# An FDA Perspective on Atypical Active Ingredients

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# Main Issues with Atypical Active

- GMP – mismatch between Q7 and standard of GMP followed by AA manufacturer (affecting certain expectations, e.g., stability, validation); if so, what constitutes appropriate GMP?

- Specification – might not adequately meet expectation for CGMP for control of components in finished pharmaceutical (ID, strength, purity)

- Labeling – NF or USP might not accurately indicate whether the article is intended to be used as API
  - At the extreme, misbranding involving falsification of labeling of typical APIs (shadow factories) is being found by FDA

# Atypical Actives are Ubiquitous

- Found in OTC and Rx drugs
- Found in approved and unapproved drugs
- Span virtually all routes of administration – internal and external
- About 150 different AA known to be in the US market

# Examples of Atypical Actives*

| ACTIVE NAME | #PROD AS API | #PRODUCT WITH NDA/ANDA AS API | #PROD AS EXCIPIENT | #PROD TOTAL | % AS EXCIPIENT |
|---|---|---|---|---|---|
| BENZOYL PEROXIDE | 417 | 27 | 21390 | 21807 | 98.1% |
| GLYCERIN | 663 | 99 | 14558 | 15221 | 95.6% |
| CALCIUM CARBONATE | 923 | 57 | 11739 | 12662 | 92.7% |
| SILICON DIOXIDE | 586 | 4 | 6864 | 7450 | 92.1% |
| SODIUM CHLORIDE | 1119 | 406 | 11553 | 12672 | 91.2% |
| ALUMINUM HYDROXIDE | 210 | 1 | 1825 | 2035 | 89.7% |
| SODIUM PHOSPHATE –all types | 296 | 116 | 2397 | 2693 | 89.0% |
| TITANIUM DIOXIDE | 3819 | 0 | 23486 | 27305 | 86.0% |
| POVIDONE-IODINE | 506 | 2 | 2700 | 3206 | 84.2% |
| PETROLATUM | 559 | 4 | 2698 | 3257 | 82.8% |
| ASCORBIC ACID | 383 | 11 | 1260 | 1643 | 76.7% |
| DIMETHICONE | 831 | 1 | 1901 | 2732 | 69.6% |
| MAGNESIUM CHLORIDE | 185 | 140 | 397 | 582 | 68.2% |
| PHOSPHORIC ACID | 308 | 8 | 638 | 946 | 67.4% |
| CALCIUM CHLORIDE | 181 | 140 | 317 | 498 | 63.7% |
| METHYL SALICYLATE | 558 | 2 | 855 | 1413 | 60.5% |
| BENZALKONIUM CHLORIDE | 997 | 0 | 1423 | 2420 | 58.8% |
| ISOPROPYL ALCOHOL | 560 | 52 | 572 | 1132 | 50.5% |
| POTASSIUM PHOSPHATE (ALL TYPES) | 236 | 30 | 214 | 450 | 47.6% |
| MENTHOL | 1507 | 2 | 1117 | 2624 | 42.6% |
| FOLIC ACID | 432 | 54 | 278 | 710 | 39.2% |
| SODIUM SULFATE | 266 | 20 | 125 | 391 | 32.0% |
| DEXTROSE MONOHYDRATE | 392 | 358 | 184 | 576 | 31.9% |
| MAGNESIUM HYDROXIDE | 361 | 56 | 97 | 458 | 21.2% |
| ZINC OXIDE | 2361 | 4 | 419 | 2780 | 15.1% |
| POTASSIUM CHLORIDE | 514 | 335 | 34 | 548 | 6.2% |
| **TOTAL** | **19170** | **1929** | | | |

*Data compiled in 2013 from FDA's drug registration and listing data base

# FDA Does Not Have an Official Definition of an *Atypical API*

- For sake of discussion in this forum I understand the following to be a useful definition of an Atypical Active:
  - "Excipient, food additive or cosmetic ingredient used as an active ingredient in pharmaceutical products"

- In any event, AA fall under the same law, regulations, guidance, inspection program and standards (e.g. USP/NF) applicable to all API in all marketed drugs

# FDA Statutory Requirements Governing API

- U.S. FDA regulatory framework for drug components (APIs and excipients) falls under following statutory requirements:
  - Definition in FD&C Act sec. 201(g)(1)(D) for "drug" includes any **component of an article** intended to be a drug
  - FD&C Act sec. 501(a)(2)(B) requires all articles defined as drugs to be manufactured, processed, packed, and held in conformity with CGMP
  - FD&C Act sec. 510 requires site that manufactures a drug in US commerce to register as drug manufacturing establishment
    - Sites manufacturing drugs used only as inactive ingredients are exempt from the requirement (see 21 CFR 207)

