BỘ Y TẾ
CỤC QUẢN LÝ DƯỢC

CỘNG HOÀ XÃ HỘI CHỦ NGHĨA VIỆT NAM
Độc lập - Tự do - Hạnh phúc

Số 1057 / QLD-ĐK
V/v thay đổi trong quy trình kiểm soát thuốc thành phẩm (bao gồm theo hướng chặt chẽ và bổ sung phép thử mới); thay đổi quy trình phân tích thuốc thành phẩm (bao gồm thay thế hoặc bổ sung phép thử mới); thay đổi bao bì đóng gói sơ cấp không tiếp xúc trực tiếp; thay đổi điều kiện bảo quản của thuốc thành phẩm sau khi hoàn nguyên

Hà Nội, ngày 16 tháng 02 năm 2022.

Kính gửi: Pfizer (Thailand) Ltd.
Địa chỉ: No. 323 United Center Building, Floors 36th and 37th, Silom Road, Silom Sub- District, Bang Rak District, Bangkok Metropolis, Thailand

Cục Quản lý Dược nhận được hồ sơ thay đổi/ bổ sung của Công ty số tiếp nhận 237/TĐNN ngày 05/02/2021 về việc thay đổi trong quy trình kiểm soát thuốc thành phẩm (bao gồm theo hướng chặt chẽ và bổ sung phép thử mới); thay đổi quy trình phân tích thuốc thành phẩm (bao gồm thay thế hoặc bổ sung phép thử mới); thay đổi bao bì đóng gói sơ cấp không tiếp xúc trực tiếp; thay đổi điều kiện bảo quản của thuốc thành phẩm sau khi hoàn nguyên đối với thuốc nước ngoài đã được cấp số đăng ký lưu hành,

Căn cứ Thông tư số 32/2018/TT-BYT ngày 12/11/2018 của Bộ Y tế Quy định việc đăng ký lưu hành thuốc, nguyên liệu làm thuốc,

Căn cứ biên bản thẩm định hồ sơ thay đổi/ bổ sung, Cục Quản lý Dược có ý kiến như sau:

Đồng ý về việc thay đổi trong quy trình kiểm soát thuốc thành phẩm (bao gồm theo hướng chặt chẽ và bổ sung phép thử mới); thay đổi quy trình phân tích thuốc thành phẩm (bao gồm thay thế hoặc bổ sung phép thử mới); thay đổi bao bì đóng gói sơ cấp không tiếp xúc trực tiếp; thay đổi điều kiện bảo quản của thuốc thành phẩm sau khi hoàn nguyên đối với thuốc Solu - Medrol, số giấy đăng ký lưu hành VN-20330-17, cụ thể:

Bảng so sánh các nội dung thay đổi được đóng dấu xác nhận của Cục Quản lý Dược và đính kèm theo công văn này.

Ngoài nội dung được thay đổi trên, tất cả các nội dung khác giữ nguyên như hồ sơ đăng ký thuốc lưu tại Cục Quản lý Dược.

Công ty đăng ký, nhà sản xuất phải chịu trách nhiệm về chất lượng đối với thuốc lưu hành trên thị trường và có trách nhiệm thông báo sự thay đổi này đến các cơ quan liên quan và khách hàng.

Sau 06 tháng kể từ ngày ký công văn này, thuốc trên không được nhập khẩu với các nội dung cũ đã đề nghị thay đổi.

Cục Quản lý Dược thông báo để Công ty biết và thực hiện đúng các quy định của Việt Nam về lưu hành thuốc./.

***Nơi nhận*:**
- Như trên;
- CT. Vũ Tuấn Cường (để b/c);
- Viện Kiểm nghiệm thuốc TƯ;
- Viện Kiểm nghiệm thuốc Tp.HCM;
- Lưu: VT, ĐKT (L).

KT. CỤC TRƯỞNG
PHÓ CỤC TRƯỞNG

CỘNG HOÀ XÃ HỘI CHỦ NGHĨA VIỆT NAM
CỤC QUẢN LÝ DƯỢC
BỘ Y TẾ

Nguyễn Thành Lâm

This grouped variation seeks approval for changes to Solu-Medrol® (methylprednisolone sodium succinate) Powder for Solution for Injection 40 mg Act-O-Vial (AOV) manufactured with sucrose as a replacement for lactose by Pfizer Manufacturing Belgium NV located at Rijksweg 12, 2870 Puurs, Belgium. Pfizer proposes to reformulate to replace the lactose excipient with sucrose and implement other changes resulting from the reformulation, such as an update in shelf life and storage conditions and a change in AOV cap color. Pfizer also proposes to implement process improvements for microbiological control, update the specifications and methods, and contemporize the dossier.

