

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211728Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

<input checked="" type="checkbox"/> Approval
<input type="checkbox"/> Approval with Post-Marketing Commitment
<input type="checkbox"/> Complete Response

NDA 211728 Assessment #1

Drug Product Name	JELMYTO™ (mitomycin) for pyelocalyceal solution
Dosage Form	Lyophilized solid for pyelocalyceal solution
Strength	40 mg per vial
Route of Administration	Instillation into the pyelocalyceal system
Rx/OTC Dispensed	Rx
Applicant	UroGen Pharma Ltd.
US agent, if applicable	Jim Ottinger

Submission(s) Assessed	Document Date	Discipline(s) Affected
SND 0002	7/11/2019	All: DS, DP, OPMA, Micro, Biopharm
SND 0003	8/30/2019	All
SND 0004	9/5/2019	All
SND 0005	9/6/2019	All
SND 0006	9/25/2019	All
SND 0007	9/30/2019	All
SND 0008 New NDA	10/18/2019	All
SND 0009	10/21/2019	All
SND 0011	11/1/2019	All
SND 0014	12/13/2019	All
SND 0016	12/19/2019	All
SND 0017	12/31/2019	All
SND 0019	1/21/2020	All
SND 0021	1/27/2020	All
SND 0023	2/3/2020	All
SND 0024	2/5/2020	All
SND 0026	2/11/2020	All
SND 0028	2/13/2020	All
SND 0031	2/18/2020	All
SND 0033	2/28/2020	All
SND 0037	3/6/2020	All
SND 0039	3/11/2020	All
SND 0040	3/16/2020	All

SND 0046	4/2/2020	All
----------	----------	-----

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Rohit Tiwari	Ali H Al Hakim
Drug Product	Nina Ni	Anamitro Banerjee
Manufacturing	Nancy Waites	Daniel Obrzut
Microbiology	Denise Miller	Bryan Riley
Biopharmaceutics	Dave Kaushalkumar	Banu Zolnik
Labeling	Nina Ni	Anamitro Banerjee
Regulatory Business Process Manager	Kristine Leahy	
Application Technical Lead	Xiao Hong Chen	
Laboratory (OTR)	Qin Shu, Kui Zeng, Nanying Cao	Jason Rodriguez
Environmental	Nina Ni	Anamitro Banerjee

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	Mitomycin	Adequate	3/9/2020	The DMF has been reviewed and found adequate and it is currently in adequate status.
	Type III	(b) (4)	(b) (4)	Adequate	4/1/2020	Sufficient information is provided in the NDA. It has been used in similar FDA approved drug products.
	Type III	(b) (4)	(b) (4)	Adequate	4/1/2020	Sufficient information is provided in the NDA. It has been used in similar FDA approved drug products.
	Type III	(b) (4)	(b) (4)	Adequate	4/1/2020	No review is necessary (b) (4) (b) (4)
	Type III	(b) (4)	(b) (4)	Adequate	4/1/2020	Sufficient information is provided in the NDA. It has been used in similar FDA approved drug products.

(b) (4)	Type III	(b) (4)	Adequate	4/1/2020	Sufficient information is provided in the NDA. It has been used in similar FDA approved drug products.
---------	----------	---------	----------	----------	--

B. Other Documents: IND, RLD, or sister applications

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
ANDA	064144	Listed Drug (LD)
IND	121922	

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
OTR	Complete	Comments were conveyed to the applicant.	3/16/2020	Qin Shu, Kui Zeng, Nanying Cao

Executive Summary

I. Recommendations and Conclusion on Approvability

The CMC review team from the Office of Pharmaceutical Quality recommends Approval for NDA 211728 for commercialization of JELMYTO™ (mitomycin) for pyelocalyceal solution.

II. Summary of Quality Assessments

A. Product Overview

The NDA for JELMYTO™ (mitomycin) for pyelocalyceal solution (also called UGN-101) contains a new formulation of mitomycin in which lyophilized mitomycin is reconstituted with sterile hydrogel to create a mitomycin gel admixture at a concentration of 4 mg per mL. JELMYTO™ drug product is available in a single use carton containing two 40-mg vials of sterile lyophilized mitomycin and one vial of 20 mL sterile hydrogel (also known as TC-3 gel). (b) (4)

UGN-101 is prepared by a health care professional prior to instillation, by mixing the components according to the preparation instruction provided as part of JELMYTO™ (mitomycin) for pyelocalyceal solution kit. The sterile hydrogel is a proprietary reverse thermal hydrogel that it has high viscosity at body temperature and low viscosity (liquid-like) at 5°C. As a result, it is in a liquid prior to instillation (keep cold) and becomes solid after instillation (body temperature). JELMYTO must be prepared under chilled conditions to keep the drug in a liquid state. Once reconstituted, the admixture will have a concentration of 4 mg of mitomycin per mL.

JELMYTO has been developed under IND 121922 for the treatment of LG-UTUC (low grade Upper Tract Urothelial Cell Cancers) that is a type of cancer that affects the lining of the upper urinary tract including the kidney, which has no current available therapy. The FDA has granted an Orphan Drug Designation (Sept. 8, 2014) for UGN-101 in the treatment of UTUC. JELMYTO has been granted Fast Track (Aug. 9, 2017) and Breakthrough Therapy Designations (Oct. 25, 2018).

The efficacy of JELMYTO is based on the results of OLYMPUS (NCT02793128), an ongoing, open-label, single-arm, multicenter trial that enrolled 71 patients with treatment-naïve or recurrent low-grade non-invasive UTUC with at least one measurable papillary tumor 5 to ≤ 15 mm located above the ureteropelvic junction. Patients received JELMYTO 4 mg per mL with total instillation volume based on individualized volumetric measurements using pyelography with the intent to fill the

renal pelvis. The major efficacy outcome measures were Complete Response (46%) at 12 months after treatment initiation with JELMYTO, based on ureteroscopic and local pathology assessment.

The NDA was submitted as a rolling submission starting on 07/11/2019, and is reviewed under priority review clock.

Proposed Indication(s) including Intended Patient Population	JELMYTO is an alkylating drug indicated for the treatment of low-grade Upper Tract Urothelial Cancer
Duration of Treatment	Six week to (b) (4) month
Maximum Daily Dose	<ul style="list-style-type: none"> • Instillation into the pyelocalyceal system once weekly for six weeks. • The dose of JELMYTO to be instilled is 4 mg per mL, with total instillation volume based on volumetric measurements using pyelography, not to exceed 15 mL (60 mg of mitomycin). • Instill JELMYTO once weekly for six weeks. For patients with a complete response 3 months after JELMYTO initiation, JELMYTO instillations may be administered once a month for a maximum of 11 additional instillations.
Alternative Methods of Administration	None

B. Quality Assessment Overview

The following is a summary of key assessments from the reviews of drug substance, drug product, manufacturing and facility, microbiology, and biopharmaceutics found in the respective technical chapters for each discipline. A summary of the assessments is provided in this section. Section D further discusses key review issues in greater detail.

Drug Substance: Adequate

The drug substance information is provided in the referenced DMF (b) (4). The DMF has been reviewed and found adequate and it is currently in adequate status. Mitomycin is an antineoplastic antibiotic against a wide variety of cancer types. Mitomycin was first isolated from *Streptomyces caespitosus* in 1950s. It is an alkylating agent that has an extraordinary ability to crosslink DNA with high efficiency. It has been used for cancer therapy to treat various types of cancers such as upper gastro-intestinal, stomach

or pancreas cancer. Mitomycin has a USP monograph for API and Mitomycin for Injection.

Drug Product: Adequate

The drug product is provided as a carton kit containing sterile lyophilized mitomycin cake and sterile hydrogel to reconstitute to admixture (reconstituted mitomycin with hydrogel).

Mitomycin for Solution: Mitomycin for Solution is a sterile lyophilized mitomycin cake to be reconstituted with hydrogel. Mitomycin for solution includes mitomycin and mannitol at the same ratio as in the LD (ANDA 064144). All the excipients and mitomycin API are USP compendial grades. The specifications for Mitomycin for Solution conform to USP monograph and are consistent with the parenteral drug products except for particulate control (essentially free of foreign particulates by visual inspection and particulate matter) since the proposed DP is not for parenteral use. Some other quality attributes such as pH is also not included in the specifications due to the nature of this product including route of administration (intra-pyelocaliceal instillation). The proposed assay acceptance criterion (b) (4) commonly used acceptance criterion for pharmaceutical product ((b) (4) %). This has been found acceptable since it is the same as that of USP monograph and the LD. Also refer to the section of admixture.

The lyophilization process has been changed significantly after the manufacturing of the three registration batches. The changes were deemed significant by the OPMA reviewers that only the new process is considered to be representative of the commercial process. The new process validation batches are designated as NDA registration batches to replace the old registration batches. The stability data generated from the new process are considered primary stability data to support the expiration dating period. The applicant was asked to demonstrate the comparability of the Mitomycin for Solution batches manufactured using the old and new process, and the data submitted by the applicant showed comparability. Although the applicant did not provide 12 months stability data for registration batches in the NDA, due to the unmet medical need, breakthrough, fast track designations, as well as 24 months stability data from the supporting batches, the submitted 6 month registration stability data deemed adequate to support the proposed expiry of 24 month shelf life when stored under the long term conditions. The applicant will put first three production scale lots of mitomycin for solution drug product on stability program to confirm the granted expiry.

Hydrogel: The sterile hydrogel is a reverse thermal hydrogel formulation used for reconstitution of mitomycin for solution, for preparation of UGN-101. It has high viscosity (gel like) at body temperature and low viscosity (liquid-like) at 5°C. This temperature-dependent viscosity characteristic allows mixing of the hydrogel with Mitomycin for Solution prior to the administration, and instillation of the cooled liquid gel into the upper urinary tract with a catheter. After the administered, it forms as a semi-solid gel containing drug, leading to extended exposure of the drug to the target

organ. Sterile hydrogel is composed of one of the most commonly used poloxamers - Poloxamer (b) (4) and other commonly used compendial excipients. All excipients are compendial, within IID limits.

Besides the common product quality controls such as identity, assay, pH, sterility, and endotoxins, the following are the Critical Quality Attributes (CQAs) of this unique Sterile Hydrogel formulation: Viscosity (at various temperatures) and average molecular weight. They are controlled for release and stability. Note that some of the CQAs are only added after the submission of the NDA per FDA comments. Therefore three of the 4 registration batches did not test for those attributes at release. Batch release data and stability data provided support a 24 month expiry.

