

Dual Use Excipients

Priscilla Zawislak
Chair, IPEC-Americas

USP Excipients Stakeholder
Forum
September 29, 2016

Multiple
stakeholders;
one objective.



▶ International Pharmaceutical Excipients Council ◀
Collaborative solutions for excipient industry stakeholders

Dual Use Excipients

- ▶ What are these materials?
- ▶ What are the regulatory expectations?
- ▶ What are the compendial expectations?
- ▶ How are users and suppliers dealing with these expectations?



What is a “Dual Use Excipient”?

- A substance that has a monograph in the USP but is manufactured and used predominantly as an excipient in a drug formulation
- Many of these may also be used as an “Active” in formulations or in applications that are associated with ‘higher’ GMP expectations, e.g. parenterals and ophthalmics
 - In some cases it is the *only* ingredient
- Another term is “Atypical Active”
 - Not limited to excipients! It may also be a food additive, a GRAS substance, a personal care ingredient or even an industrial product

Excipient or API?

Carboxymethylcellulose Sodium, USP-NF

Hypromellose, USP, Ph.Eur., JP

Povidone, USP

- Can you tell from the label?
- Can you tell from the COA?
- Can you tell from the compendial compliance?

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

Why are 'Dual Use Excipients' Important from a Compendial Perspective?

- ▶ The USP and NF are unique in comparison to other compendia
 - In general, USP monographs are intended for APIs and NF monographs are intended for excipients
- ▶ Many of these dual use materials are manufactured predominately, or in most cases, exclusively as excipients, not APIs
 - The NF cross-reference is confusing to makers and users
- ▶ "Appropriate GMPs" is a requirement in the General Notices
 - API GMPs = ICH Q7
 - Excipient GMPs = <1078>, IPEC GMPs, EXCiPACT, NSF/IPEC/ANSI 363



Dual Use Excipients -> Atypical Actives

Characteristics of Atypical Actives

Often have one or more of the following features:

- ✓ Predominately produced for non-medicinal markets and applications or as pharmaceutical excipients
- ✓ Typically, their use as an API is not their primary purpose or use and includes only a very small percentage of their overall volume/sales
- ✓ Unlike traditional APIs, these materials typically have a physical effect rather than pharmacological activity but are defined as an active ingredient by regulators
- ✓ Commonly used in long standing pharmaceutical products that have a demonstrated history of patient safety
 - *Generic drugs*
 - *Over-the-Counter (OTC) products*

Where are these used?



Purell
Health.Care.

Shop the wide variety of PURELL Advanced products.



A Brief List of Atypical Actives

Over 100 have been identified

- ▶ Borax
- ▶ Caffeine
- ▶ Celluloses
- ▶ Dimethicone
- ▶ Glycerin
- ▶ Hypromellose
- ▶ Isopropyl Alcohol
- ▶ Kaolin
- ▶ Lanolin
- ▶ Paraffin
- ▶ Povidones
- ▶ Sodium Chloride
- ▶ Sorbitol
- ▶ etc...

| Other common examples of Atypical Actives | | |
|---|---------------------|-----------------------|
| Alginic acid | Glycerine | Phenol |
| Aluminum oxide | Honey | Pine tar |
| Ammonium acetate | Isopropanol | "Plant oils" |
| Ammonium chloride | Kaolin | Polyethylene glycol |
| Amylmetacresol | Lanolin | Potassium bicarbonate |
| Borax | Lemon juice | Potassium citrate |
| Butanediol | Magnesium carbonate | Potassium chloride |
| Calcium carbonate | Magnesium hydroxide | Potassium phosphate |
| Cellulosics | Magnesium phosphate | Urea |
| Chorhexidine gluconate | "Paraffin" | "Vegetable oils" |
| Chorxylenol | Pentane | Zinc oxide |

What's the issue?

If these have been around
for decades.....

Why are they getting this
attention now?



New Regulatory Requirements

▶ What's changed?