# GMP for Atypical Actives = GMP for APIs

- FDA has not promulgated CGMP regulations specifically for APIs or excipients
- FDA has a Compliance Policy Guidance Manual for API inspection(CPGM 7356.002F)
  - ICH Q7 provides FDA's current thinking on what constitutes the best approach
    - **However, alternative approaches to satisfying requirements of FDCA 501(a)(2)(B) might similarly ensure purported purity, identity and quality characteristics**

      **https://www.fda.gov/downloads/ICECI/ComplianceManuals/ComplianceProgramManual/UCM125420.pdf**

# Possible root cause is communication - misunderstanding or lack of transparency

- Reasons given include
  - "There is a lack of transparency on part of suppliers and users of AA"
  - "There is poor or miscommunication between manufacturers of AA and users"
    - "Suppliers and manufacturer of AA might be 2 totally different entities"
- These problems are not unique to AA and can exist just the same with "typical actives"

# In the event of communication issues, what may result?

- Lack of preparedness for an FDA GMP inspection
- Refusal on attempt to import API into US
  - Site will have to register with FDA as an API manufacturing site
- Customer audit identifies deficiencies
  - Supplier ignores audit findings and corrective actions not taken
  - Customer does not have information to properly assess and mitigate risk promptly

# The primary responsibility is owned by the manufacturer of the drug product

- FDA expects all raw material suppliers to be managed by the finished product manufacturer (and product owner)
- FDASIA amended statutory definition of “drug CGMP” to include management of risk and oversight by manufacturer of its suppliers of drug raw materials
  - Supplier qualification program, audits, gaps identified
  - Risk management approaches
  - Are the users of AAs reviewing the monographs that serve as API specification to ensure they are adequate?
    - Strength
    - ID
    - Purity

# Bumps in the road in management of global sourcing of API

- Falsification by API supplier
  - COA
  - Site of manufacture
  - Records of manufacturing and testing
- Lack of access to API site
  - Distance
  - Language barriers

# FDA Warning Letter to API manufacturing site – Misbranding

- “You omitted the name and address of the original API manufacturers on the certificates of analysis (COA) you issued to your customers, and did not include copies of the original batch certificate…….. Customers and regulators rely on COA for information about the quality and sourcing of drugs and their components. Omitting information from COA compromises supply-chain accountability and traceability, and may put consumers at risk.“

# Another FDA Warning Letter to API manufacturing site – Misbranding

- "During our inspection, we found that two of your suppliers were not registered with the FDA as drug manufacturers at the time of inspection. However, you shipped API from these firms to the United States, and declared on importation documents and the COA that you provided to your customers that you were the manufacturer. Your failure to declare the original manufacturers on your importation documents and COA provided to your customers enabled the entry of unregistered firms' products into the United States."

# Another FDA Warning Letter to API manufacturing site – Misbranding

- Moreover, your firm relabeled [API] and included on the label an official stamp that identifies your firm…as the manufacturer of the product, rather than the actual manufacturer... Based on our findings, the active pharmaceutical ingredient is misbranded within the meaning of Section 502(a) of the Act [21 U.S.C. 352(a)] in that its labeling is false or misleading in any particular. See also 21 CFR 201.1(h)(2).

# What is the excipient supplier's responsibility in this instance?

- Awareness that an ingredient it supplies may be used as AA
- Willingness of AA manufacturing site to be audited
- Familiarity with ICH Q7 standard
  - Determining how to best satisfy the intent of recommendations in the standard that appear to be N/A or unmanageable (e.g. stability, validation) would be prudent