Admixture: The UGN-101 admixture is prepared by a healthcare professional using the components of the UGN-101 carton in accordance with the Instructions for Pharmacy (IFP). The admixture preparation process is to the use of 2 mL of water for injection (b) (4) to facilitate dissolution of mitomycin with sterile hydrogel. The final admixture is (b) (4) mL of mitomycin gel in a concentration of 4 mg/mL mitomycin. The maximal dose of UGN-101 is 15 mL (i.e., 60 mg mitomycin).

(b) (4)

[Redacted]

[Redacted]

(b) (4)

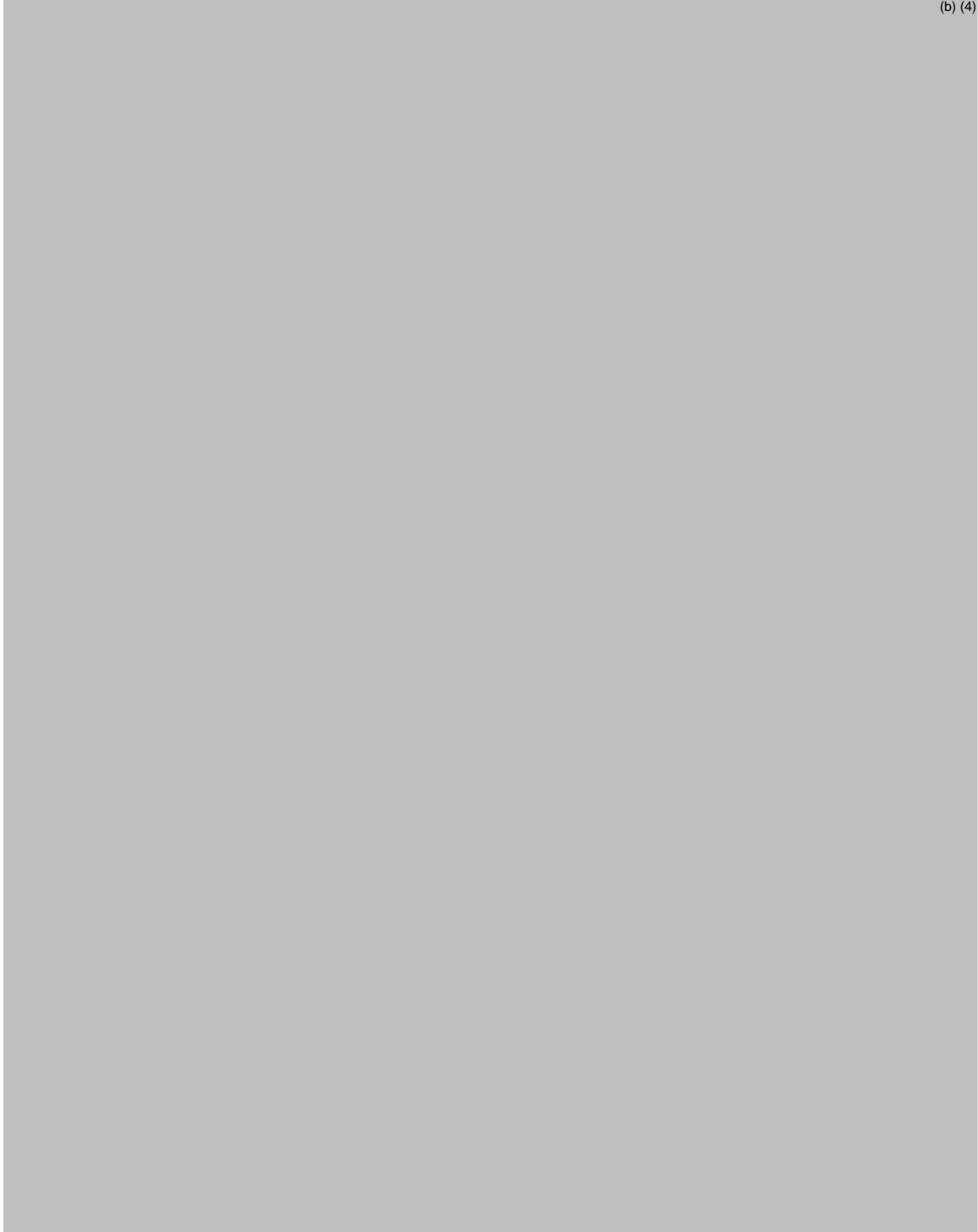
[Redacted] Based on the supportive stability data and the comparability data, the proposed 24 months shelf life has been found acceptable. The applicant is committed to conduct full stability studies using the first three commercial batches per NDA stability protocol to confirm the shelf life of 24 months stored under the long term conditions of 25°C with excursions permitted between 59°F and 86°F (15°C and 30°C).

Analytical Method Verification: During the review we have requested the FDA lab to conduct analytical method verification, and the report for the method verification came

back on 3/16/2020 (in Panorama). The deficiency/comment provided in the report has been conveyed to the applicant. The applicant's response to the deficiency/comment via email dated 4/9/2020 is deemed acceptable.

Manufacturing and Facility Inspection: Adequate

(b) (4)



Microbiology: Adequate

The application contains three separate 3.2.P sections; one for the Admixture carton, one for the sterile hydrogel component, and one for the sterile mitomycin component. The Admixture carton section is information regarding the co-packaging of the hydrogel and mitomycin component, which needs to be prepared to make mitomycin admixture for instillation into pyelocaliceal system. Admixture carton section does not require a microbiology review; however, the admixture hold time is assessed in the mitomycin section. The hydrogel and the mitomycin components are each reviewed for sterility assurance separately, and they are found adequate.

Biopharmaceutics: Adequate

The Biopharmaceutics review is focused on the evaluation of (1) the proposed dissolution method and acceptance criteria, and (2) bridging of clinical and to-be-marketed (TBM) drug products.

Dissolution: The Applicant conducted drug substance solubility studies and drug product dissolution studies by evaluating the dissolution testing conditions in order to select the optimal dissolution method for quality control (QC) purposes. The Applicant submitted the dissolution method development and validation report, which provided justification for the selection of the dissolution medium, suspension cell, sample size, and rotation speed. The Applicant adequately demonstrated the discriminating ability of the proposed dissolution method including that with regard to Poloxamer concentration. The Applicant's revised dissolution acceptance criteria are based on the dissolution data from the clinical batch at the time of batch release. Also, the data from the discriminating ability studies indicate that the proposed revised dissolution acceptance criteria are likely to identify deviation in the product's quality. Based on the provided information/data, the proposed dissolution method and acceptance criteria are deemed adequate for quality control testing of the proposed drug product.

Bridging between Clinical and to-be-marketed (TBM) Products: There is no difference in the composition of the formulations of the clinically tested drug product and the TBM drug product. However, the lyophilization (freeze-drying) process used for manufacturing of mitomycin in the proposed drug product is significantly different between the registration batches and the TBM batches. The Applicant provided comparative in vitro dissolution data between the pre-change drug product and the post change drug product using the proposed dissolution method and performed the similarity (f2) test analysis to evaluate this change. The provided dissolution data indicate that there is no significant effect on the dissolution profile of the proposed drug product, due to the change in the lyophilization process for mitomycin. From a Biopharmaceutics perspective, the proposed TBM product is deemed to be adequately bridged to the clinical batch of the proposed drug product.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Assay, Stability	Low	(b) (4) unstable in aqueous solution	Low	Adequate control is in place
Physical stability (b) (4) small molecule products	Medium	(b) (4) Low solubility	Low	Adequate control is in place
Uniformity of dose	Low	(b) (4)	Low	Adequate control is in place
pH	Low		Low	Adequate control is in place
Leachable/extractables	Low		Low	Conducted adequate risk assessment
Appearance	Low		Low	Adequate control is in place

Sterility	High	(b) (4)	Medium	Adequate control is in place
Endotoxin (b) (4)	Medium	(b) (4)	Low	Adequate control is in place
In vitro drug release	High	(b) (4)	Medium	Adequate control is in place

Application Technical Lead Name and Date: Xiao Hong Chen April 10, 2020



Xiao
Chen

Digitally signed by Xiao Chen
Date: 4/11/2020 02:33:49PM
GUID: 508da7220002a138fcc70fbccbfd08bf

241 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

MICROBIOLOGY

Product Background: Sterile hydrogel Gel product for the treatment of low grade Upper Tract Urothelial Cancer (UTUC). This is a kit containing two vials of sterile mitomycin for solution at 40 mg/vial and 1 vial of sterile hydrogel at 20 mL/vial. Sterile Water for Injection (SWFI) is used to reconstitute the mitomycin prior to mixing with the sterile hydrogel. SWFI is not supplied in the kit. The admixture process and the administration must be performed cold as the hydrogel is temperature responsive and is a liquid at refrigerated temperatures and gels at room temperature. This is a sterile topical product instilled into the upper urogenital tract.

NDA: 211-728

Drug Product Name / Strength: UNG-101 (mitomycin gel) for instillation, 0.4%

Route of Administration: Upper urogenital track

Applicant Name: UroGen Pharma Ltd.

Manufacturing Site:

(b) (4)

Method of Sterilization:

(b) (4)

Review Recommendation: Adequate

Theme (ANDA only): N/A

Justification (ANDA only): N/A

Review Summary: The application contains three separate 3.2.P sections; one for the Admixture carton, one for the sterile hydrogel component, and one for the sterile mitomycin component. The Admixture carton section is information regarding the co-

packaging of the hydrogel and mitomycin component and does not require a microbiology review; however, the admixture hold time is addressed in the mitomycin section. The hydrogel and the mitomycin components are each reviewed for sterility assurance separately.

List Submissions Being Reviewed:

Original Submission (CMC section): 11 July 2019

Amendment SD0007 (Response to IR #1): 30 September 2019

Amendment SD0016 (Response to IR #2): 19 December 2019

Amendment SD 0021 (Response to IR #3): 27 January 2020

Amendment SD 0031 (Response to IR #4): 18 February 2020

Highlight Key Outstanding Issues from Last Cycle: NA**Remarks:**

This is a 505(b)(2) rolling submission.