The following detailed list of proposed changes, numbered 1 through 13, is applied for the 40 mg AOV presentation:

1. Replacement of lactose excipient with sucrose, including change in excipient concentration
2. Contemporization of the dossier to describe storage of the bulk in a holding tank under controlled temperature
3. Contemporization of the dossier to establish loading, freezing, and drying temperature range in the lyophilization cycle
4. Lower and upper limit change (<10 fold increase) in batch size resulting from product reformulation
5. Changes in In-Process Controls: Introduction of a second, identical, in-line sterilizing grade filter at the filling line to act as redundant filtration
6. Addition of a bioburden reducing filter prior to the holding tank
7. Addition of a pre-filtration in-process control bioburden test for the unprocessed bulk
8. Contemporization of the compendial reference for Volume of Injection from USP <1> to USP <697>
9. Addition of method and limits for Solubility
10. Replace the compendial Loss on Drying method with an in-house Loss on Drying method
11. Addition of Residual Moisture by Near Infrared (NIR) as alternate test method for Loss on Drying at time of release
12. Change in color of AOV activator cap (to distinguish sucrose-containing formulation) that does not affect product information
13. Change in the storage conditions of the reconstituted product resulting from product reformulation

The implementation of the proposed changes will not have an adverse impact on the quality, safety, and efficacy of Solu-Medrol. No further changes other than those indicated were made.

2.3.P.1. DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

Solu-Medrol 40 mg AOV, manufactured by Pfizer Manufacturing Belgium NV located at Rijksweg 12, 2870 Puurs, Belgium, is a lyophilized drug product that currently includes lactose as an excipient in their composition. Lactose functions as a bulking agent and is derived from bovine milk. All available sources of lactose contain trace amounts of residual bovine proteins. Some patients can experience anaphylactic reactions to these proteins. The

reactions are particularly difficult to recognize when the patients are being administered the product for anaphylaxis. In this case the secondary reaction can be confused with lack of effect. This in turn could lead to repeated dose administration of Solu-Medrol thereby worsening the patient's condition.

Pfizer proposes a change to the current formulation to replace the lactose excipient with sucrose, a similar bulking agent that is not derived from animal sources. Whereas hydrated lactose is used in the current formulation, anhydrous sucrose is used in the proposed formulation; and as a result, the amount of sucrose within the drug product composition is slightly lower than that of the current lactose-containing formulation. Note that for the AOV, only the lower (lyophilized) compartment is affected by the proposed change. There will be no change to the diluent portion of the finished drug product.

A comparison between the current and proposed formulation for Methylprednisolone Sodium Succinate for Solution for Injection 40 mg AOV is presented in Table 2.3.P-1, respectively. The active ingredient is described as the amount of Methylprednisolone hydrogen succinate (active ingredient) per vial, as Methylprednisolone.

Replacement of lactose with sucrose is not expected to affect the stability profile of the active powder/diluent drug product as the proposed sucrose excipient has the same functional characteristics and the amount of active substance per unit dose remains the same.

Table 2.3.P-1. Comparison between Current and Proposed Formulations for 40 mg AOV[a]

Current Formulation		Proposed Formulation		Comments
Constituent	**Amount per Vial**	**Constituent**	**Amount per Vial**	
Methylprednisolone Hydrogen Succinate [b]	40 mg [c]	Methylprednisolone Hydrogen Succinate[b]	40 mg [c]	No change
Monobasic Sodium Phosphate Monohydrate	1.8 mg	Monobasic Sodium Phosphate Monohydrate	1.8 mg	No change
Dibasic Sodium Phosphate Dried	17.5 mg	Dibasic Sodium Phosphate Dried	17.5 mg	No change
Lactose	25 mg	**Sucrose**	**23.7 mg**	**Change in excipient, decreased amount due to change from lactose to sucrose**
Sodium Hydroxide [d,e]	q.s.	Sodium Hydroxide [d,e]	q.s.	No change
Water for Injections [f]	q.s.	Water for Injections [f]	q.s.	No change

Ph. Eur.: the current edition of the European Pharmacopoeia; USP: the current edition of the United States Pharmacopoeia

[a] Does not include a 29% overfill.
[b] Converted into methylprednisolone sodium succinate when Sodium Hydroxide is added.
[c] Expressed in methylprednisolone equivalents.
[d] During the manufacturing process a 10% solution is used. No tests are performed on the 10% solutions. Only the raw materials are tested according to the USP monograph.
[e] To adjust pH.
[f] Removed during the freeze-dry process.

Updated formulations are provided in 3.2.P.1 Composition of the Drug Product – 40 mg AOV.

2.3.P.2. PHARMACEUTICAL DEVELOPMENT

Change in Excipient

In support of the composition change to replace lactose, the selection was based on the following criteria:

- No change in the functional characteristics of the finished drug product
- The excipient must not contain residual bovine proteins and preferably not derived from animal based material
- Safety profile of the excipient should show a very low risk for anaphylaxis

- Provide comparable manufacturing properties

Selection was further limited to excipients already in commercial products administered by the same routes of administration, IV and IM. One of the purposes of lactose in the product is to absorb moisture due to ingress through the rubber stopper over shelf life. Previous studies concluded that the excipient must remain amorphous (such as lactose or any other disaccharide) in the freeze-dried cake and not crystalline (such as with mannitol), because the crystallizable excipient will not absorb the moisture which in turn may lead to degradation of the API via hydrolysis. Therefore, this moisture absorbing property of the replacement excipient is required in order to sequester the water away from the API in the formulation.

Pilot studies were performed using formulations containing different bulking agents, including lactose, sucrose, and trehalose. Accelerated stability studies were conducted to assess moisture and total impurities, and results of the studies showed that sucrose proved to be the most suitable replacement based on equivalent performance in lab lyophilization trials, (low) moisture sorption and accelerated stability studies, and pristine clinical safety and precedented use profile. An initial comparison of the manufacturing properties, density and viscosity, for the current lactose-containing and proposed sucrose-containing formulations is presented in Table 2.3.P-2.