- The regulations....which were not designed for these types of medicinal products
 - Regulations that require registration of APIs/facilities
 - Facility inspections/audits - what GMPs will be used?
 - Labelling requirements



Greater level of exposure and risk for manufacturers who have products used as Atypical Actives

Historical Perspective



Because of their long history of safe use, manufacturers may not be aware that their material is being used as an “active” ingredient

- When labeled USP or USP/NF users may assume it is API grade manufactured using ICH Q7 GMPs
- Use of these as actives in drugs was established long before ICH Q7 API GMPs were developed
- The manufacturing equipment and design, packaging and supply chain were not designed with this market in mind

User's Perspective

- ▶ We've been using this substance for decades in this product without any issues
- ▶ How do we qualify/manage these now?
 - Audit the supplier?
 - To what standard?
 - Quality Agreement?
 - API or excipient?
 - Tighter/additional specifications?
 - Monograph requirements are the same
 - What specs differentiate between API and excipient use?
 - Supplier/process capability?
- ▶ Follow API regulations.....

Supplier's Perspective

- ▶ The supplier is manufacturing an excipient, food additive, cosmetic ingredient, etc.....
- ▶ And does not know the substance has been used/registered as an Active until the user tells them
- ▶ **You are doing what with my product?**
 - Knowledgeable supplier:
 - OMG 
 - Supplier separated from customer many times in the supply chain:
 - Who are you?
 - What are you talking about? 



Regulatory Expectations

U.S. Regulations Impacting the Use of “Atypical Actives”

- ▶ Facilities manufacturing APIs are required by law to register with the FDA as drug manufacturing establishments
 - FD&C Act (Chapter V Section 510)
 - FDA Regulations (21 CFR 207)
 - 2012 Generic Drug User Fee Act (GDUFA) Title III
- ▶ GDUFA Title III requires an annual site registration fee and a one-time fee for a Type II Drug Master File and a Completeness Assessment

Food and Drug Administration Safety and Innovation Act (FDASIA)



U.S. Regulatory Implications

- ▶ Risk-based FDA inspections for compliance to drug substance GMP (ICH Q7)
- ▶ FDA will be increasing the level of attention of supplier control programs, especially for ingredients during these inspections.



GDUFA Concerns for Atypical Actives

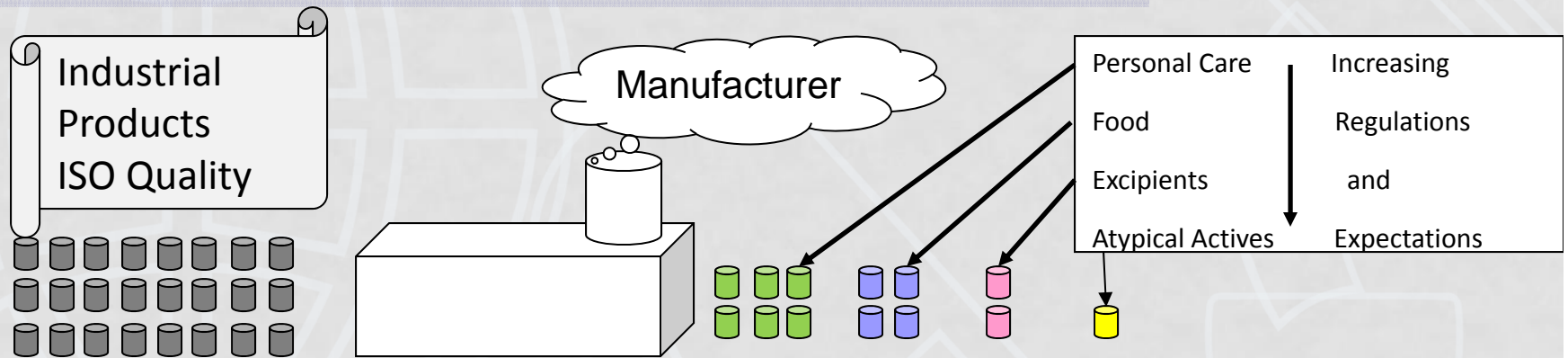
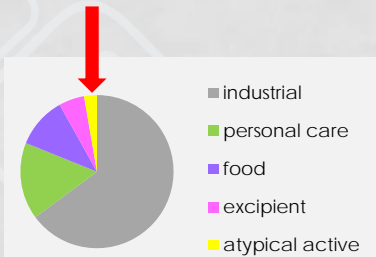
Self-identification of “Atypical Active” manufacturers

