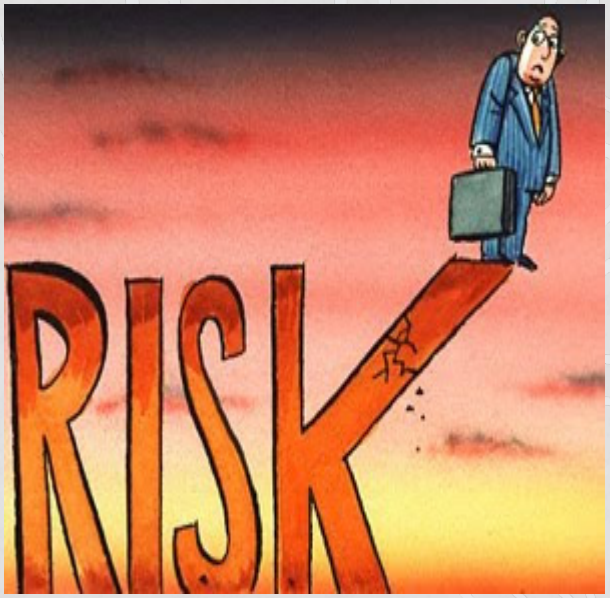
There are no confirmed API grades of some of these produced by manufacturers!

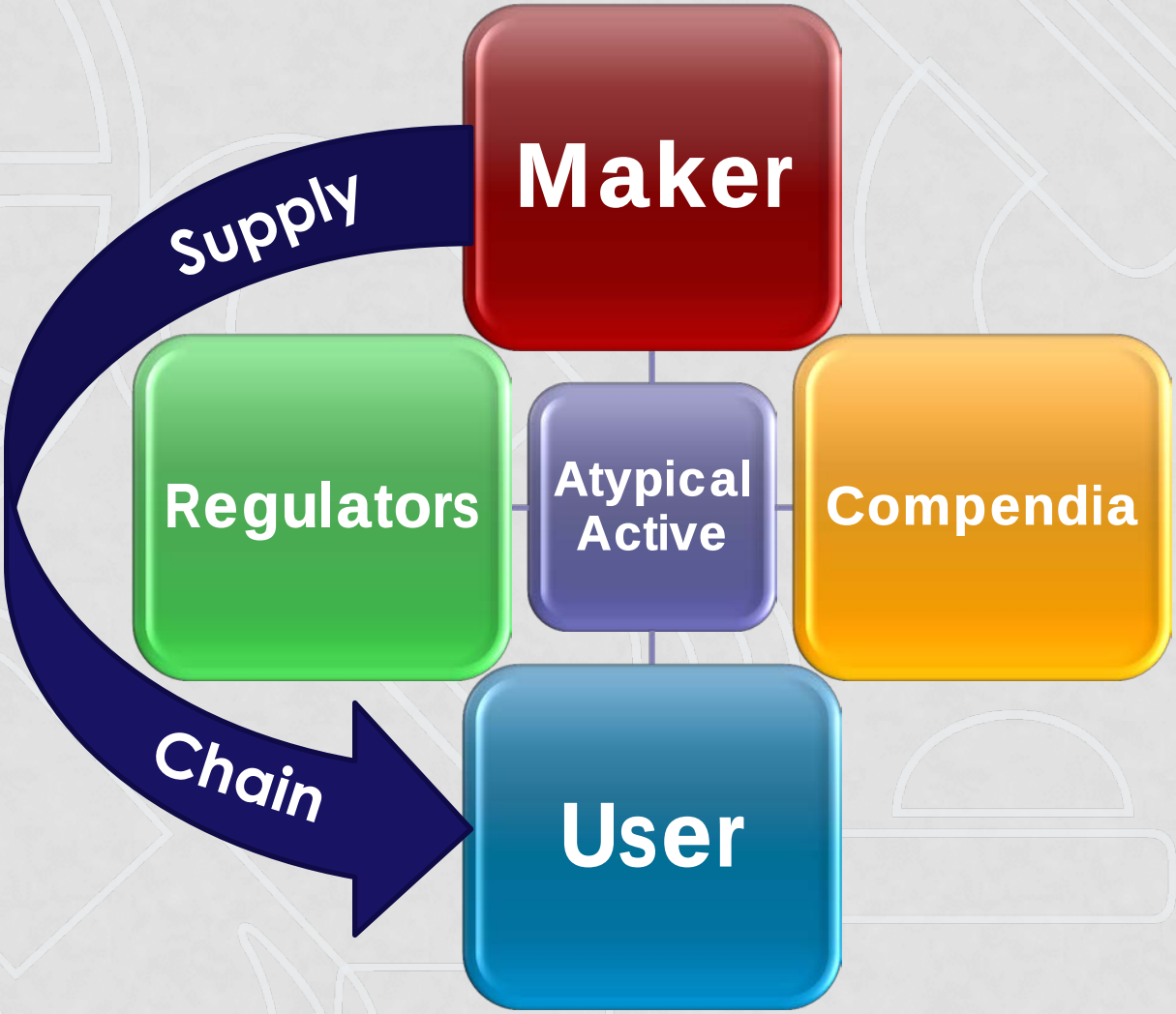
Need for acceptable solution

- A realistic balanced regulatory approach based on risk must be developed to provide flexibility.
- Many Rx, Gx and OTC drugs depend on Atypical Actives which may not have any suppliers of material made to ICH Q7 API GMPs.
- If these common non-complex actives are made using excipient or other GMPs, what is the real risk?

Drug Tablet

Risk assessment & management





Regulatory considerations

- **Viable approaches** to controlling Atypical Actives quality and appropriate GMPs are needed between industry and regulators
- 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

Excipient Manufacturer

Drug Product Manufacturer

FDA | Health Canada | European Medicines Agency | ANVISA

Regulators

Patient/ Consumer

Manufacturers of Atypical Actives – 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

- Perform on-site audits of Atypical Actives manufacturers
- Agree on and document the GMPs used
- Conduct risk assessments to determine acceptability of the material as an API or in a particular application
  - Focus on key control points that will be implemented for the Atypical Active
  - Do any specs differentiate between API and excipient use?
- Conduct full testing of the incoming material
- Price premium possible for additional controls?
- Know your supply chain and understand the risks!
- Close working relationship with suppliers to increase understanding
- Continually assess supplier(s) – openness and transparency are key to success

Next steps regarding monographs?