Table 2.3.P-2. Initial Comparison of Current and Proposed Formulation for Bulk Solution Density and Viscosity

	Current Formulation With Lactose	Proposed Formulation With Sucrose
Density (8 °C) (mg/mL)	1.055	1.051
Density (20 °C) (mg/mL)	1.054	1.050
Viscosity (8 °C) (mPa-s)	2.388	2.364
Viscosity (20 °C) (mPa-s)	1.702	1.672

Engineering batches for the 40 mg AOV were executed in Puurs under lot number W56950, respectively, using the current manufacturing process and production equipment. An assessment of filling was performed, with favorable comparability for the AOV presentation. The actual fill weight average for the AOV engineering batch was equal to the current target fill weight of 1.055 g for the lower compartment (product solution prior to lyophilization). Methylprednisolone assay results for the engineering lot, shown in Table 2.3.P-3, demonstrate that the proposed formulation containing sucrose provides comparable results with that of the current formulation for active substance content using the current manufacturing process at the current AOV target fill weights.

Table 2.3.P-3. Methylprednisolone Assay Results from Engineering Batches

Stage	Sample #	Methylprednisolone Assay (mg/cont or mg/mL)	
		Acceptance Criteria	40 mg AOV Batch W56950 (mg/mL)
Beginning	1. 2. 3. 4. 5.	38.0 to 42.0 mg/cont or mg/mL	40.1 40.2 40.1 40.3 40.3
Middle	1. 2. 3. 4. 5.	38.0 to 42.0 mg/cont or mg/mL	40.2 40.4 40.3 40.0 40.2
End	1. 2. 3. 4. 5.	38.0 to 42.0 mg/cont or mg/mL	40.2 40.5 40.0 40.3 40.4

Data demonstrating the quality and suitability of the proposed excipient change and Vial target fill weight change and are provided in Section 3.2.P.2.2 Pharmaceutical Development Drug Product and Section 3.2.P.2.3 Pharmaceutical Development Manufacturing Process Development.

Pfizer does not intend to submit any non-clinical data in support of the proposed formulations for the Solu-Medrol 40 mg AOV because sucrose has a well-established toxicological safety profile and is present at a similar level in the formulation as lactose. The criteria for a waiver of clinical bioequivalence (BE) studies for parenteral solutions, as laid out in Committee for Medicinal Products for Human Use (CHMP) guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1), indicates the "BE studies are generally not required if the test product is to be administered as an aqueous IV, IM and subcutaneous solution containing the same active substance as the currently approved product." The in vivo BE of the proposed formulation for Solu-Medrol 40 mg AOV is self-evident since it is administered as an aqueous IV or IM true solution, containing the same active ingredient at the same concentration and quantity as the currently approved Solu-Medrol formulations. Pfizer considers sucrose to be a well-established excipient. The level of sucrose in the proposed formulations is unlikely to cause a safety concern when used in accordance with the product information.

Compatibility

Using the samples from the long-term stability batches, an admixture study using samples at the end of expiry is planned for the reformulated 40 mg drug product. Pfizer commits to providing admixture stability data upon completion of the admixture stability study, as provided in Section 3.2.R.

2.3.P.3. MANUFACTURE

Batch Size Changes

The current batch size range for Methylprednisolone Sodium Succinate for Solution for Injection 40 mg AOV is "75,830 – 462,113 units (80.0 kg – 487.53 kg)". Pfizer proposes to increase the lower batch size limit of the 40 mg AOV to 109 kg, which is within the existing range. The proposed changes to the lower batch size limit are within the current batch size, resulting from harmonizing the (bulk) reformulation across presentations to replace lactose with sucrose, and has been validated.

Pfizer also proposes to increase the upper limit of the 40 mg AOV batch size from 487.53 kg to 593 kg. This proposed increase is within 10 times of the current batch size. The increased batch size has been validated and the validation report is provided in Section 3.2.P.3.5 Process Validation and Evaluation – 40 mg AOV.

A comparison between the current and the proposed batch size range for Methylprednisolone Sodium Succinate for Solution for Injection, 40 mg AOV is presented in Table 2.3.P-3.

Table 2.3.P-4. Comparison Between Current and Proposed Batch Size Range for 40 mg AOV

Current Batch Size Range	Proposed Batch Size Range
75,830 – 462,113 units (80.0 kg – 487.53 kg)	**109 kg (103,520 units) – 593 kg (562,119 units)**

The current media fill studies available at the Puurs site support the proposed change, and therefore, no additional studies are required.

The amended batch formula is provided in Section 3.2.P.3.2 Batch Formula – 40 mg AOV.

Fill Weight Parameter

Fill weight of the lyophilized solution is a critical process parameter, impacting the strength and efficacy, based on correct dosage, of the drug product. For the Solu-Medrol 40 mg AOV drug product, Pfizer proposes to add the In-Process Control fill weight of the bulk solution prior to lyophilization to the Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls and Section 3.2.P.3.4 Control of Critical Steps and Intermediates as part of CTD contemporization and to reflect current manufacturing practices. The current target fill weight for the 40 mg AOV is 1.055 g. The AOV target fill weight includes a 29% overfill to achieve 1 mL withdrawable volume. Fill weight upper and lower limits will be added to Section 3.2.P.3.4 rather than the target.