This application was granted an orphan designation (14-4451) and fast track.

The packaged product consists of the following

- 1) Sterile Hydrogel vial (one 30 mL vial with a 20 mL fill)
- 2) Mitomycin for Solution (two 100 mL vials containing 40 mg lyophilized powder)
- 3) Separate instructions for reconstitution, preparation, and administration.

Not provided but needed for administration include:

- 1) Sterile water for Injection (10 mL)
- 2) Sterile 10 mL Luer Lock syringe (x2)
- 3) Sterile 20 mL Luer Lock syringe (x1)
- 4) 20-25g needle (x1)
- 5) Vial adaptor - Tevadaptor® (x3)
- 6) Syringe adaptor - Tevadaptor® (x3)
- 7) Female/Female Luer Lock adaptor (x1)
- 8) Chilling block (x1)

Items (b) (4) are to be provided by the pharmacy.

(b) (4)

The filing review of the CMC information identified the following items for an information request (IR#1). The IR was sent out on 29 August 2019. The responses were received on 30 September 2019 and are incorporated into the appropriate sections of the review.

Initial Information Request:

(b) (4)

It is acknowledged that brief summaries of the manufacturing procedures and in-process controls were provided, however the provided summaries were not of sufficient detail to assess the sterilization process effectiveness for the equipment that comes into contact with sterile product. Provide the following information or a Letter of Authorization (LOA) to a Drug Master File (DMF) for each facility in which this information is located

(b) (4)

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

S Drug Substance: The drug substance is not sterile. It is noted that the drug substance has release specifications for microbial quality including USP <61> for TAMC of (b) (4) cfu/gram and TYMC of (b) (4) cfu/gram and an endotoxin specification of (b) (4) EU/mg.

P Drug Product (Hydrogel):

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – the drug product is a thermally responsive hydrogel used for the reconstitution of mitomycin for solution. The hydrogel has a high viscosity at body temperature and low viscosity at 5°C. It is stored at room

temperature. The hydrogel must be cooled for use in diluting the mitomycin. Once instilled into the urogenital tract, the hydrogel solidifies and forms a drug reservoir for the slow release of mitomycin into the target organ.

- **Drug product composition** – the composition of the hydrogel was copied from application section 32p1 table 1. This is an aqueous product provided in a 30 mL glass vial with a 20 mL fill.

Table 1 Sterile Hydrogel Qualitative and Quantitative Unit Composition

Component	Quantity (g per vial) ¹	Concentration (%w/w)	Quality Standard	Function
Poloxamer (b) (4)	(b) (4)	(b) (4)	NF	(b) (4)
Hydroxypropyl Methyl Cellulose (b) (4)	(b) (4)	(b) (4)	NF	(b) (4)
Polyethylene Glycol (b) (4)	(b) (4)	(b) (4)	NF	(b) (4)
Water for Injection (WFI)			USP	
Total				(b) (4)

NF = National Formulary; QS = quantity sufficient; USP = United States Pharmacopeia

- **Description of container closure system** –
 - **Vial:** 30 mL (b) (4) clear glass vial
 - **Stopper:** 20 mm (b) (4) gray stopper

P.2 Pharmaceutical Development

(b) (4)

44 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Post-Approval Commitments: NA

Reviewer's Assessment: NA

List of Deficiencies: No deficiencies were identified in the information provided.

Primary Microbiology Reviewer: Denise Miller
Sr. Microbiologist, OPQ/OPMA/DMA Branch 5

Secondary Reviewer Name: Bryan Riley Ph.D.
Branch Chief, OPQ/OPMA/DMA Branch 5



Denise
Miller

Digitally signed by Denise Miller
Date: 2/26/2020 09:02:40AM
GUID: 508da7280002a5d546459b998253d1aa



Bryan
Riley

Digitally signed by Bryan Riley
Date: 2/26/2020 09:51:02AM
GUID: 503450f200004f5816a1d3ae902b5e91

BIOPHARMACEUTICS

Application No: 505(b)(2) NDA 211728
Drug Product Name/Strengths: Mitomycin Gel (UGN-101) for Instillation/0.4%
Route of Administration: Upper Tract Instillation
Indication: For the treatment of low-grade Upper Tract Urothelial Cancer (UTUC)
Applicant Name: UroGen Pharma Ltd.
Date of Submission: 12/13/2018 (Module 3 of Rolling NDA)
Review Recommendation: Adequate

Primary Reviewer: Kaushalkumar Dave, Ph.D.
Secondary Reviewer: Angelica Dorantes, Ph.D.

REVIEW SUMMARY

Submission: The proposed drug product, 0.4% Mitomycin Gel (UGN-101) for Instillation is provided as a single use carton containing two vials of mitomycin for solution and one vial of sterile hydrogel. UGN-101 admixture is prepared by a healthcare professional prior to clinical use from the UGN-101 carton components – mitomycin for solution and sterile hydrogel. The proposed drug product is indicated for the treatment of low grade Upper Tract Urothelial Cancer (UTUC).

Review Objective: The Biopharmaceutics review is focused on the evaluation of (1) the proposed dissolution method and acceptance criteria, and (2) bridging of clinical and to-be-marketed (TBM) drug products.

Dissolution Method: The Applicant conducted drug substance solubility studies and drug product dissolution studies by evaluating the dissolution testing conditions in order to select the optimal dissolution method for quality control (QC) purposes. The Applicant submitted the dissolution method development and validation report, which provided justification for the selection of the dissolution medium, suspension cell, sample size, and rotation speed. The discriminating ability of the method with respect to Poloxamer concentration was also demonstrated. The Applicant adequately demonstrated the discriminating ability of the proposed dissolution method. Based on the Applicant's appropriate selection of the dissolution testing conditions, and the provided data demonstrating discriminating ability, the following dissolution method is deemed adequate for quality control testing of the proposed 0.4% Mitomycin Gel (UGN-101) for Instillation product at release and on stability: *USP Apparatus 2 (paddle) with Suspension Cups at 25 rpm; 500 mL of pH 6.8 Phosphate Buffer at 37°C*

Dissolution Acceptance Criteria: The Applicant's revised dissolution acceptance criteria of NMT (b) (4) % at 30 minutes; (b) (4) % at 90 minutes; and NLT (b) (4) % at 180 minutes are based on the dissolution data from the clinical batch at the time of batch release. Also, the data from the discriminating ability studies indicate that the proposed revised dissolution acceptance criteria are likely to identify deviation in the product's quality. Based on the

provided information/data, the proposed dissolution acceptance criteria are deemed 'adequate' for quality control testing of the proposed drug product.

The final approved dissolution method and acceptance criteria for the quality control testing of 0.4% Mitomycin Gel (UGN-101) for Instillation at release and on stability are summarized below.

FDA's Approved Dissolution Method and Acceptance Criteria for 0.4% Mitomycin Gel for Instillation	
Apparatus	USP Apparatus 2 (paddle) with Suspension Cups
Paddle Speed	25 rpm
Volume	500 mL
Medium	pH 6.8 Phosphate Buffer
Temperature	37.0 ± 0.5 C
Acceptance Criteria	30 minutes: NMT (b) (4) % 90 minutes: (b) (4) % 180 minutes: NLT (b) (4) %

Bridging between Clinical and to-be-marketed (TBM) Products: There is no difference in the composition of the formulations of the clinically tested drug product and the TBM drug product. However, the lyophilization (freeze-drying) process used for manufacturing of mitomycin in the proposed drug product is significantly different between the registration batches and the TBM batches. The Applicant provided comparative in vitro dissolution data between the pre-change drug product and the post change drug product using the proposed dissolution method and performed the similarity (f2) test analysis to evaluate this change. The provided dissolution data indicate that there is no significant effect on the dissolution profile of the proposed drug product, due to the change in the lyophilization process for mitomycin. From a Biopharmaceutics perspective, the proposed TBM product is deemed to be adequately bridged to the clinical batch of the proposed drug product.

RECOMMENDATION:

From a Biopharmaceutics perspective, the information/data provided is adequate and acceptable and NDA 211728 for 0.4% Mitomycin Gel (UGN-101) for Instillation is recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

LIST OF SUBMISSIONS REVIEWED

Submissions Reviewed		
eCTD sequence #	Received Date	Document
0001	12/13/2018	Original NDA Submission (Rolling Submission)
0002	07/11/2019	Original NDA Submission (Module 3)
0031	02/18/2020	Quality/Response to Information Request
0037	03/06/2020	Quality/Response to Information Request

BACKGROUND

The proposed drug product, UGN-101 (Mitomycin Gel) for Instillation is provided as a single use carton containing two vials of mitomycin for solution and one vial of sterile hydrogel. Once reconstituted, the product is referred to as UGN-101 admixture. The composition of UGN-101 admixture (after reconstitution) is as follows:

Table 1: UGN-101 Admixture Qualitative and Quantitative Unit Composition

Components	Quantity [g] per 15 mL of Admixture	Concentration (w/w)	Pharmaceutical Grade	Functions
Mitomycin	0.06	0.4%	USP	Active pharmaceutical ingredient (b) (4)
Mannitol	0.12	0.8%	USP	
Poloxamer (b) (4)	3.83	24.1%	NF	
Hydroxypropyl Methyl Cellulose (b) (4)	0.03	0.2%	USP	
Polyethylene Glycol (b) (4)	0.14	0.9%	NF	
Water for Injection (b) (4)			USP	
			USP	

NF = National Formulary, USP = United States Pharmacopeia
(b) (4)

Mitomycin for solution is a lyophilized sterile powder that contains a mixture of 40 mg mitomycin and mannitol as an excipient. Sterile hydrogel is a proprietary reverse thermal hydrogel formulation used for reconstitution of UGN-101 (mitomycin gel) for instillation. It has high viscosity at body temperature and low viscosity (liquid-like) at 5°C. As a result, the gel flows easily at low temperature and becomes semi-solid at body temperature. This temperature-dependent viscosity characteristic allows mixing of the gel with mitomycin

for solution followed by instillation of the cooled liquid gel into the upper urinary tract. After the gel is administered into the body, it solidifies and forms a drug reservoir, which allows extended exposure of the drug to the target organ.

