

# Regulatory Gaps Regarding Sugars Used in Injectable Biopharmaceuticals



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Are sugars used to stabilize lyophilized proteins appropriate for the end use?

generally involves numerous highly variable and specialized steps, which must be tightly controlled to ensure the consistent production of pure, potent, and high-quality products. The manufacturing process is particularly critical to the overall safety and effectiveness of protein products. Seemingly trivial changes to the purification process have the potential to alter the purity profile of the product and cause changes to its safety and effectiveness. The ability to identify impurities during the manufacturing process enables manufacturers to design a purification process that will isolate and remove the contaminants.”<sup>1</sup>

Regarding formulation and filling of the purified product, BIO notes that, “a change in any of the equipment, the product contact materials, or methods used in these final steps (including freeze-drying) may affect product integrity.”<sup>1</sup>

From the initial cell lines to fill and finish, high-value, sensitive proteins have been handled in cleanroom conditions with validated and documented processes that meet cGMP criteria for active pharmaceutical ingredients (APIs) or injectable ingredients. The sugars used to stabilize

**I**n the rapidly evolving biopharmaceuticals industry, technical developments frequently outpace regulatory developments. One such area is in current good manufacturing practice (cGMP) guidelines for the manufacture of excipient sugars used to stabilize lyophilized proteins for injectable biopharmaceutical drugs. The industry needs clarification of the cGMP expectations for selecting and qualifying these injectable drug ingredients.

In a 2004 letter to the FDA, the Biotechnology Industry Organization (BIO) stated that:

“the manufacture of all protein products

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these proteins for lyophilization, however, often have not been subjected to similar standards of scrutiny, purity, and documentation.

Since the initial research findings that adding excipients to solutions helped protect protein structures during the folding and unfolding involved in freeze-drying and reconstitution, sugars that are qualified as excipients for oral drugs typically have been utilized. In the early days of the biopharm industry, these sugars were widely available as pharmaceutical ingredients. They are often produced under food-processing GMP conditions, with limited testing of samples for the presence of impurities, and labeled as meeting compendial specifications for orally administered drugs.

Most therapeutic protein drugs must be administered by injection, which requires a much higher purity level than is required for drugs taken orally (Figure 1, p.54). Food-grade sugars used as taste-improving pill coatings are a minor ingredient, and their impurities are filtered by digestion. When stabilizing lyophilized proteins, however, sugars are regularly used in ratios of up to 100:1 by weight, and are injected—sometimes directly into the bloodstream. Adverse patient reactions have been associated with sugar polymers in injectable drugs,<sup>2,3</sup> and protein stability and efficacy can also be compromised by microbial contaminants and trace metal ions.

### CURRENT REGULATIONS

According to Rafidison and Ulman:

“Currently, control of excipient manufacturing and distribution is not a key priority for regulatory authorities or pharmaceutical manufacturers, perhaps due to the fact that most of these excipients originated in the food industry and have generally recognized as safe (GRAS) status. However, with the emergence of novel excipients

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and delivery systems, better control of these materials becomes increasingly important.”<sup>4</sup>

Typically, regulatory agencies are not directly involved in monitoring excipient manufacturers. Or, as indicated in the FDA guidance to investigators of Bulk Pharmaceutical Chemicals (BPC), “inspections of manufacturers of inactive ingredients will only be conducted by special assignment or for cause.”<sup>5</sup>

While the BPC guidance document states that there are situations in which these materials should be produced under the same GMP conditions as finished drugs, it also

A comparison of cGMP requirements for food ingredients, pharmaceutical excipients, and APIs and intermediates.

Table 1a. Current good manufacturing practices for foods (including dietary supplements)

Activity X = Required      O = Optional	Final Product	Raw Material	In Process
Specification	X	X	
Standard operating procedure	X		
Production batch record			
QA batch record review			
Out of specification			
Deviation reporting & investigation*	X		
Label control	X	X	
Certificate of analysis	X		
Raw material testing		X	
Supplier audit		X	
Records retention			
Process validation			
Test method validation**	X		
Finished product testing	X		
Stability testing			
Cleaning validation			
Other volatile impurity testing			
Drug master file + updates			
Annual quality review & report			

\* Hazard Analysis And Critical Control Point Program

\*\* Food Codex

*USP <1078>* notes that many excipients have other applications than for pharmaceutical uses, thus their manufacture often reflects chemical industry standards rather than the pharmaceutical industry.

stresses that such controls are not necessary in most cases. Sugars seem to be regarded in the latter category due to their long-term safe usage in oral applications. Notably, this guidance was last published in May 1994, but that was due to “editorial changes;”<sup>5</sup> the last content revision was in September 1991—more than 14 years ago.