A comparison of the current and proposed fill weights for Methylprednisolone Sodium Succinate for Solution for Injection 40 mg AOV (lower compartment) is presented in Table 2.3.P-4.. A comparison of the current and proposed fill weights for the Water for Injection (WFI) in the upper AOV compartment is presented in Table 2.3.P-6.

Table 2.3.P-5. Comparison Between Current and Proposed Fill Weights for 40 mg AOV (Lower Compartment)

Current Fill Weight		Proposed Fill Weight	
Target	**Range**	**Target**	**Range**
1.055 g	N/A	N/A	1.030 g – 1.080 g

Table 2.3.P-6. Comparison Between Current and Proposed Fill Weights for 40 mg AOV (Upper Compartment)

Current Fill Weight		Proposed Fill Weight	
Target	**Range**	**Target**	**Range**
1.220 g	N/A	N/A	1.186 g – 1.258 g

Process validation was performed using the proposed fill weight ranges with the proposed reformulated drug products at the proposed batch sizes. Section 3.2.P.3.5 Process Validation – 40 mg AOV is provided in addition to amended 3.2.P.3.3 and 3.2.P.3.4 sections.

Storage in Holding Tank

As part of contemporization of the registration and to reflect current manufacturing practices, the use of a holding tank for storage of the bulk under controlled temperature is described in the overview and manufacturing process flowchart of Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls. Process validation was performed, including challenge time of 102 hours from start of API addition to start of lyophilization. Details of the process validation are provided in Section 3.2.3.5 Process Validation and/or Evaluation.

While a maximum 14-day hold time within the tank has been established, the bulk

holding time within the tank is limited in practice by the maximum process restriction time of 102 hours from API addition until start of lyophilization, and Section 3.2.P.3.3 reflects this maximum 102 hour in-process control processing time.

Table 2.3.P-7. Comparison Between Current and Proposed Storage Conditions and Process Restriction Time

Current Conditions		Proposed Conditions	
Step	**Parameter Description**	**Step**	**Parameter Description**
Storage in Holding Tank	N/A	Storage in Holding Tank	**The bulk in the holding tank is kept under controlled temperature and transferred to the filling lines.**
Process Restriction Time	N/A	Process Restriction Time	**Maximum of 102 hours from start of API addition to start of lyophilization**

Lyophilization Cycle Change

Addition of lyophilization parameters to Section 3.2.3.4 Control of Critical Steps and Intermediates is proposed as part of contemporization of the registration. A comparison of current and proposed for the lyophilization cycle is presented in Table 2.3.P-8 for the Solu-Medrol 40 mg AOV.

Table 2.3.P-8. Comparison Between Current and Proposed Freeze Dry Parameters for 40 mg AOV

Current Freeze Dry Parameters		Proposed Freeze Dry Parameters	
Step	**Parameter Description**	**Step**	**Parameter Description**
Loading and Freezing	N/A	Loading and Freezing	Load filled vials under aseptic conditions into a lyophilization chamber and freeze vials to -40 ± 5 °C.
Drying	N/A	Drying	Raise the shelf temperature in the chamber gradually up to 55°C ± 5°C at a pressure maximum of 0.400 ± 0.1 mbar.

IPC: Redundant Sterile Filtration, Bioburden Reducing Filtration

The drug product manufacturing at Pfizer, Puurs is described in 3.2.P.3.3 Description of Manufacturing Process and Process Controls. The following manufacturing process changes are proposed:

- Introduction of a second identical in-line sterilizing grade filter placed in series between holding tank and surge vessel at the filling line (redundant filtration).
- IPC bioburden sample is taken before the first redundant filter at filling line.

- Introduction of an extra in-line filter integrity test at the filling line. Prior to the start of the filling, a pre-use filter integrity test of both in-line sterilizing grade filters is performed. After completion of the filling process, a post-use filter integrity test is performed. The second redundant filter will be post-use tested only if the post-filtration filter integrity test of the first redundant filter failed.

- Introduction of a bioburden reducing filter after the mixing tank and prior to the holding tank.