UGN-101 admixture is prepared by a healthcare professional prior to clinical use from the UGN-101 carton components – mitomycin for solution and sterile hydrogel. The product is prepared under aseptic conditions to create an admixture containing 4 mg of mitomycin per mL. Once prepared, UGN-101 admixture has a shelf life of not more than 8 hours at room temperature and one additional hour on ice before instillation. Once instilled into the upper tract as a liquid under cooled conditions, the admixture converts into a semi-solid gel which releases mitomycin for a period of 4 to 6 hours.

The Applicant attempted to establish a scientific bridge to the Listed Drug (LD) product, Mutamycin (mitomycin for injection; approved under NDA 050450) based on pharmacokinetic (PK) data collected from non-muscle invasive bladder cancer patients following intravesical instillation of mitomycin gel (120 mg mitomycin in 60 mL hydrogel per instillation [Study BL004]). Pharmacokinetic (PK) data obtained in this study was compared to the PK parameters available in the mitomycin label. The in vivo PK data provided to establish the bridge between the proposed and the LD products are being reviewed by the Clinical Pharmacology Reviewer (*for details, refer to the Clinical Pharmacology review*).

The lyophilization process used for manufacturing of mitomycin in the proposed product is significantly different between the clinical/registration batches and the TBM batches. The Applicant provided comparative in vitro dissolution data between the pre-change drug product and the post change drug product using the proposed dissolution method and performed similarity (f2) test analysis to support this change.

Biopharmaceutics Review: The Biopharmaceutics review is focused on the evaluation of the 1) proposed dissolution method and acceptance criteria, and (2) bridging of clinical and TBM products, as presented below.

Dissolution Method Development: During the IND development stage (IND 121922), the proposed dissolution method listed below in Table 2, was reviewed by the Division of Biopharmaceutics (Dr. Jing Li) and was deemed adequate for quality control testing of the proposed drug product¹. Based on the provided information/data in this submission, the proposed dissolution method remains adequate and acceptable.

Table 2: FDA’s Accepted Dissolution Method for Mitomycin Gel for Instillation/0.4%

Apparatus	USP Apparatus 2 (paddle) with Suspension Cups
Paddle Speed	25 rpm
Volume	500 mL
Medium	pH 6.8 Phosphate Buffer
Temperature	37.0 ± 0.5 C

¹https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80416e0c&_afRedirect=5129804508786880

The Applicant’s originally proposed dissolution acceptance criteria were as follows:



Based on the provided dissolution data, the Applicant was requested² to implement the following dissolution acceptance criteria for QC testing of the proposed drug product:

30 minutes: Not more than (b) (4) %

90 minutes: (b) (4) %

180 minutes: NLT (b) (4) %

The Applicant accepted the FDA’s recommendation and accordingly revised the dissolution acceptance criteria. The Applicant’s response is adequate. The FDA’s approved dissolution method and acceptance criteria for the proposed drug product are as follows:

Table 3: FDA’s accepted dissolution method and acceptance criteria for the proposed drug product

Apparatus	USP Apparatus 2 (paddle) with Suspension Cups
Paddle Speed	25 rpm
Volume	500 mL
Medium	pH 6.8 Phosphate Buffer
Temperature	37.0 ± 0.5 C
Acceptance Criteria	30 minutes: Not more than (b) (4) % 90 minutes: (b) (4) % 180 minutes: NLT (b) (4) %

Bridging of Clinical and TBM Products: As per the Applicant, there was no difference in the composition of the formulations of the clinically tested product and the TBM product. However, the lyophilization (freeze-drying) process used for manufacturing of mitomycin in the proposed product is significantly different between the registration batches and the TBM batches (Figure 4). The Applicant was recommended^{2,3} to provide comparative dissolution data (n= 12) between the pre-change drug product (pivotal clinical study batch at the time of batch release) and the post change drug product (three registration batches, if available) using the proposed dissolution method. The Applicant was asked to perform appropriate statistical analysis [e.g., similarity (f2) test analysis] to demonstrate that the proposed change in the lyophilization process does not significantly affect the dissolution behavior of the proposed drug product. The Applicant provided the requested dissolution profiles (Figure 1) and the f2 statistical analysis³. This Reviewer also performed the similarity f2 test analysis and verified that there was no significant difference in the

² [Application 211728 - Sequence 0031 - Response to February 11, 2020 Quality Information Request](#)

³ [Application 211728 - Sequence 0037 - Response to February 21, 2020 Quality Information Request: Biopharmaceutics](#)

dissolution profiles of the pre-change (clinical batch) and the post-change batches (Table 4).

(b) (4)



The provided dissolution data indicate that there is no significant effect of the change in the lyophilization process for mitomycin on the dissolution profile of the proposed drug product. From a Biopharmaceutics perspective, the proposed TBM product is deemed to be adequately bridged to the clinical batch of the proposed drug product.



Kaushalkumar
Dave

Digitally signed by Kaushalkumar Dave
Date: 4/02/2020 05:15:48AM
GUID: 5575db68006e2262805f2e6449c54250



Angelica
Dorantes

Digitally signed by Angelica Dorantes
Date: 4/02/2020 10:12:17AM
GUID: 502d0913000029d59f1c87e0a380c7f7

CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

JELMYTO™ (mitomycin) for pyelocalyceal solution

Initial U.S. Approval: 1974

For pyelocalyceal solution: A carton containing the following:

- Two 40 mg (each) single-dose vials of mitomycin for pyelocalyceal solution
- One vial of 20 mL sterile hydrogel for reconstitution (3)

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	JELMYTO	Provided and adequate
Established name(s)	Mitomycin for pyelocalyceal solution	Updated and adequate
Route(s) of administration	For pyelocalyceal solution	Updated and adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	For pyelocalyceal solution: 40 mg	Updated and adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	single-dose vials of mitomycin for pyelocalyceal solution	Updated and adequate

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

JELMYTO must be prepared under chilled conditions. Once reconstituted, the admixture will have a concentration of 4 mg of mitomycin per mL and will appear as a viscous liquid for instillation. Reconstituted JELMYTO has reverse thermal properties with a gelation point of approximately 19°C (66°F). Reconstituted JELMYTO should be instilled (b) (4) after reconstitution. If immediate instillation is not possible, store reconstituted JELMYTO at 20°C to 25°C (68°F to 77°F) for up to 8 hours (b) (4) will appear as a semisolid gel. Protect reconstituted JELMYTO from light.

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	See above	Update and adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

For pyelocalyceal solution: A carton containing the following:

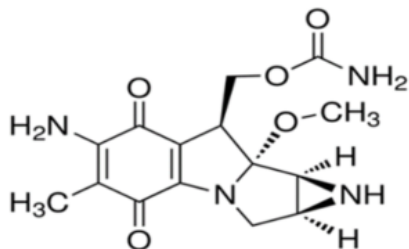
- Two 40 mg (each) single-dose vials of sterile, lyophilized, grey to greyish-purple, cake-like or powder of mitomycin for solution
- One vial of 20 mL of sterile, clear, colorless, gel with or without bubbles at room temperature or clear, colorless liquid at 2°C – 8°C, to be used as a vehicle for reconstitution

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	For pyelocalyceal solution	Updated and adequate
Strength(s) in metric system	40 mg per vial	Provided and adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	NA	NA
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	See above	Updated and adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	See above	Updated and adequate

1.2.3 Section 11 (DESCRIPTION)

11 DESCRIPTION

Mitomycin (also known as mitomycin-C) is an alkylating drug isolated from the broth of *Streptomyces caespitosus*. Mitomycin is a blue-violet crystalline powder with a molecular formula of $C_{15}H_{18}N_4O_5$, and a molecular weight of 334.33. Its chemical name is 7-amino-9 α -methoxymitosane and it has the following structural formula:



Mitomycin is heat stable, has a high melting point, and is freely soluble in organic solvents.

JELMYTO is supplied in a single-dose carton containing two vials of sterile lyophilized mitomycin for pyelocalyceal solution, 40 mg each, and one vial of 20 mL of sterile hydrogel, to be used as a vehicle for reconstitution.

Mitomycin for pyelocalyceal solution is a sterile, lyophilized, grey to greyish-purple, cake-like or powder which contains mitomycin 40 mg and mannitol 80 mg in each vial.

Sterile hydrogel is a sterile, clear, colorless, gel with or without bubbles at room temperature or clear, colorless liquid at 2°C – 8°C, which contains 5.67 g poloxamer, 0.21 g polyethylene glycol, 0.04 g hydroxypropyl methylcellulose, and water for injection in each vial.

Once reconstituted, JELMYTO is a clear, purple, viscous liquid at 2°C – 8°C or semisolid gel at room temperature with a concentration of 4 mg per mL of mitomycin, which may contain a few visible particles and have a pH between 6.0 and 8.0.

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	See above	Updated and adequate
Dosage form(s) and route(s) of administration	See above	Updated and adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	DS is not a salt	NA
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	See above	Updated and adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	See above	Updated and adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)	See above	Provided and adequate
Pharmacological/ Therapeutic class	See above	Provided and adequate
Chemical name, structural formula, molecular weight	See above	Provided and adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	See above	Provided and adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	NA
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	NA	NA

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

JELMYTO (b) (4) - NDC 72493-103-03

A (b) (4) containing the following:

- Two 40 mg (each) single-dose vials of mitomycin for pyelocalyceal solution supplied as a sterile, lyophilized, grey to greyish-purple, cake-like or powder (NDC 72493-101-40)
- One 20 mL single-dose vial of sterile hydrogel supplied as a sterile, clear, colorless, gel with or without bubbles at room temperature or clear, colorless liquid at 2°C – 8°C, to be used as a vehicle for reconstitution (NDC 72493-102-20)

16.2 Storage and Handling

Store the JELMYTO (b) (4) at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Avoid excessive heat over 104°F (40°C).

JELMYTO is a cytotoxic drug. Follow applicable special handling and disposal procedures.¹

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	See above	Provided and adequate
Strength(s) in metric system	See above	Provided and adequate
Available units (e.g., bottles of 100 tablets)	See above	Provided and adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	See above	Updated and adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	See above	Updated and adequate

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	See above	Updated and adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	NA	NA

Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	See above	Updated and adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	NA	NA
Include information about child-resistant packaging	NA	NA

1.2.5 Other Sections of Labeling

NA

1.2.6 Manufacturing Information After Section 17 (for drug products)

Distributed by:

UroGen Pharma, Inc.