- Possible considerations:
  - Should the excipient monographs impacted be moved to the NF?
  - Should there be further clarification regarding ‘appropriate GMPs’ in the General Notices?
  - 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?
    - Other options?

Atypical Actives Coalition

- Established by IPEC-Americas to address the issues.
  - Members: IPEC-Americas, IPEC Europe, AAM, AHPA, Sindusfarma (Brazil), CHPA, SOCMA-BPTF, IFAC
- Expected results:
  - Clear, harmonized definition of what an Atypical Active is/includes.
  - Proposal(s) for how risk assessments can be used to determine appropriate controls that can be used to ensure manufacture, distribution, safe and effective use of Atypical Actives.
  - Engage regulatory agencies to recognize the issues and develop guidance and/or policies that provide practical solutions.

Conclusions

- The fundamentals are the same globally
- Important that industry and regulators agree on viable approaches to controlling Atypical Actives quality and appropriate GMPs
- Unrealistic to expect compliance with ICH Q7 API GMPs
  - Manufacturers of Atypical Actives need to demonstrate compliance to a general, realistic quality standard
- EU, Canadian & Brazilian authorities are balancing the risks to the patient with regulatory compliance
- The U.S. FDA has not yet formally addressed this topic
  - The Atypical Actives Coalition's objective is to work with regulators to develop a pragmatic approach to atypical actives

Acknowledgements

Special thanks to the following for the presentation content:

Meera Raghuram – Lubrizol

David Schoneker – Colorcon

Janeen Skutnik-Wilkinson - Biogen

Katherine Ulman – Consultant

Thank You!