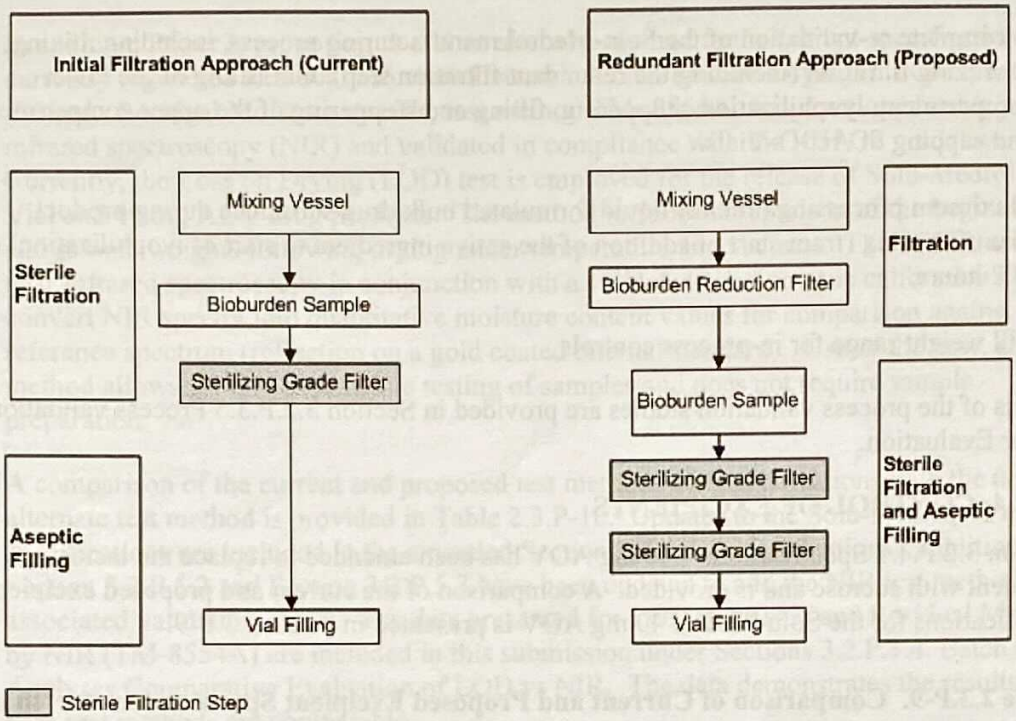
A redundant sterilizing filter close to the filling step in the manufacturing process is introduced. This provides enhanced microbial control during the drug product manufacturing process.

The introduction of the redundant filter reduces the risk related to sterility if one of the two filters fails prior to the filling step. If the post-filtration filter integrity test of the first filter fails, the redundant filter is tested. If the result of this test meets the acceptance criteria, it is considered that the sterile filtration is successful. In compliance with the current GMP standards, the potential microbial burden of the process is controlled through an additional bioburden sampling before the first filter at the filling line. Figure 2.3.P-1 outlines the differences before and after the introduction of the redundant filtration step.

The bulk drug product is filtered through a 0.22 µm bioburden reducing filter from the formulation tank into a mobile holding tank. After the filtration is complete, the holding tank is transferred to the filling lines. If storage is required, the jacketed holding tank will be stored under controlled temperature prior to connection to the filling line. The maximum processing time for liquid formulated bulk drug substance during product manufacturing (from start of addition of the active ingredient to start of lyophilization) is 102 hours.

The sterile filtration at the filling line is performed with two sterile 0.22 µm membrane filters in series. The first in-line sterilizing filter at the filling line undergoes membrane integrity testing both before and after sterile filtration to ensure that the filters are intact. A second identical in-line sterilizing grade filter is placed in series between holding tank and surge vessel (redundant filtration). The second redundant filter will be pre-filtration tested and possibly post-filtration tested, if the post-filtration filter integrity test of the first filter fails. For the filter integrity testing, the sterilizing grade filter is tested via bubble point determination using a qualified filter integrity tester.

Figure 2.3.P-1. Overview of the Initial Filtration and Redundant Filtration Approach



For clarification purposes, the first filter of bulk drug product is termed a bioburden reducing filter, while the filters prior to filling (including redundant filtration) are called sterile filters. Both the bioburden reducing filter and sterile filters are 0.22 µm filters.

Process Validation

A complete process validation section is provided in Section 3.2.P.3.5 that summarises all validations that have occurred for the Solu-Medrol 40 mg AOV drug product at Pfizer, Puurs, Belgium.

Process validation was performed to support process changes to the filling line. Three successful process validation lots were used to demonstrate that the Solu-Medrol 40 mg AOV drug product manufacturing process, executed within established operating parameters, consistently produced Solu-Medrol drug product that met its pre-determined quality attributes.

The AOV process validation included:

- Sucrose-containing formulation for Solu-Medrol drug product
- Batch size range of 109 kg to 593 kg

- Conditions during freezing of vials to -40°C ± 5°C and an increase in the shelf temperature for the drying stage of lyophilisation cycle to 55°C ± 5°C.

- A complete re-validation of the Solu-Medrol manufacturing process, including mixing, sterilizing filtration (including the redundant filtration step), vial filling of the lower compartment, lyophilization, stoppering, filling and stoppering of the upper compartment and capping of Act-O-Vials.

- Maximum processing time for liquid formulated bulk drug substance during product manufacturing (from start of addition of the active ingredient to start of lyophilization) of 102 hours.

- Fill weight range for in-process controls

Details of the process validation studies are provided in Section 3.2.P.3.5 Process validation and/or Evaluation.

2.3.P.4. CONTROL OF EXCIPIENTS

Section 3.2.P.4.1 Specifications – 40 mg AOV has been amended to replace the lactose excipient with sucrose and is provided. A comparison of the current and proposed excipient specifications for the Solu-Medrol 40 mg AOV is presented in Table 2.3.P-9.