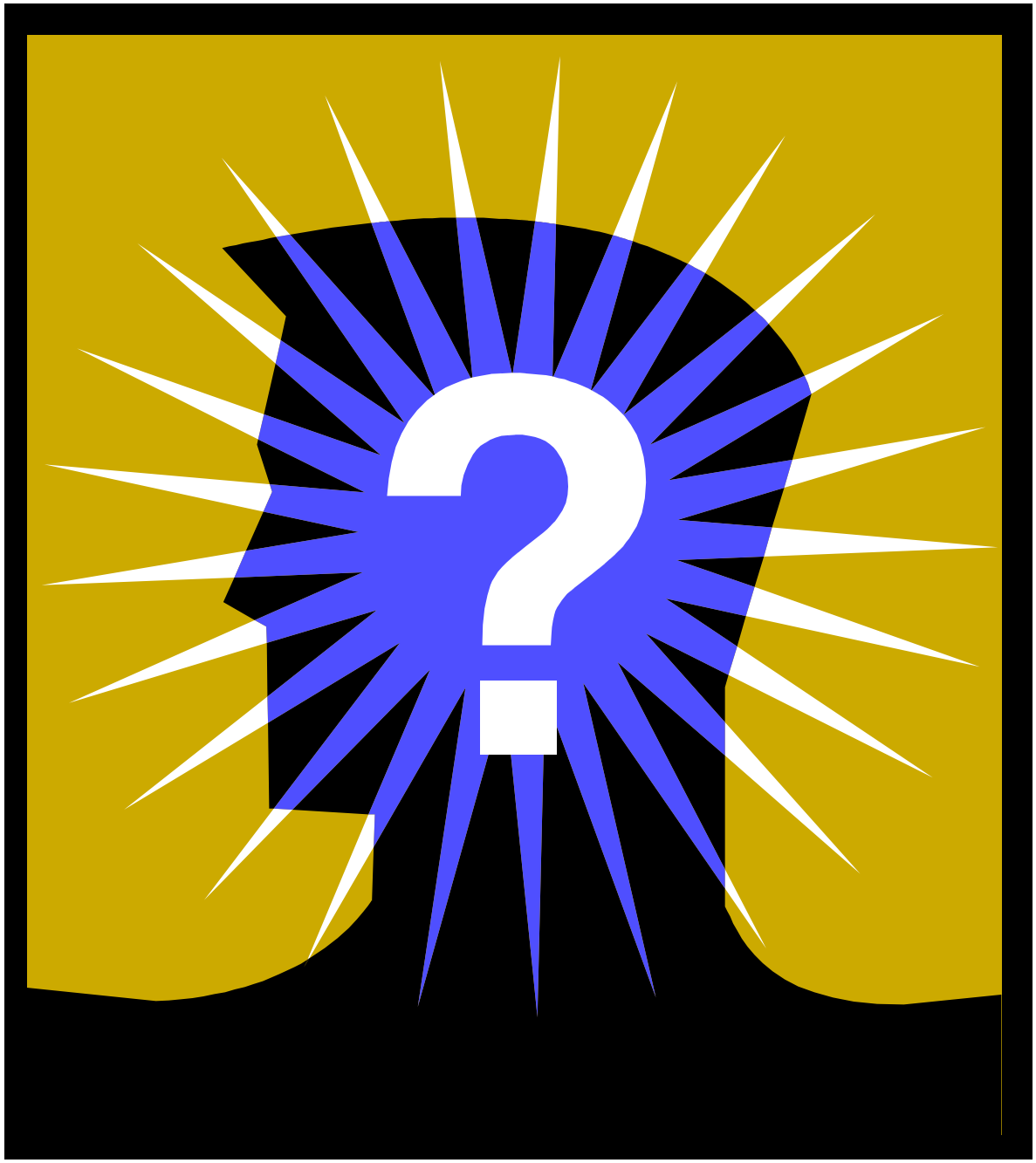
# Current and future status of GMP for Atypical Actives

- Currently nonexistent, so only standard recognizable by FDA is ICH Q7
  - Guidance is nonbinding, and alternative approaches that are considered equal or better are acceptable
- Other regulatory agencies (Health Canada and EMA) have addressed the issue with guidance
- Does FDA need to write guidance?
  - Obvious, fair question to ask
  - What are the pain points when excipient manufacturers attempt to comply with ICH Q7?

# Patients are depending on us to assure safe, effective, high quality drugs are available

# Avoid Sudden Discovery of a Problem by Working as a Team

- Finished product manufacturers (and product owners) are responsible for ensuring products in domestic commerce are safe, suitable and of purported quality
  - same is true for all of their drug components
- Finished product manufacturer (or product owner) ought to be able to tell whether their API supplier is a distributor (pass through or re-packager) or the **original manufacturer of the API**
  - FPM ought to be able to verify the site from which the API originates is compliant
    - Qualification, monitoring and oversight by FPM help ensure the atypical active is suitable for its intended use
- Supplier ought to know how the ingredient is being used (if you don't ask you might not know)

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