API SELECTION DECODED:

Mastering the art of bulk compounding

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Component selection is a vital part of the quality process. Even the best processing and technique cannot compensate for the use of inappropriate starting materials. Component selection is afforded its own section in USP <797> and <795> and the Food and Drug Administration (FDA) has also instituted specific requirements for active pharmaceutical ingredients (APIs) for bulk compounding.

USP Requirements

Nonsterile APIs:

- MUST comply with the criteria in the corresponding USP-NF monograph if one exists
- MUST be accompanied by a CoA that includes specifications and results
- MUST be manufactured by an FDA-registered facility*

Sterile APIs:

- MUST comply with the criteria in the corresponding USP-NF monograph if one exists
- MUST be accompanied by a CoA that includes specifications and results
- MUST be manufactured by an FDA-registered facility*
- Must NOT be labeled with statements such as “not for pharmaceutical use”, “not for injectable use”, “not for human use”, “for lab use only” or other similar statements

*applies to pharmacies in the US

FDA Requirements for 503A Pharmacies

In addition to the above requirements, all APIs must:

1. Comply with an applicable USP-NF monograph if one exists, and the USP chapter on pharmacy compounding

OR

2. Are components of FDA-approved drug products

OR

3. Appear on the FDA's list of bulk drug substances that can be used in compounding (Category 1 list)

The bulks list is divided into three categories:

Category 1: The FDA does NOT intend to take action against compounders compounding with APIs on this list so long as other requirements are met.

Category 2: Associated with significant safety risks: the FDA would consider taking action against a compounder working with a material on this list

Category 3: Not enough evidence: the FDA would consider taking action against a compounder working with a material on this list

A Note on Alternative Monographs

Some substances that are eligible for compounding via inclusion on the Category 1 503A bulks list only have Dietary Supplement monographs, such as methylcobalamin, L-citrulline, and glutathione, among others. In this case, substances that meet other requirements for use as a bulk API, such as coming from an FDA registered facility, may come as alternative grade products.

The FDA's Office of Pharmaceutical Quality published a guidance Acceptability of Standards from Alternative Compendia (BP/EP/JP) that clarifies that it is reasonable to use an alternative quality standard from the British Pharmacopeia (BP), the European Pharmacopeia (EP), or the Japanese Pharmacopeia (JP) in place of the corresponding USP-NF monograph if the monograph specifications are equivalent to or better than those specified in the USP-NF monograph.

Additional Considerations

In addition to requirements set forth by the FDA or by regulatory bodies adopting USP guidelines, there are other considerations for API selection, especially for use in sterile preparations. Though the following are often not addressed on the USP monograph for a given bulk API, heavy metal testing, endotoxin testing, and bioburden (microbe count) testing can all be key parameters for evaluating the quality and appropriateness of a material for use as a sterile product.

A Note on API Requirements per the APF

- The Australian Pharmaceutical Formulary and Handbook (APF) and guidance from the Australian Pharmacy Board also address the appropriate qualification of components.
- Australian manufacturers SHOULD hold a License to Manufacture Therapeutic Goods
- Overseas manufacturers SHOULD hold a certificate of GMP compliance or equivalent
- All ingredients MUST comply with the default standards under the Therapeutic Goods ACT (BP, Ph. Eur., USP-NF) or other relevant standards
- A pharmacist MUST obtain evidence that ingredients comply with default pharmacopeial standards or other relevant standards and are safe for human use (or vet use as applicable)
- A pharmacist SHOULD obtain a CoA, if a CoA is not obtained the pharmacist should have the ingredient tested by a laboratory

References:

1. United States Pharmacopeia and National Formulary. USP <795> Pharmaceutical Compounding – Nonsterile Preparations. Current DocID: GUID-98DCB48D-DC23-4A63-AD2E-01CA8979FB7E_5_en-US
2. United States Pharmacopeia and National Formulary. USP <797> Pharmaceutical Compounding – Sterile Preparations. Current DocID: GUID-A4CAAA8B-6F02-4AB8-8628-09E102CBD703_6_en-US
3. United States Food and Drug Administration. Office of Pharmaceutical Quality: Acceptability of Standards from Alternative Compendia (BP/EP/JP). MAPP 5310.7 Rev 1.
4. Office of Pharmaceutical Quality. Acceptability of Standards from Alternative Compendia (BP/EP/JP). MAPP 5310.7 Rev. 1 Effective Date 12/8/2022. Accessed 10/3/2025.

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