Table 2.3.P-9. Comparison of Current and Proposed Excipient Specifications for 40 mg AOV

Current Excipient		Proposed Excipient	
Ingredients	**Specifications**	**Ingredients**	**Specifications**
Lactose	USP	**Sucrose**	USP, Ph Eur., JP

Ph. Eur.: Current version of the European Pharmacopoeia
USP: Current version of the United States Pharmacopoeia
JP: Current version of the Japanese Pharmacopoeia

2.3.P.5. CONTROL OF DRUG PRODUCT

Specifications, Residual Moisture Alternate Test Method

Pfizer proposes to replace the Loss on Drying method (USP <731>) with an In-House Loss on Drying method (GP0143) that provides additional details for execution. GP0143 uses the same principles and basic steps as USP <731> for drying a sample of prescribed quantity under specified conditions in an oven, and calculating the loss of mass as % m/m. However, significant parameters and details are absent from the United States Pharmacopoeial method; these have been specified in GP0143 to allow for improved setup, execution of the method, and calculation. For example, GP0143 specifies to dry the substance for 3 hours at 105°C under vacuum, whereas USP <731> states to dry the substance "in an oven within a specified temperature range." Further, only GP0143 provides instructions for cleaning the glass container to determine the tare weight and equations for calculating the difference in mass before and after drying, normalized to the USP and In-House methods are equivalent, with

GP0143 offering significantly more details for performing the method. USP <731> Loss on Drying and GP0143 Loss on Drying are both provided in Section 3.2.R.

In addition, Pfizer is proposing to add an alternate method to the current specifications for the currently registered Residual Moisture Determination – Loss on Drying (GP0143) test method. Residual Moisture by NIR, test method TM- 8554A, was developed using near infrared spectroscopy (NIR) and validated in compliance with the ICH Q2 guideline. Currently, the Loss on Drying (LOD) test is employed for the release of Solu-Medrol 40 mg Vial and 40 mg AOV drug products. The method includes comparison of the beginning and end sample weights following drying under temperature and vacuum. TM-8554A utilizes near infrared spectroscopy in conjunction with a validated chemometric calibration model to convert NIR spectra into quantitative moisture content values for comparison against a reference spectrum (reflection on a gold coated internal standard). Use of the new, alternate method allows for non-destructive testing of samples and does not require sample preparation.

A comparison of the current and proposed test methods and specifications with the new alternate test method is provided in Table 2.3.P-10. Updates to the Solu-Medrol 40 mg AOV specifications are included in the amended Section 3.2.P.5.1 Specifications. Additionally, Section 3.2.P.5.2 and Section 3.2.P.5.3 have been updated to add the NIR test method and associated validation report. The data presented for LOD (GP0143) and Residual Moisture by NIR (TM-8554A) are included in this submission under Sections 3.2.P.5.4. Batch Analyses Comparative Evaluation of LOD vs NIR. The data demonstrates the results from both test methods are comparable.

Pfizer proposes to add the test and limits for Solubility (by visual inspection) and contemporize the compendial reference for Volume of Injection and replace USP<1> with USP<697>. The Volume of Injection test is a current compendial method and does not require additional validation. The Solubility test is being added for contemporization and alignment of the specifications across all markets. The test for solubility is a visual test method, and as such, method validation is not necessary. Therefore, no additional method validation is provided in Section 3.2.P.5.3 Validation of Analytical Procedures to support the test addition and replacement of compendial methods.

No other changes to the specifications are proposed. There were no changes to the currently registered analytical procedures. The implementation of the alternate proposed NIR method will not have an adverse impact on quality, safety, and efficacy the Solu-Medrol 40 mg AOV drug product.

Table 2.3.P-10. Comparison of Present and Proposed Specifications for Methylprednisolone Sodium Succinate 40 mg Vial

Test	Method		Acceptance Criteria		Comments
	Current	Proposed	Current	Proposed	
Lyophilized Cake					
Description: lower compartment	Visual	Visual	White to off-white cake	White to off-white cake	No change
Description: upper compartment	Visual	Visual	Clear colourless solution	Clear colourless solution	No change
Residual Moisture Determination - Loss on drying (LOD) or **- Residual Moisture by NIR [a]**	USP <731> ---	**GP0143** **or** **TM-8554A**	NMT 2.0% ---	NMT 2.0% NMT 2.0%	**Descriptor heading added for clarification. Test method and limits replaced by Residual Moisture (LOD or NIR). Replaced with In-House method, added alternate method, footnote added to reflect testing at release only.**
Uniformity of Dosage Units (UDU) by Mass Variation (MV) [a]	USP <905>	USP <905>	Meets USP requirements	Meets USP requirements	No change
Reconstituted solution					
Methylprednisolone Identification – IR [a]	USP <197M>	USP <197M>	Positive	Positive	No change
Methylprednisolone - Identification [a] - Assay	USP or HPLC (TA5425) or UPLC (TM1155A)	USP or HPLC (TA5425) or UPLC (TM1155A)	Positive 36.0 to 44.0 mg/mL (90% to 110%)	Positive 36.0 to 44.0 mg/mL (90% to 110%)	No change No change
Free Methylprednisolone (MR)	USP or HPLC (TA5425) or UPLC (TM1155A)	USP or HPLC (TA5425) or UPLC (TM1155A)	NMT 6.6%	NMT 6.6%	No change
Volume of Injection [a]	USP <1>	**USP <697>**	Meets USP requirements	Meets USP requirements	**Contemporize to add current compendial method; no change in analysis**
pH	Potentiometric	Potentiometric	7.0 to 8.0	7.0 to 8.0	No change
Sterility [b]	USP <71>	USP <71>	Meets USP requirements	Meets USP requirements	No change
Bacterial endotoxins [a]	USP <85>	USP <85>	Meets USP requirements (NMT 0.17 EU/mg)	Meets USP requirements (NMT 0.17 EU/mg)	No change
Constituted Solution [b]	USP <1>	USP <1>	Meets USP requirements	Meets USP requirements	No change
Particulate Matter	USP <788>	USP <788>	Meets USP requirements	Meets USP requirements	No change

