Glucagon for Injection

Type of Posting	Revision Bulletin
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Expert Committee	Biologics Monographs 1—Peptides and Insulins
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Biologics Monographs 1—Peptides and Insulins Expert Committee has revised the Glucagon for Injection monograph. This revision was requested following the FDA approval of a synthetic glucagon product with the same name as the recombinant product. The purpose for the revision is to update the *Labeling* section to state that the material is of recombinant DNA or of synthetic origin. An additional revision will be proposed for public comment in the future with additional requirements for products of synthetic origin.

The Glucagon for Injection Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Elena Curti, Associate Science & Standards Liaison (301-998-6803 or eac@usp.org).

Glucagon for Injection

DEFINITION

Glucagon for Injection is a sterile lyophilized mixture of the hydrochloride of glucagon with one or more suitable buffering and stabilizing agents. It contains NLT 65% and NMT 110% of the labeled amount of glucagon.

IDENTIFICATION

- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **B. GLUCAGON BIOIDENTITY TESTS** ⟨123⟩**:** Meets the requirements

ASSAY

- **PROCEDURE**

Solution A: Dissolve 16.3 g of monobasic potassium phosphate in 750 mL of water, adjust with phosphoric acid to a pH of 2.7 (± 0.05), add water to 800 mL, add 200 mL of acetonitrile, and degas.

Solution B: Prepare a degassed solution of acetonitrile and water (4:6).

Mobile phase: See *Table 1*. [NOTE—The ratio of *Solution A* to *Solution B* can be adjusted to obtain a retention time of about 21 min for the main peak.]

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	61	39
25[a]	61	39
29	12	88
30	12	88
31	61	39
70	61	39

[a] The end time of the isocratic elution can be adjusted so that the gradient begins after the 4th desamido peak elutes (relative retention time about 1.4). The rest of the program is then adjusted accordingly with this offset.

System suitability solution: Reconstitute a vial of USP rGlucagon RS in 0.01 N hydrochloric acid to obtain a solution having a concentration of about 0.5 mg/mL. Let stand at 50° for 48 h. At least 7% total of all four desamido glucagons should be present in the solution.

Standard solution: Reconstitute a vial of USP rGlucagon RS in 0.01 N hydrochloric acid to obtain a solution having a concentration of about 0.5 mg/mL.

Sample solution: Dissolve an adequate amount of Glucagon for Injection in order to obtain a 0.5-mg/mL concentration of glucagon in 0.01 N hydrochloric acid.

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 214 nm
Column: 3-mm × 15-cm; 3-µm or less packing L1
Column temperature: 45°
Flow rate: 0.5 mL/min
Injection volume: 15 µL

System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 1.5 between the main peak and the first eluting desamido peak. Four peaks eluting after the glucagon peak that correspond to the desamido glucagons are clearly visible, *System suitability solution*
Tailing factor: NMT 1.8 for the glucagon peak, *Standard solution*
Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of glucagon ($C_{153}H_{225}N_{43}O_{49}S$) in the portion of Glucagon for Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
C_U = concentration of the *Sample solution* (mg/mL)

Acceptance criteria: 65%–110%

PERFORMANCE TESTS

- **UNIFORMITY OF DOSAGE UNITS** ⟨905⟩**:** Meets the requirements

IMPURITIES

- **ORGANIC IMPURITIES**

Solution A, Solution B, Mobile phase, System suitability solution, Standard solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.

Sample solution: Dissolve the substance to be examined in water in order to obtain a concentration of 0.5 mg/mL of glucagon.

Analysis
Sample: *Sample solution*
Calculate the percentage of each impurity in the portion of Glucagon for Injection taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response for each impurity
r_T = sum of the responses of all peaks

Acceptance criteria: NMT 14% total of all four desamido glucagons is found, and NMT 31% of total impurities and related compounds is found.

SPECIFIC TESTS

- **WATER DETERMINATION,** *Method I, Method Ic* ⟨921⟩**:** NMT 4.0%
- **pH AND CLARITY OF SOLUTION:** Dissolve it in the solvent and in the concentration recommended in the labeling: the pH of the solution is between 1.7 and 3.5, and the solution is clear.
- **BACTERIAL ENDOTOXINS TEST** ⟨85⟩**:** It contains NMT 10 USP Endotoxin Units/mg.
- **STERILITY TESTS** ⟨71⟩**:** Meets the requirements
- **CONSTITUTED SOLUTION:** At the time of use, it meets the requirements for *Injections and Implanted Drug Products* ⟨1⟩*, Product Quality Tests Common to Parenteral Dosage Forms, Specific Tests, Completeness and clarity of solutions.*

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve as described in *Packaging and Storage Requirements* ⟨659⟩*, Injection Packaging, Packaging for Constitution.*

Change to read:

- **LABELING:** The labeling states that the material is of recombinant DNA ▲or of synthetic▲ (RB 1-Feb-2019) origin.
- **USP REFERENCE STANDARDS** ⟨11⟩
USP rGlucagon RS

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