(b) (4)

U.S. Patent Nos. 9,040,074 and 9,950,069

JELMYTO™ and UroGen® are trademarks of UroGen Pharma.

Copyright © 2020 UroGen Pharma, Inc.

All rights reserved.

JEL-PI-XXX

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	See above	Provided and adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): Adequate

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT." None

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Updated	Updated
Dosage strength	Provided	Updated
Net contents	Provided	Provided
“Rx only” displayed prominently on the main panel	Provided	Provided
NDC number (21 CFR 207.35(b)(3)(i))	Provided	Provided
Lot number and expiration date (21 CFR 201.17)	Provided	Provided
Storage conditions	Updated	Updated
Bar code (21CFR 201.25)	Provided	Provided
Name of manufacturer/distributor	Provided	Provided
And others, if space is available	NA	NA

Assessment of Carton and Container Labeling: Adequate after revision

The following comments were conveyed to the applicant:

For both immediate and carton container labels:

- Revise the product name from “(b) (4)” to “Jelmyto (mitomycin) for pyelocalyceal solution”. **Revised**
- Revise from “(b) (4)” to “single dose vial” and from “(b) (4)” to “single dose carton”, DMEPA has conveyed comment to the applicant. **Revised**
- Revise the storage condition to be consistent with the language provided in the PI, need to correct the temperature expression. **The following follow up comment was conveyed to the applicant:**
 - To be consistent with current labeling practices, Celsius should be before Fahrenheit. Make appropriate changes throughout labeling.

For Jelmyto vial label:

- Add “sterile”. **Revised**
- ~~Add strength~~, DMEPA has conveyed the comment to the applicant. **Revised**

For sterile hydrogel vial label:

- Add quantitative amount for each ingredient. **Revised**
- Change from “(b) (4)” to “20 mL per vial”. **Revised**

Any deficiencies should be listed at the end in the “ITEMS FOR ADDITIONAL ASSESSMENT.” None

ITEMS FOR ADDITIONAL ASSESSMENT

Patient Information (PPI), Instructions for Pharmacy (IFP), and Instructions for Administration (IFA)

Overall Assessment and Recommendation:

Adequate after revision of the following on the temperature expression:

- To be consistent with current labeling practices, Celsius should be before Fahrenheit. Make appropriate changes throughout labeling.

Primary Labeling Assessor Name and Date: Nina Ni, Ph.D., 04/01/2020

*Secondary Assessor Name and Date (and Secondary Summary, as needed):
Anamitro Banerjee, Ph.D., 04/01/2020*



Nina
Ni

Digitally signed by Nina Ni
Date: 4/01/2020 04:09:13PM
GUID: 502d1ab500002afb6e642f8f37136920



Anamitro
Banerjee

Digitally signed by Anamitro Banerjee
Date: 4/01/2020 05:19:05PM
GUID: 5075764700003844b7bc89632228509f

4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page



**METHOD VERIFICATION
REPORT SUMMARY**

Date: March 16, 2020

To: Rohit Tiwari, Drug Substance Reviewer
Nina Ni, Drug Product Reviewer
Kristine Leahy, RBPM

Through: Jason Rodriguez, Ph.D., Lab Chief, CDER/OPQ/OTR/DCDA

From: Qin Shu, Ph.D., Chemist, CDER/OPQ/OTR/DCDA
Kui Zeng, Ph.D., Chemist, CDER/OPQ/OTR/DCDA
Nanying Cao, Ph.D., ORISE Fellow, CDER/OPQ/OTR/DCDA
Cynthia Sommers, Ph.D., Method Verification Coordinator,
CDER/OPQ/OTR/IO

Subject: Method Verification for NDA 211728: UGN-101 (Mitomycin gel) for instillation, 0.4%

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

1. Hydrogel Drug Product: Appearance at 2-8 °C **Pass:** Clear colorless liquid
2. UGN-101 Admixture Drug Product: Appearance at (b) (4) 8 °C **Pass:** Clear purple liquid

The following methods were evaluated and are acceptable with modifications for quality control and regulatory purposes:

1. Hydrogel Drug Product: Identification by NMR and poloxamer (b) (4) assay by NMR
Pass: see comments below

The following methods failed system suitability and could not be adequately evaluated:

1. Mitomycin for solution, 40 mg, (b) (4). Impurities and degradation products by HPLC.
2. Determination of Mitomycin C and impurities in UGN-101 (Mitomycin gel) for instillation, 0.4%, by HPLC, SOP # (b) (4).
3. Molar mass distribution analysis of Poloxamer (b) (4) in Sterile Hydrogel for UGN 101 by (b) (4)

The Division of Complex Drug Analysis (DCDA) has the following results and comments pertaining to the methods:

1. Method: Identification by NMR, poloxamer (b) (4) assay by NMR

1.1 The NMR (b) (4) reference standard (RS), raw material (RM) and Sterile Hydrogel (Batch #170918) are consistent with the examples reported in SOP (b) (4).

Identification result: **Pass.**

(b) (4)



2. Method: Mitomycin for solution, 40 mg, (b) (4). Impurities and degradation products by HPLC.

System suitability requirements in the resolution solution:

2.1 Identification: The relative retention times of the specified impurities must be respected as listed in Table 3 below: **Fail**

2.2 Resolution: The resolution between Mitomycin C and the nearest peak must be (b) (4), and the resolution between any specified impurity and the nearest peak must be (b) (4). The resolution acceptance is shown in Table 3 and applied to all significant peaks, i.e., peak area ~ (b) (4) % of the LOQ. **Fail**

Table 3: Test results of the resolution for impurities in Mitomycin for solution, 40 mg (Lot 19H12).

Name	RT (min)	RRT	Acceptance criteria (b) (4)	Pass/Fail	Resolution	Acceptance criteria (b) (4)	Pass/Fail
Impurity 1	(b) (4)	(b) (4)	(b) (4)	Fail	(b) (4)	(b) (4)	Fail
Impurity 2				Pass			Fail
Impurity 3				Pass			Fail
(b) (4)							Pass
Impurity 4				Fail			Pass

3. Method 2: Determination of Mitomycin C and impurities in UGN-101 (mitomycin gel) for instillation, 0.4%, by HPLC, SOP # (b) (4).

System suitability requirements: Resolution must be (b) (4) from the nearest peak. **Fail**

Table 4: Test results of the resolution for impurities in UGN-101 (mitomycin gel) for instillation, 0.4% (Mitomycin Lot 19H12; hydrogel lot 170918).

Analyte name	*Half height classic resolution from nearest peak	Result	Pass/Fail
Impurity (b) (4)	(b) (4)	(b) (4)	Pass
(b) (4)	(b) (4)	(b) (4)	Fail
Impurity (b) (4)	(b) (4)	(b) (4)	Fail
Impurity (b) (4)	(b) (4)	(b) (4)	Pass

3.1 Comment: There is a discrepancy in the RRF values for (b) (4) in the Mitomycin for Injection and UNG-101 methods. The mitomycin method has an (b) (4) where the UNG-101 method lists an (b) (4).

3.2 Comment: The methods for Mitomycin C and UNG-101 use the same buffer, mobile phases, and diluent. However, they have different timeframes for storing these solutions which should be clarified.

4. (b) (4)

(b) (4)

Original analyst worksheets can be viewed using this ECMS link:



Jason
Rodriguez

Digitally signed by Jason Rodriguez
Date: 3/16/2020 03:21:46PM
GUID: 508da7360002b158f072de914f432fe5

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

XIAOHONG CHEN
04/13/2020 09:59:06 AM

Inter-Center Consulting Review Memo

Date: March 31, 2020

From: [James Seiler](#)
([OPEQ/OHT3/DHT3B/THT3B3](#))
Office of Product Evaluation & Quality ([OPEQ](#))
Office of Health Technology 3 ([OHT3](#))
Division of Health Technology 3B ([DHT3B](#))
Urology Devices (THT3B3)
WO66, Rm G0232
(301) 796-6558 (T)
(301) 847-8111 (F)
james.seiler@fda.hhs.gov

To: Fatima Rizvi, Ph.D. Regulatory Project Manager
Office of Hematology Regulatory Affairs Branch 1 ([OHRAB1](#))
Division of Oncology & Hematology Regulatory Affairs ([DOHRA](#))
Office of New Drugs ([OND](#))
Center for Drug Evaluation and Research ([CDER](#))
U.S. Food and Drug Administration ([U.S. FDA](#)) Tel: 240-402-7426
Fatima.Rizvi@fda.hhs.gov

Scope:

- Consult Type: Delivery device - technical engineering
(e.g., autoinjectors, on-body infusion pumps, electroporation devices)
- Consult Request: **Please review Uroject12 Syringe lever (compatibility with UGN-101) as well as the chilling block being used with this product**
- NDA21178 ([here](#)) (40 modules)
 - Reviewed Sections
 - Volume 002/ Module M1: [114a](#) – draft labeling (IFU and IFP)
 - 002/M2: [23](#) – Introduction Admixture (how it is instilled)
 - 002/M3: 3.2.P.24 – Admixture carton Table 2 list of device components 1.4.2, 1.6.3, 1.14.1, [1.14.1.3](#), 2.3, 3.2S, [3.2P](#), [3.2R](#), [3.2r-device.pdf](#)

Resources:

- [ICC1900901](#) ((b) (4))
- NDA 211728 UGN_101 (mitomycin gel; Jelmyto™)



RE_ FDA

- **Email:** Information Reques

Due: 03/24/2020

Product Name	Urogen Pharma
Description	UGN 101 (mitomycin gel) for instillation low-grade upper tract urothelial carcinoma
Submission #	NDA 211728
Requesting Reviewer	Fatima Rizvi
Salesforce Link	(b) (4)
Consult Type	Delivery device - technical/ engineering (e.g., autoinjectors, on-body infusion pumps, electroporation devices)
Lead Center	CDER

Case Number	00013818
ICCR Product Number	ICCR-Prod-52512
Indication for Use	low-grade upper tract urothelial carcinoma
Device Type Notes	UGN-101 must be instilled using a Uroject12 syringe level
Document Details (Salesforce Link)	\\CDSESUB1\evsprod\NDA211728\211728.enx
Request Details	Please review Uroject12 Syringe lever (compatibility with UGN-101) as well as the chilling block being used with this product
Consult Due Date	03/24/2020
FDA Action Date	04/03/2020
Consulted Center Tracking Number	ICC1900901
Windows link	\\CDSESUB1\evsprod\NDA211728
CTS Link	http://webapps.cdrh.fda.gov/division-tracking/findTrackable.do?docNum=ICC1900901&reviewType=GEN

Background:

The email history relevant to this assignment is listed below

- 02/25/2020 Email from Nina Ni (FDA) referencing 3.2.P.2 (p. 26) that lists medical devices to prepare and deliver the admixture seeking confirmation whether CDRH review is needed. Dr. Ni stated that the chemical compatibility study which deems adequate from a Chemistry, Manufacturing and Controls (CMC) perspective. Noted studies: Closed system (vial/syringe adaptor) using aerosol challenge test, sterility maintenance, and dry disconnections; and delivery chain validation
- 09/09/2019 email from Kristina Leahy, CDER to Sharon Andrews, CDRH - CMC perspective this is not a combination product.
- 08/21/2019 email from Kristina Leahy, CDER to sponsor listing the information needed (6 points) about the devices used to prepare and deliver the drug.