Table 2.3.P-10. Comparison of Present and Proposed Specifications for Methylprednisolone Sodium Succinate 40 mg Vial

Test	Method		Acceptance Criteria		Comments
	Current	Proposed	Current	Proposed	
Solubility	---	**Visual**	---	**NMT 60 seconds**	**Inclusion of a new parameter**

Current Footnotes	Proposed Footnotes
[a] GP = general procedure; EU= endotoxin units; NMT = not more than; TA/TM = test/assay method; USP = current edition of the United States Pharmacopoeia	**GP = general procedure; EU= endotoxin units; NMT = not more than; TA/TM = test/assay method; USP = current edition of the United States Pharmacopoeia; UHPLC = ultrahigh-performance liquid chromatography**
[b] Tested at release only	**a. Tested at release only**
[c] Addiitonal ID test, not performed routinely	**b. Test performed during initial testing period and at the end of shelf-life**
[d] Test performed during initial testing period and at the end of shelf-life	---

Changes in Batch Size

Solu-Medrol 40 mg AOV has been manufactured according to the proposed formulation (with sucrose replacing lactose) at the proposed larger batch size. In support of the increase in batch size, a comparative batch evaluation was performed between the current and proposed formulations at the larger batch size. The results of this evaluation demonstrate equivalency between the current formulation and the proposed sucrose-containing formulation, inclusive of the manufacturing process changes. The data is provided in Table 2.3.P-11. Batch analysis data for three batches formulated with sucrose instead of lactose and manufactured at the larger batch size is provided in Section 3.2.P.5.4 Batch Analyses – 40 mg AOV.

Table 2.3.P-11. Comparative Batch Data - Current vs Proposed Formulation of Solu-Medrol 40 mg AOV

Formulation			Current Formulation with Lactose			Proposed Formulation with Sucrose		
Batch Number			**DL9482**	**DN9587**	**DW1745**	**DW1572**	**DW1573**	**EA7495**
Manufacturing Date			**April 2020**	**May 2020**	**May 2020**	**June 2020**	**June 2020**	**July 2020**
Test	**Method**	**Limit**	**Test Results**					
Lyophilized Cake								
Description - Lower compartment - Upper compartment	Visual	White to off-white cake A clear colourless solution	Meets Test Meets Test	Meets Test Meets Test	Meets Test Meets Test	Meets test Meets test	Meets test Meets test	Meets test Meets test
Residual Moisture Determination - Loss on drying (LOD) or - Residual Moisture by NIR [a]	GP0143 OR TM-8554A	NMT 2.0 %	0.1%	0.2%	0.2%	0.1%	0.2%	0.1%
Uniformity of Dosage Units (UDU) by Mass Variation (MV)	USP <905>	Meets USP requirements	Meets Test	Meets Test	Meets Test	Meets Test	Meets Test	Meets Test
Reconstituted Solution								
Methylprednisolone Identification – IR	USP <197M>	Positive	N/A	N/A	N/A	Positive	Positive	Positive
Methylprednisolone - Identification - Assay	UHPLC	 Positive 36.0 to 44.0 mg/mL (90% to 110%)	 Positive 39.9 mg/mL	 Positive 40.7 mg/mL	 Positive 40.2 mg/mL	 Positive 40.3 mg/mL	 Positive 40.0 mg/mL	 Positive 40.0 mg/mL
Free Methylprednisolone (MR)	UPLC (TM1155A)	NMT 3.0%	0.9%	1.0%	1.1%	1.0%	1.1%	0.7%

Table 2.3.P-11. Comparative Batch Data - Current vs Proposed Formulation of Solu-Medrol 40 mg AOV

Formulation			Current Formulation with Lactose			Proposed Formulation with Sucrose		
Batch Number			DL9482	DN9587	DW1745	DW1572	DW1573	EA7495
Manufacturing Date			April 2020	May 2020	May 2020	June 2020	June 2020	July 2020
Test	Method	Limit	Test Results					
pH	Potentiometrically	7.0 to 8.0	7.6	7.5	7.6	7.6	7.6	7.6
Volume of injection	USP <697>	Meets USP requirements	Meets Test	Meets Test	Meets Test	Meets Test	Meets Test	Meets Test
Sterility	USP <71>	Meets USP requirements	Meets Test	Meets Test	Meets Test	Meets Test	Meets Test	Meets Test
Bacterial endotoxins	USP <85>	Meets USP requirements (NMT 0.17 EU/mg)	Meets Test	Meets Test	Meets Test	Meets Test	Meets Test	Meets Test
Particulate Matter	USP <788>	Meets Ph. Eur. requirements	Meets Test (597 part/cont at 10 µm; 6 part/cont at 25 µm)	Meets Test (245 part/cont at 10 µm; 2 part/cont at 25 µm)	Meets Test (345 part/cont at 10 µm; 2 part/cont at 25 µm)	Meets Test (818 part/cont at 10 µm; 5 part/cont at 25 µm)	Meets Test (42 part/cont at 10 µm; 1 part/cont at 25 µm)	Meets Test (165 part/cont at 10 µm; 5 part/cont at 25 µm)
Constituted Solution	USP <1>	Meets USP requirements	Meets Test	Meets Test	Meets Test	Meets Test	Meets Test	Meets Test
Solubility	Visual	NMT 60 seconds	---	---	---	8 seconds	8 seconds	12 seconds