#### Food and Drug Administration (FDA)

The FDA guide to inspection of BPCs is applicable to all BPCs produced in the United States or in foreign countries intended to be exported to the US or to be delivered to a US overseas base. A key part reads:

“Although the GMP regulations under 21 CFR, Parts 210 and 211, apply only to finished dosage for drugs, Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act requires that all drugs be manufactured, processed, packed, and held in accordance with current good manufacturing practice (cGMP). No distinction is made between BPCs and finished pharmaceuticals, and failure of either to comply with cGMP constitutes a failure to comply with the requirements of the Act. There are many cases where GMPs for dosage for drugs and BPCs are parallel. For this reason, the requirements under Part 211 will be used as guidelines for inspection of BPC manufacturers, as interpreted in this document. Although strict

observance of GMPs, approaching or equaling those expected for finished drug products, may be expected in some types of bulk processes, in most others it is neither feasible nor required to apply rigid controls during the early processing steps.”<sup>5</sup>

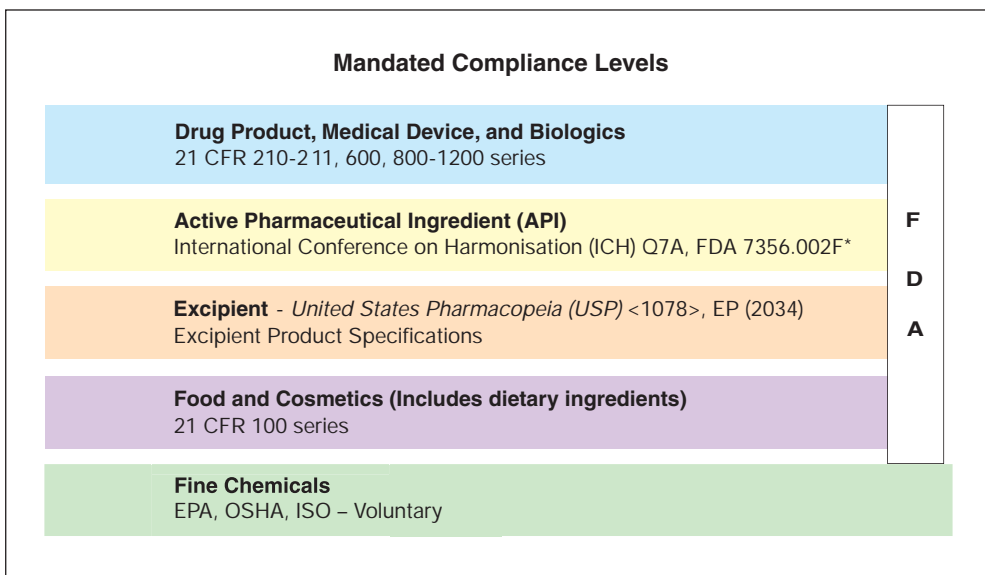
#### United States Pharmacopoeia and National Formulary (USP—NF)

*USP <1078>* “Good Manufacturing Practices for Bulk Excipients — General Guidance” combines existing governmental regulatory GMP principles and international quality management system requirements as developed by the International Organization for Standardization (ISO), using as its framework ISO 9002, which is appropriate for manufacturing. The sections of *USP <1078>* provide an overview; as the chapter says, “no attempt has been made to include details specific to particular excipients.”<sup>6</sup> The chapter notes that many excipients have other applications than for pharmaceutical uses, thus their manufacture often reflects chemical industry standards rather than those of the

Table 1b. Manufacturing requirements for excipients, according to *USP <1078>*<sup>6</sup>

Activity	Final Product	Raw Material	In Process
X = Required    O = Optional			
Specification	X	X	
Standard operating procedure	X		
Production batch record	X		
QA batch record review	X		
Out of specification	X	X	
Deviation reporting & investigation	X		X
Label control	X	X	
Certificate of analysis	X	X	
Raw material testing	X	X	
Supplier audit		X	
Records retention	X	X	X
Process validation	X		X
Test method validation	X		
Finished product testing	X		
Stability testing	X		
Cleaning validation			
Other volatile impurity testing	X		
Drug master file + updates	O		
Annual quality review & report			

Figure 1. Degree of regulatory control by product category, ranked in descending order.



\*FDA Compliance Program Guidance Manual, Program 7356.002F, chapter 56, "Drug Quality Assurance," 2003 Sept.