Date: Wednesday, August 21, 2019 at 1:26 PM
 To: Jim Ottinger <jim.ottinger@urogen.com>
 Cc: "Rizvi, Fatima" <Fatima.Rizvi@fda.hhs.gov>
 Subject: FDA Information Request NDA 211728 - Please respond by 2pm 8/30/19

Dear Mr. Ottinger,

Please refer to your NDA 211728 submission dated July 11, 2019, for UGN-101 (mitomycin gel) for instillation, 0.4%.

The Product Quality team have the following comments and information requests. We request a written response by 12 noon, August 30, 2019, in order to continue our evaluation of your application. Please provide your response via email followed by an official amendment.

Device information should be located in the appropriate eCTD module, as recommended in the FDA's eCTD Technical Conformance Guide: Technical Specifications Document: "Guidance for Industry Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" (<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf>).

When submitting a marketing application for the final finished combination product, provide the following information related to your device:

- 1) Device Description Documentation
 - a) Provide a description of your device constituent design, including any novel features and/or functionalities. This should include drawings / diagrams of the device, descriptions of device components, or any other available information to explain the device design.
 - b) Describe the principles of operation of your device.
 - c) Describe any accessories or other devices labeled for use with your device.
- 2) Design Control (21 CFR 820.30) – The application should include design documentation. The use of recognized standards and FDA guidance to inform design and testing is recommended, as applicable. For questions about

design control documentation, we recommend that you reference the FDA Design Control Guidance for Medical Device Manufacturers, <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm070642.pdf>. We recommend that the design control information provided in your application include the following:

- a) Design Input Requirements (e.g., safety, performance, and reliability requirements of a device that are used as a basis for device design)
 - b) Design Output Specifications (e.g., device description, drawings, specifications, bill of materials, etc.)
 - c) Design Verification Plan/Summary Report, supporting data and traceability
 - d) Design Validation Plan/Summary Report, supporting data and traceability
 - e) Risk Management File
- 3) Essential Performance – Identify essential performance requirements (EPR) for the device.

For each identified essential performance requirement, your marketing application should include verification and validation information of EPR specifications. While the final set of essential performance requirements should be based on your design control process, we are providing the following example EPRs for your device type. This is not an exhaustive list and product specific factors should influence your EPR selection.

Syringe EPRs:

- Delivered Volume Accuracy
 - Break loose & Extrusion Force
 - Vial insertion force (for vial adapter)
- 4) Stability– Your stability program should include endpoints to verify that device essential performance is maintained at expiry. You may exclude certain EPRs from the stability study if you can provide scientific rationale that the excluded EPR is unlikely to change over time.
- 5) Shipping - Provide documentation for the final finished product to demonstrate that the device EPRs are met after shipping.
- 6) Control Strategy – Provide a control strategy that ensures that the final finished combination product maintains its essential performance requirements. The control strategy may consist of, but is not limited to, lot release, in-process, control of incoming materials, purchasing controls, etc.

Kindly confirm receipt upon delivery of this email.

Thank you,
Kristine

Kristine F. Leahy, RPh.
Regulatory Business Process Manager, Branch 1
Pharmacist

Center for Drug Evaluations and Research (CDER)
Office of Pharmaceutical Quality (OPQ)
Office of Program and Regulatory Operations (OPRO)
U.S. Food and Drug Administration
WO75; Office 4668
Tel: 240-402-5834
kristine.leahy@fda.hhs.gov

- **10/18/2018 Clearance for [K180345/S001](#) - Uroject12 Syringe Lever**

Section 12 Executive Summary with prior submission history

<http://i2kplus.fda.gov/documentumservice/view.jsp?objectId=0900262183a6e40c>

that references (b) (4) (Robert Meyer lead) and (b) (4) (Dulciana Chan lead).

- **04/23/2018 email from Keith Marin**

(b) (4), UroGen Pharma, Ltd. [Investigational New Drug \(IND\)121922 / SN0024 Pre-\[New Drug Application \\(NDA\\)\]\(#\)Meeting Information Package](#)

Summary:

The drug submission describes 8 devices used to prepare a drug in a sterile, sealed transfer device, and 5 devices to instill the admixed drug. There was a question regarding whether the devices used to make the drug were consistent with their cleared indication for use under 510(k) and that question was satisfactorily

addressed in the device folder (3.2 f) that explicitly stated and documents the cleared indications do align with how the physician uses it. This was confirmed with informal checks by email of the devices with appropriate CDRH review divisions.

There was also a question whether the device is a combination product. While it appears to fit a definition 3 combination product, the labeling specifically notes that the devices are supplied by the preparing and using facilities so they are not co-packaged or co-labelled with the drug and are not sold as a combination product. This conclusion is attributed to the information noted in the 03/24/2020 email from Sarah Mollo.

The submission supported the performance of the device in a number of tests which are completed.

Interactive review with the drug sponsor adequately addressed concerns regarding labeling issues with the chilling block.

Drug Description

A description of the drug is available in Volume 1, Module 1 [Reviewer Guide](#). It is intended for local Treatment of low-grade Upper Tract Urothelial Cancer (UTUC).

The proprietary name, JELMYTO is the name for mitomycin (MMC) gel (UGN-101) for installation, 0.4%. It is provided as a single use carton containing two 40 mg vials of mitomycin for solution and one vial of sterile hydrogel (TC-3). Reconstitution of mitomycin for solution with the sterile hydrogel prior to instillation and instillation of the admixture into the upper urinary tract through a ureteral catheter. It is instilled into the upper urinary tract once a week for six weeks.

The reconstituted mitomycin gel, described as the admixture (mitomycin and sterile hydrogel) is prepared prior to instillation and needs to be mixed together (reconstituted) by a healthcare professional prior to administration (instillation). The preparation requires number of FDA-cleared or exempt devices including syringes, needles, closed system transfer devices and Leur Lock connectors. Once the cooled liquid gel is instilled into the upper tract, the admixture converts into a “semi-solid gel drug reservoir” which releases mitomycin for a period of 4 to 6 hours to the target organ.

Section 3.2P (\\CDSESUB1\evsprod\NDA211728\0002\m3\32-body-data\32p-drug-prod\admixture-carton\32p2-pharm-dev)

The IFP instructions for pharmacy (drug preparation) and IFU instructions for use (drug installation) list the devices used with the drug.

The two forms of instructions can be used to test whether the drug and device qualify as a Combination Product defined under [21 CFR 3.2 \(e\)](#).

Instructions for Pharmacy (IFP) - Preparation

The IFP does note that the devices are supplied by the facility preparing the drug ([1.14.1.3. IFP](#), p. 2 of 7).

- **Specific device needed to prepare the drug** (p. 1 of 6)

“These components have a special characteristic that makes them liquid at cold temperatures and gel at around room temperature, so everything needs to be kept cold throughout the entire preparation. You need a UroGen Pharma Chilling Block for this purpose. You cannot prepare JELMYTO™ without the Chilling Block or other means of chilling the admixture.”

Combination Product Qualification

Therefore the drug requires the use of specific devices. While this appears to meet [Combination Products definition #3 \(2 CFR 3.2 \(e\)\)](#) for items co-labelled, the devices are supplied by the pharmacy facility and are not packaged, sold with the drug and are not packaged as a kit for use with the drug.

The device components that are used to prepare and administer the drug product appear to be provided by the facility and are not included (e.g. co-packaged or pre-filled) with the drug product, which is provided in a vial; if that is the case, then the product would be considered a combination product. This conclusion is attributed to the information noted in the 03/24/2020 email from Sarah Mollo.

I confirmed that the device components are used according to their indications for use by discussing with the appropriate CDRH review divisions as listed below:

- **Urology** - Ureteral catheter ([K180354](#)) and the UroJect 12 Syringe Lever ([K180345](#) and [K190987](#) (Sterile)) are, in the instructions for Pharmacy (IFP) and Instructions for use (IFU), consistently used according to the device indications for use.
- **General Hospital** – 03/26/2020 email from Alan Stevens (through Sapana Patel) regarding Tevadaptor Syringe Adaptor, and the COP Medallion 20 ml Luer Lock Syringe - The use of these devices to transfer and administer drugs is within their indications.
- **Physical Medicine** - 03/23/2020 email from Vivek Pinto, regarding the chilling block. The chilling block does not appear to fit its nearest classification category. It is a cylindrical unit which maintains a specific chilled temperature for 2 hours. Vivek Pinto, a supervisor in the Physical Medicines team has never seen a submission for this type of device and he suggested to investigate the two devices under [890.5940](#) - chilling unit is a refrigerative device intended for medical purposes to chill and maintain cold packs at a reduced temperature (see [IMF](#) product code). The two devices ([K871112](#) and [K900419](#)), reviewed over 30 years ago where both from the same company and used to deliver a cooling type therapy to the device. The Chiller Unit is not used to deliver treatment to a patient. Therefore, I agree that the chiller unit is a tool and not a device as it is not intended to treat a disease and is not labelled that way.
- **Disinfectant instructions consistent with labeling of the device?** - Disinfect the Chilling Block by spraying with 70% Isopropyl alcohol or equivalent, allow to air dry and then place it upright inside the hood or isolator.