GP = general procedure; EU= endotoxin units; NMT = not more than; TA/TM = test/assay method; USP = current edition of the United States Pharmacopoeia

2.3.P.7. CONTAINER CLOSURE SYSTEM

The variation for the orange AOV activator cap for the preservative-free lactose-containing Solu-Medrol 40 mg AOV drug product is currently under review with the Vietnam health authority. Pfizer is proposing the replacement of the orange high density polyethylene (HDPE) AOV activator cap under review with a white colored one of the same material from supplier Gerresheimer in order to distinguish the new sucrose-containing formulation for the 40 mg AOV strength. A Certificate of Conformance for the proposed white cap is provided in Section 3.2.R Certificates of Conformance.

For the AOV activator cap, there are no changes to the dimensions, specifications or description of the container closure system.

Table 2.3.P-12 provides a comparison of the current and proposed cap colors.

Table 2.3.P-12. Comparison of the Current and Proposed Cap Color

Presentation	Current Cap Color	Proposed Cap Color
40 mg AOV (activator cap)	Orange (Preservative-Free, lactose-containing)	**White (Preservative-Free, sucrose-containing)**

The container closure section of the dossier has been updated to include the AOV activator cap color in the specifications and description of the container closure system. The updated Section 3.2.P.7.1, Section 3.2.P.7.2, and Section 3.2.P.7.3 are provided for the Solu-Medrol 40 mg AOV.

2.3.P.8. STABILITY

Replacement of Lactose with Sucrose, Batch Size and Manufacturing Changes

With respect to the formulation change to replace lactose with sucrose and in support of the batch size changes and manufacturing changes, stability evaluation of Solu-Medrol 40 mg AOV was conducted on three consecutive batches. Information on the batches tested is summarized in Table 2.3.P-13.

Table 2.3.P-13. Methylprednisolone Sodium Succinate 40 mg AOV Batches Manufactured with Sucrose, Proposed Batch Size Range

Batch Number	Storage Conditions	Storage Period	Data Available	Mfg. Date	Stability Start Date	Lot Size (kg)	Mfg. Site
X30046	30°C/75%RH	24 months	24 months	Jun 2018	Jun 2018	109	Pfizer Puurs
X30047	30°C/75%RH	24 months	24 months	Jun 2018	Jul 2018	593	Pfizer Puurs
X79092	30°C/75%RH	24 months	24 months	Aug 2018	Sep 2018	593	Pfizer Puurs
X30046	40°C /75%RH	06 months	06 months	Jun 2018	Jun 2018	109	Pfizer Puurs
X30047	40°C /75%RH	06 months	06 months	Jun 2018	Jul 2018	593	Pfizer Puurs
X79092	40°C /75%RH	06 months	06 months	Aug 2018	Sep 2018	593	Pfizer Puurs

RH = Relative Humidity

Stability studies were also conducted to support the reconstitution hold time. Batch information for these studies is presented in Table 2.3.P-14. A summary of the stability results is described in Section 3.2.P.8.1 Stability Summary and Conclusion, and detailed stability data are provided in Section 3.2.P.8.3 Stability Data.

Table 2.3.P-14. Methylprednisolone Sodium Succinate 40 mg AOV Batches Manufactured with Sucrose, Proposed Batch Size for Reconstituted Stability

Batch Number	Storage Conditions (Unreconstituted Vial)	Storage Condition After Reconstitution	Test Intervals (Hours)
X79092	24 months at 30°C/75% RH	30°C	0, 12, 24, 48
X79092	24 months at 30°C/75% RH	5°C	0, 12, 24, 48

RH = relative humidity.

Based on evaluation of the available in-use reconstituted stability data for the 40 mg AOV drug product, the testing time point at which all specifications were met before an OOS result was observed is provided in Table 2.3.P-15. Comparison of the current and proposed reconstituted stability is provided in Table 2.3.P-16.

Table 2.3.P-15. Stability of the Reconstituted Drug Product[a]

Storage Condition	40 mg AOV
30°C	24 h
5°C	48 h

a. The testing time point (hours) at which all specifications were met before an OOS result was observed.

Table 2.3.P-16. Comparison Between Current and Proposed Reconstituted Stability

Current	Proposed
Store reconstituted solution below 25°C and use within 24 hours.	**Use within 24 hours if stored at or below 30°C or within 48 hours of reconstitution if stored at 2°C to 8°C.**

Stability Conclusion

Based on the stability data for the Solu-Medrol 40 mg AOV drug product formulated with sucrose (as a replacement for lactose) and manufactured at the new batch sizes with redundant filtration, the 24 months expiration dating period is supported for Solu-Medrol 40 mg Act-O-Vial when stored in commercial packaging at or below 30°C. Based on the stability data, the proposed in-use reconstituted stability for the Solu-Medrol 40 mg AOV when stored in commercial packaging is to "Store reconstituted solution below 30°C and use within 24 hours OR Store reconstituted solution at 2-8°C and use within 48 hours." Section 3.2.P.8.1, Stability Summary and Conclusion – Solu-Medrol 40 mg AOV has been amended to reflect the change; the product information has been revised accordingly.