- ▶ May inadvertently or choose not to self-identify
 - Manufacturers may not be aware that:
 - Their materials are being used as APIs
 - Self-identification is required
 - Manufacturers often market product as excipient only and may not promote or support use of product as an API and/or may have concerns over potential liability
- ▶ Cost of registration may be more than revenue generated from sales into small volume applications
- ▶ Concern that registration will require adherence to ICH Q7 API GMPs & costs associated with achieving this
 - Manufacturer may not be capable of bringing a facility into compliance with ICH Q7 API GMPs based on the small portion of production diverted to an unsupported use by the end user
- ▶ Unclear liability concerns over mislabeling and misbranding

EU Regulations Impacting the Use of “Atypical Actives”

- [Directive 2004/27/EC](#) (2001/83/EC as amended) required that [APIs used as starting materials](#) in dose form pharmaceutical manufacture [be manufactured in compliance with API GMPs](#)
- [Falsified Medicines Directive \(FMD\) Directive 2011/62/EU](#) requires
 - Each API imported into an EU member state to be accompanied by a ["written confirmation" of GMP compliance](#)
 - [Registration](#) of EU API manufacturers, importers & distributors
 - Manufacturing Authorization Holders to [audit](#) (or have audited on its behalf) manufacturers and distributors of API and to submit a [written statement confirming that the API is manufactured in accordance with GMPs](#)

Atypical Active Manufacturer Example



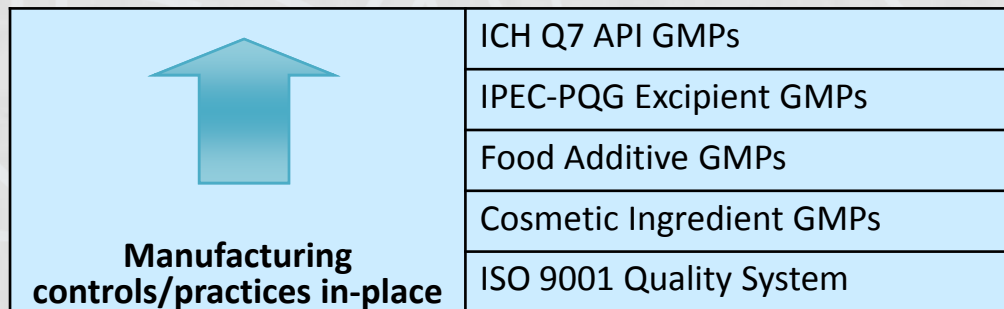
- Typical "Atypical Active" manufacturer produces products for a variety of markets
- Majority of production supplies industrial markets – customers buy on price
- Profit margins are typically low
- Personal Care, Food Additives, Excipients and Atypical Actives represent increasingly smaller percentages of production
- Increasing and differing regulations and expectations in regulated markets make it difficult to develop and maintain a sustainable quality system
- Geographic differences in regulations and customer expectations add another layer of complexity

API (ICH Q7) GMPs vs. Other Appropriate GMPs

- ▶ An Atypical Active supplier will have significant practical issues with implementing ICH Q7 API GMPs due the manufacturing circumstances:
 - Natural raw materials or products
 - Large scale manufacturing equipment
 - Outdoor manufacturing equipment
 - Bulk shipment, terminals, field tanks, etc.
 - Master batch manufacturing record not available with continuous processing
- ▶ Costs to apply ICH Q7 API GMPs would rarely be justified from a business perspective
 - Sometimes simply not possible due to feasibility of operational activities and physical limitations in manufacture.

API (ICH Q7) GMPs vs. Other Appropriate GMPs

- ▶ ICH Q7 API GMPs are not necessarily required
 - Existing data shows that the current continuum of GMPs used has adequately protected the quality and safety of atypical actives



- ▶ Biggest ICH Q7 API GMP gaps typically involve:
 - Validation
 - Process control
 - Documentation

Uncertainty is Dangerous!