Isopropyl alcohol may sanitize the device surface however this method does not produce a sterile or high-level disinfected device. CDER needs to determine whether this method of cleaning is appropriate for drug preparation of a sterile mixture for cancer patients.

Interactive Review (03/26/2020 – Sent by Fatima Rizvi)

#1 Your instructions for pharmacy (IFP) state that the chilling block can be disinfected with isopropyl alcohol. Please provide the justification why this component does not need to be sterile for the preparation of a sterile drug for use in cancer patients.

Deficiency Response

The chilling block does not come in contact with the actual sterile product. JELMYTO preparation, is conducted in an aseptic area, i.e., not sterile area, and all non-sterile equipment including the chilling block, the vial of mitomycin, and the vial of sterile hydrogel are disinfected with alcohol following Section 8.2 of [USP monograph <797>](#) *Pharmaceutical Compounding of Sterile Preparations*. JELMYTO Instructions for Pharmacy requires the use closed system transfer devices (CSTD) for preparation of the admixture, devices designed to protect the product and the operator from cross contamination, including both microbial and chemical contamination.

The response adequately addresses the concern.

- List of devices needed to prepare the admixture.



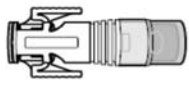


Supplies Needed:	
JELMYTO™ Single-Use Carton (b) (4)	
<p>Pharmacy Supplies</p> <p>3 x Tevadaptor® (b) (4) vial adaptor</p> <p>3 x Tevadaptor® Syringe adaptor (b) (4)</p> <p>1 x Luer lock connector</p> <p>(b) (4) sterile water</p> <p>2 x 10 mL Luer lock syringes</p> <p>1 x 20 mL Luer lock syringe</p> <p>1 x (b) (4) needle for drawing up sterile water</p> <p>70% Isopropyl alcohol or equivalent</p> <p>1 x UroGen Pharma Chilling Block</p> <p>Note: The day before your preparation, put the Chilling Block in the freezer (-4°F / -20°C) upside down overnight.</p> <p>(b) (4) Please refer to the Chilling Block Instructions for Use for more information.</p>	<p> 3 x Tevadaptor® (b) (4) vial adaptor</p> <p> 3 x Tevadaptor® syringe adaptor (b) (4)</p> <p> 1 x Luer lock connector</p> <p> 1 x UroGen Pharma Chilling Block</p>

Table 1 UGN-101 Admixture Preparation (Section 3.2.P.2 - Compatibility Admixture)

Component	Manufactured By (b) (4)	Quantity per preparation
Mitomycin for solution (vial)		2 vials × 40 mg
Sterile hydrogel (b) (4)		1 vial × 20 mL
Sterile Water for Injection (b) (4)		

Sterile 10 mL Luer Lock syringe	(b) (4)
Sterile 20 mL Luer Lock syringe	
20–25 G syringe needle	
Vial adaptor (Tevadaptor [®])	
Syringe adaptor (Tevadaptor [®])	
^{(b) (4)} Luer Lock connector	
Chilling block	

^aSupplied by pharmacy; G = gauge

Instructions for Use (IFU) - Instillation

The instructions for use (IFU) does note that the devices are supplied by the facility preparing the drug ([1.14.1.3. IFP](#), p. 2 of 7).

UGN-101 single-use carton printed with a label consists of 2 vials of mitomycin for solution (2 x 100-mL vials filled each with 40 mg mitomycin and 80 mg mannitol; total of 120 mg mitomycin for solution lyophilized powder in each vial), 1 vial of sterile hydrogel (30-mL vial filled with 20 mL of hydrogel) and labels (e.g. admixture label for the vial; Instructions for Use [IFU], Instructions for Pharmacy [IFP], US Package Insert [USPI]).

The mixing process of the UGN-101 admixture preparation consists of withdrawal and injection of UGN-101 materials through closed system adaptors and stainless-steel needles and holding the admixture in one of the mitomycin for solution vials, capped, and connected to a vial adaptor, refer to Table 2.

- JELMYTO™ is highly viscous, even when it is a liquid in a chilled state. Therefore, you will need a Uroject12 Syringe Lever to instill JELMYTO™ into the patient. You cannot instill JELMYTO™ without the Uroject12 device.

List of devices needed to inject the admixture.

Supplies Needed

(b) (4)

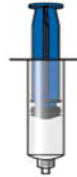
- 1 x vial of reconstituted JELMYTO™
- 1 x Tevadaptor® syringe adaptor (b) (4)
- 1 x COP Medallion® 20 mL Luer Lock syringe
- 1 x Ureteral Catheter (5 Fr or 7 Fr)



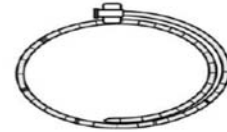
JELMYTO™ vial
syringe



Tevadaptor®
adaptor (b) (4)



COP Medallion® 20 mL
Luer Lock syringe



Ureteral Catheter

Ancillary Supplies (provided by your facility):

- 1 x UroGen Pharma Uroject12 Syringe Lever

Note: The Uroject12 Syringe Lever is a multi-use device and must be sterilized or disinfected before use. Please follow the Sterilization or disinfection Instructions detailed in the Uroject12 Syringe Lever Instructions for Use.

- An ice bath to chill the vial of JELMYTO™ prior to instillation.



UroGen Pharma Uroject12 Syringe Lever



Ice Bath

The IFU does not specify disinfect or sterilization for injection of the drug (p. 2 of 7)?

Interactive Review (03/26/2020 – Sent by Fatima Rizvi)

#2 instructions for use (IFU) allow for either disinfection or sterilization of the Uroject12 Syringe Lever to inject the sterile drug into patients with cancer. Please justify the lack of specifying sterilization of the device for its use in the target patient population for the JELMYTO™ drug.

Deficiency Response

UroGen validated a high-level disinfection and (b) (4) sterilization **procedures** for the Uroject12 Syringe Lever ([K900419](#) – Ángel A. Soler-García, Lead Review).

The high-level disinfection procedure of the Uroject12 Syringe Lever was added its to the IFU (b) (4). Hence, this procedure was developed and validated to facilitate Uroject12 Syringe Lever use in all treatment facilities. (b) (4)

Based on the validation outcome, the high-level disinfection procedure can be considered acceptable for use and was cleared by the FDA in the Uroject12 IFU.

Additionally, the Uroject12 Syringe Lever does not come in contact with JELMYTO is filled in the sterile Medallion® instillation syringe, which is attached externally to the Uroject12 (only the syringe barrel, barrel flange and plunger flange come in contact with the device) and therefore is protected from cross-contamination.

The response adequately addresses the concern.

Table 2 UGN-101 Instillation Components (Section 3.2.P.2, p. 5 of 9)			
Device Name	Manufacturer	K Number	LOA Available
Vial Adaptor	Teva Medical	K141448	Yes
Syringe Adaptor	Teva Medical	K141448	Yes
20 mL Medallion® COP sterile syringe	Merit Medical	K152783	Yes
Uroject12 Lever	UroGen Pharma	K180345	Yes
Ureteral Catheter, 7Fr	UroGen Pharma	K180354	Yes
Or			
Ureteral Catheter, 5Fr	Multiple	Various	N/A
LOA = letter of authorization			

The drug IFU appears to apply the cleared devices in a way consistent with its cleared Indication for Use in the manner it is using the devices in the drug labeling. The General Hospital confirmed that they concur with this assessment.

General Hospital Devices

- [K141448](#) – TEVADAPTOR® Closed Drug Reconstitution and Transfer System
TEVADAPTOR® is a Closed System Drug Transfer Device (CSTD) that mechanically prohibits the release of the drug in vapor, aerosol or liquid form during preparation and administration, and prevents the introduction of microbial and airborne contaminants into the drug or fluid path, allowing the system to minimize exposure of individuals, healthcare personnel, and the environment to hazardous drugs.
- [K152783](#) – Merit 20 mL Syringe
Merit Syringe is used to inject fluids into, or withdraw fluids from, the body.

Urology Devices

- [K180354](#) – Uroject 12 Lever and UroGen Ureteral Catheter
The UroGen Ureteral Catheter is indicated for use by physicians for facilitating access to the urinary tract through a retrograde route and may be used in conjunction with guidewire or for the injection of gels or fluids into the urinary tract.
- Also [K190987](#) for Uroject12 - Uroject12 Syringe Lever Device is intended for use in the administration of sterile materials under aseptic conditions in a clinical urology setting, by a clinician and in accordance with the best judgement of a physician.

The Uroject 12 Lever and UroGen Ureteral Catheter and are both owned by the drug manufacturer and are used for the same indication cleared in it's the 510(k)s. The merit syringe and Tevadaptor are used in line with their indication. Therefore, there is no conflict between the drug labeling and the cleared indications for the devices used to both prepare and instill the drug.

Volume 002, Module 3, Section 3.2R ([\\CDSESUB1\evsprod\NDA211728\0002\m3\32-body-data\32r-reg-info](#)) and [3.2r-device.pdf](#) - link unknown – downloaded to PC

This document aims to show that all general requirements and essential performance requirements

(ERP) related to the UGN-101 development program are met. A [matrix](#) that follows provides traceability to the relevant documents which provide specific conclusions and results. The aim of the process is also to provide data in support of each medical device fitness for use, individually and together, as appropriate, with UGN-101.

The matrix is included below in this memo because it follows the elements suggested in 08/20/2019 email from Kristina Leahy to the sponsor and aligns the supporting documentation and reports to fulfil the 6 points of documentation listed in that email.

The referenced reports listed in the last column were reviewed and are adequate.