Table 1c. Manufacturing procedures required for active pharmaceutical ingredients and intermediates according to Q7A.<sup>10</sup>

Activity	O = Optional	Final Product	Raw Material	In Process
Specification		X	X	X
Standard operating procedure		X	X	X
Production batch record		X		X
QA batch record review		X		X
Out of specification		X	X	
Deviation reporting & investigation		X	X	X
Label control		X	X	
Certificate of analysis		X	X	
Raw material testing			X	
Supplier audit			X	
Records retention		X	X	X
Process validation		X		X
Test method validation		X		X
Finished product testing		X		
Stability testing		X		
Cleaning validation		X		
Other volatile impurity testing		X		
Drug master file + updates		O		
Annual quality review & report		X		

pharmaceutical industry.<sup>6</sup> It also states that the end use of the excipient should be identified and considered during facility inspections.

However, as the first guidance that specifically addressed the manufacture of bulk pharmaceutical excipients, the provisions of USP <1078> are more appropriate for oral product specifications. NF monographs typically include the name of the excipient, description, packaging and storage conditions, labeling, identification,

microbial limits, acidity or alkalinity, loss on drying, specific surface area, limit tests, organic volatile impurities, and assay. The NF monograph for sucrose, which is commonly used to stabilize proteins, currently has no compendial testing requirement for microbial limits.<sup>7</sup>

USP standards are enforceable by the FDA for drugs manufactured or sold in the US. The US Pharmacopeial Convention, Inc., is an independent standards organization; the USP—NF that it publishes contains legally recognized standards for more than 3,500 drugs and 250 excipients, vitamins, minerals and botanicals, and is the only official pharmaceutical compendium in the world that is not published by a government agency. It is sold in 131 countries and “acts as a reference point to many regulators in countries that lack an official Pharmacopoeia, which it will continue to do as pharmaceutical manufacturing becomes increasingly globalised.”<sup>8</sup>

**International Conference on Harmonisation (ICH)**

The ICH Q6B guidance “Specifications: Test Procedures and

Acceptance Criteria for Biotechnological or Biological Products” states that “the quality of the materials used in the production of the drug substance (or drug product) should meet standards appropriate for their intended use.”<sup>9</sup> Further, “the quality of the excipients used in the drug product formulation (and in some cases, in the drug substance). . . should meet pharmacopoeial standards, where available and appropriate. Otherwise, suitable acceptance criteria should be established for the nonpharmacopoeial excipients.”<sup>9</sup> Standards that would appear to be appropriate for injectable drugs would be those enumerated in ICH-Q7A, which covers APIs.<sup>10</sup>

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together the regulatory authorities of Europe, Japan, and the United States and experts from the pharmaceutical industry in the three regions. They make recommendations to harmonize the interpretation and application of technical guidelines and requirements for product registration. The FDA is adopting ICH guidances, but publications note that they “represent the FDA’s current thinking . . . and do not operate to bind the FDA or the public.”<sup>10</sup>

#### European Pharmacopoeia (EP)

The EP’s general monograph, “*Substances for Pharmaceutical Use*” (2034) governs active substances and excipients for the production of medicinal products for human or veterinary use. It states, “Unless otherwise indicated or restricted in the individual monographs, a substance for pharmaceutical use. . . is of appropriate quality for manufacture of all dosage forms in which it can be used.”<sup>11</sup> The provisions of EP general chapter 5.10, “Control of impurities in substances for

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pharmaceutical use,” however, exclude excipients from quantitative threshold levels of organic impurities, and say only that, “the general concepts of reporting, identification (wherever possible) and qualification of impurities are equally valid.”<sup>11</sup> The EP also is adopting ICH Guidances.

### CGMP EXPECTATIONS

As tables 1a, 1b and 1c clearly illustrate, the gap in cGMP requirements between food and API quality levels is vast. Even sugars that are truly processed in accordance with *USP* (1078) lack the degree of in-process controls for many of the criteria they have in common with APIs. More importantly, they are produced without key API GMPs, such as cleaning validation and annual quality reviews and reports. While drug makers may be able to perform raw materials tests on *USP*—*NF* sugars to check for particular impurities, they do not have the assurance of consistent impurity profiles provided by the manufacturers of these sugars, or the documented traceability that would come with these profiles.

### BETTER GUIDELINES NEEDED

As previously discussed, most protein-based therapeutics are administered parenterally and oral standards aren’t appropriate for excipients used in their manufacture. In spite of this situation, stabilizing excipients manufactured according to API standards are not yet mandated. Although such products have recently become avail-

able, formulators are often hesitant to incorporate such new materials not specified in regulatory guidelines; the need for regulatory compliance tends to lock in use of existing ingredients. As growing numbers of new drugs in development are protein-based, it is critical that regulatory guidelines be updated to clarify the situation for manufacturers and reduce risk to their products and patients. ♦

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