In many cases, the manufacturer did not choose to enter this market segment and may be unwilling to accept this additional risk

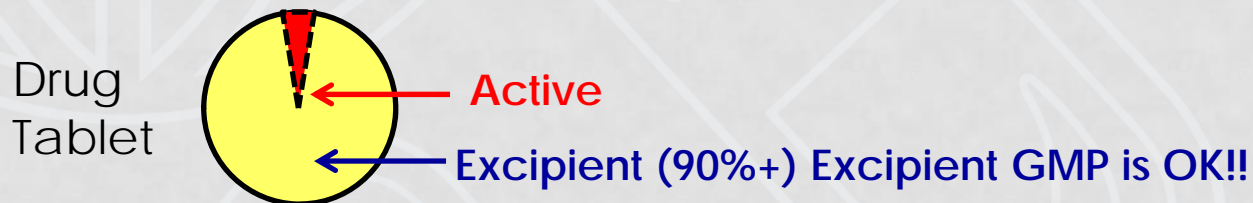
- ▶ FDA inspectors still show up at excipient manufacturing plants expecting ICH Q7 API GMPs!
- ▶ **Viable approaches** to controlling “Atypical Active” quality and appropriate GMPs **are needed** between industry and regulators
 - Appropriate guidance is needed to clarify regulator expectations regarding the expected level of GMP or technical information to support their continued use



Next Steps and Future of Dual Use Excipient Monographs?

Need for Pragmatic Solution

- ▶ Many OTC and generic 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 GMPs or other GMPs, what is the real risk?



- ▶ A realistic balanced regulatory approach based on risk must be developed to provide flexibility
- ▶ Acknowledgement of the unique nature of Atypical Actives in regulatory structure

IPEC – Initial Concepts for Atypical Actives

- ▶ GMPs aligned with Excipient GMPs or other appropriate GMPs for the type of use intended should be acceptable
 - GMP controls should consider a risk-based approach for the manufacture, storage, distribution and use of the ingredients
 - Consider and identify risks from all aspects of manufacture and use

IPEC – Initial Concepts for Atypical Actives

- ▶ Technical considerations may need to be addressed, examples:
 - Composition and potential variability
 - Tighter specifications (when needed)
 - 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

Manufacturers of 'Atypical Actives' – Risk Management

- ▶ Clearly indicate the grade and intended use for the product on the label, COA and product literature
 - E.g., “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
 - Mutual understanding of level of GMPs in place
 - Focus on key control points
- ▶ Conduct risk assessments to determine acceptability of the material as an API or in a particular application
- ▶ Conduct full testing of the incoming material
- ▶ Financial incentive (price premium if additional controls are needed)
- ▶ Close working relationship with suppliers to increase understanding
- ▶ Continually assess supplier(s) – openness and transparency are key to success
- ▶ Agree and document the GMPs that will be implemented for the Atypical Active

Summary

- ▶ It is important that industry and regulators agree on viable approaches for controlling Atypical Active quality and appropriate GMPs
- ▶ Unrealistic expectations by regulators could have a serious impact on availability of OTCs, generics and other medicines
- ▶ Appropriate guidance is needed to clarify regulator expectations so industry knows how to proceed
- ▶ Can USP provide support for addressing the issues related to dual use excipients in monographs?

IPEC-Americas Next Steps

- ▶ Recently established an industry Coalition to address the issues related to Atypical Actives
 - Members: IPEC-Americas, IPEC Europe, GPhA, CRN, AHPA, Sindusfarma (Brazil)
 - In discussion: CPhA and SOCMA-BPTF
- ▶ 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

Next Steps Regarding Monographs?

- ▶ Clarification regarding dual use monographs is needed to address some of the issues related to Atypical Actives
- ▶ 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 parenteral or other applications be addressed in certain monographs, e.g. the JP and ChP have monographs that include 'for injection' and 'for inhalation'?
 - Other options?

THANK YOU!



Special thanks to the following for the presentation content:

Ann VanMeter – Dow Chemical

Katherine Ulman – Dow Corning

Meera Raghuram – Lubrizol

David Schoneker – Colorcon

Iain Moore - Croda