Index	Requirement or EPR	Description	Applicable Standards, Guidelines,	Results and Conclusions	Applicable Document
1.	Preparation Devices				
1.1.	A sterile CSTD system is required for preparation	The CSTD system shall comply with the requirements of FDA product code "ONB"	N/A	The specifications for the CSTD system to be used with UGN-101 require that it be FDA cleared under 510(k) for product code ONB. Conclusion: The component is sterile.	Specifications for devices utilized in support of UGN-101 drug use: PSP-0011950
		The CSTD system shall be provided sterile	N/A	The specifications for the CSTD system to be used with UGN-101 require that it be provided sterile Conclusion: The component is sterile.	Specifications for devices utilized in support of UGN-101 drug use: PSP-0011950
1.2.	The CSTD system shall enable use with the designated Luer-lock syringes	The CSTD system shall be compatible with a Luer- lock syringe	ISO 80369-7 (or ISO 594-1/2)	The specifications for the CSTD system to be used with UGN-101 require that it be compatible with a Luer-lock syringe Conclusion: The component is compatible with a luer-lock syringe.	Specifications for devices utilized in support of UGN-101 drug use: PSP-0011950

Index	Requirement or EPR	Description	Applicable Standards, Guidelines,	Results and Conclusions	Applicable Document
1.3.	The CSTD system shall enable use with the designated Vials	The CSTD system shall be compatible with a 20 mm crimp-neck vial	N/A	The specifications for the CSTD system to be used with UGN-101 require that it be compatible with a 20 mm crimp-neck vial Conclusion: The component is compatible with the vial.	Specifications for devices utilized in support of UGN-101 drug use: PSP-0011950

Index	Requirement or EPR	Description	Applicable Standards, Guidelines,	Results and Conclusions	Applicable Document
1.4.	EPR for the CSTD system – the CSTD system shall enable preparation of UGN-101 per the approved IFP document	The CSTD system shall enable preparation of UGN- 101 using routine processes for said – shall be verified and validated per predefined usability specifications	FDA Usability Guidance, 3-Feb-16	<p>The CSTD system enables preparation of the UGN-101 drug product using routine processes for – shall be verified and validated per predefined usability specifications</p> <p>Conclusion: The component is verified and validated per predefined usability specifications.</p>	<p>2. In-use stability and mixing Procedure robustness: DEV-(b)(4)-R-03</p> <p>3. Report for (b)(4) IFP validation test by Human Factors MD: VAL-R-0005188</p>
		The CSTD system shall be compatible with the UGN-101 drug product	N/A	<p>The CSTD system is compatible with the UGN-101 drug product</p> <p>Conclusion: The component is compatible.</p>	<p>In-use stability and mixing Procedure robustness: DEV-(b)(4)-R-03</p>

Index	Requirement or EPR	Description	Applicable Standards, Guidelines,	Results and Conclusions	Applicable Document
1.5.	A 20 mL Luer-lock syringe is required for preparation	The 20 mL Luer-lock syringe shall comply with the requirements of FDA product code "FMF"	N/A	The specifications for the 20 mL Luer-lock syringe to be used with UGN-101 require that it be FDA cleared under 510(k) for product code FMF Conclusion: The component is 510(k) cleared.	Specifications for devices utilized in support of UGN-101 drug use: PSP-0011950
The 20 mL Luer-lock syringe shall comply with all applicable standards		<ul style="list-style-type: none"> · ISO 80369-7 (or ISO 594-1/2) · ISO 7886-1 	The specifications for the 20 mL Luer-lock syringe to be used with UGN-101 require compliance with applicable standards Conclusion: The component complies with standards.	Specifications for devices utilized in support of UGN-101 drug use: PSP-0011950	
The 20 mL Luer-lock syringe shall be provided sterile		N/A	The specifications for the 20 mL Luer-lock syringe to be used with UGN-101 require that it be provided sterile Conclusion: The component is sterile.	Specifications for devices utilized in support of UGN-101 drug use: PSP-0011950	

Index	Requirement or EPR	Description	Applicable Standards, Guidelines,	Results and Conclusions	Applicable Document
1.6.	A 10 mL Luer-lock syringe is required for preparation	The 10 mL Luer-lock syringe shall comply with the requirements of FDA product code "FMF"	N/A	The specifications for the 10 mL Luer-lock syringe to be used with UGN-101 require that it be FDA cleared under 510(k) for product code FMF Conclusion: The component is 510(k) cleared.	Specifications for devices utilized in support of UGN-101 drug use: PSP-0011950
The 10 mL Luer-lock syringe shall comply with all applicable standards		<ul style="list-style-type: none"> · ISO 80369-7 (or ISO 594-1/2) · ISO 7886-1 	The specifications for the 10 mL Luer-lock syringe to be used with UGN-101 require compliance with applicable standards Conclusion: The component applies standards.	Specifications for devices utilized in support of UGN-101 drug use: PSP-0011950	
The 10 mL Luer-lock syringe shall be provided sterile		N/A	The specifications for the 10 mL Luer-lock syringe to be used with UGN-101 require that it be provided sterile Conclusion: The component is sterile.	Specifications for devices utilized in support of UGN-101 drug use: PSP-0011950	

Index	Requirement or EPR	Description	Applicable Standards, Guidelines,	Results and Conclusions	Applicable Document
1.7.	A 20-25G, 1" syringe needle, is required for preparation	The syringe needle shall comply with the requirements of FDA product code "FMI"	N/A	The specifications for the syringe needle to be used with UGN-101 require that it be FDA cleared under 510(k) for product code FMI Conclusion: The component is sterile.	Specifications for devices utilized in support of UGN-101 drug use: PSP-0011950
		The syringe needle shall comply with all applicable standards	ISO 7864	The specifications for the syringe needle to be used with UGN-101 require compliance with applicable standards Conclusion: The component applies standards.	Specifications for devices utilized in support of UGN-101 drug use: PSP-0011950
		The syringe needle shall be provided sterile	N/A	The specifications for the 20-25G, 1" syringe needle to be used with UGN-101 require that it be provided sterile Conclusion: The component is supplied sterile.	Specifications for devices utilized in support of UGN-101 drug use: PSP-0011950

Index	Requirement or EPR	Description	Applicable Standards, Guidelines,	Results and Conclusions	Applicable Document
1.8.	A Luer-lock to Luer-lock connector is required for preparation	The connector shall comply with the requirements of FDA product code "FMF"	N/A	The specifications for the connector to be used with UGN-101 require that it be FDA cleared under 510(k) for product code FMF Conclusion: The component is 510(k) cleared.	Specifications for devices utilized in support of UGN-101 drug use: PSP-0011950
		The connector shall comply with all applicable standards	ISO 80369-7 (or ISO 594-1/2)	The specifications for the connector to be used with UGN-101 require compliance with applicable standards Conclusion: The component applies standards.	Specifications for devices utilized in support of UGN-101 drug use: PSP-0011950

Index	Requirement or EPR	Description	Applicable Standards, Guidelines,	Results and Conclusions	Applicable Document
		The connector needle shall be provided sterile	N/A	The specifications for the connector to be used with UGN-101 require that it be provided sterile Conclusion: The component is sterile.	Specifications for devices utilized in support of UGN-101 drug use: PSP-0011950
1.9.	A chilling means is required for preparation	The chilling means shall enable cooling to 27 °F to 41 °F (-3 °C to 5 °C) for at least (b) (4) hours	N/A	The specifications for the chilling means to be used with UGN-101 require that it enable cooling to 27 °F to 41 °F (-3 °C to 5 °C) for at least (b) (4) hours Conclusion: The component maintains cooling accordingly.	Specifications for devices utilized in support of UGN-101 drug use: PSP-0011950
		The chilling means shall enable aseptic use	N/A	The specifications for the chilling means to be used with UGN-101 require that it enable cleaning and disinfection Conclusion: The component is labelled in a confusing manner. See deficiency 2.	Specifications for devices utilized in support of UGN-101 drug use: PSP-0011950

Index	Requirement or EPR	Description	Applicable Standards, Guidelines,	Results and Conclusions	Applicable Document
1.10.	EPR for the chilling means – the chilling means shall enable preparation of UGN-101 per the approved IFP document	The chilling means shall enable preparation of UGN-101 using routine processes for said – shall be verified and validated per predefined usability specifications	FDA Usability Guidance, 3-Feb-16	The chilling means enables preparation of the UGN-101 drug product using routine processes for said– shall be verified and validated per predefined usability specifications Conclusion: The component passes usability specification.	4. In-use stability and mixing Procedure robustness: DEV-(b)(4)-R-03 5. Report for (b)(4) IFP validation test by Human Factors MD: VAL-R-0005188
1.11.	EPR for all the preparation devices – the defined devices shall enable safe and effective preparation of UGN-101 per the approved IFP document and routine processes	The use of the mentioned devices shall be verified and validated for the safe and effective preparation of UGN-101 per predefined usability specifications.	FDA Usability Guidance, 3-Feb-16	The mentioned devices were verified and validated to be safe and effective for the preparation of UGN-101 per predefined usability specifications. Conclusion: The component passes usability specification.	1 In-use stability and mixing Procedure robustness: DEV-(b)(4)-R-03 2 Report for (b)(4) IFP validation test by Human Factors MD: VAL-R-0005188

Index	Requirement or EPR	Description	Applicable Standards, Guidelines,	Results and Conclusions	Applicable Document
2.5.	EPR for the catheter – the catheter shall enable administration of UGN- 101 per the approved IFU document	The catheter shall withstand the administration of UGN-101 without leaking at working temperature of 27 °F to 41 °F (-3 °C to 5 °C) at a rate of at least 15 mL/min	N/A	The catheter enables administration of the UGN-101 without leaking at the predefined parameters Conclusion: The component meets the predefined parameters.	<p>6. Evaluation of (b) (4) delivery chain for UTUC: DEV (b) (4) -R-01</p> <p>7. Report for evaluation of UGN-101 delivery chain performance with 5F catheter: Ver-R-0003719</p>
		The catheter shall withstand the administration of UGN-101 without breaking at working temperature of 27 °F to 41 °F (-3 °C to 5 °C) at a rate of at least 15 mL/min	N/A	The catheter enables administration of the UGN-101 without breaking at the predefined parameters Conclusion: The component does not break at the predefined parameters.	<p>3 Evaluation of (b) (4) delivery chain for UTUC: DEV (b) (4) -R-01</p> <p>4 Report for evaluation of UGN-101 delivery chain performance with 5F catheter: Ver-R-0003719</p>

Index	Requirement or EPR	Description	Applicable Standards, Guidelines,	Results and Conclusions	Applicable Document
		The catheter shall be compatible with the UGN-101 drug product	N/A	The catheter is compatible with the UGN-101 drug product Conclusion: The component is compatible	i. Catheter effect on Assay & IDD profile of (b) (4)™ Admixture: DEV- (b) (4)-R-05 ii. Evaluation Report of 5Fr Delivery Chain Effect on Assay & IDD Profile of UGN-101: DEV-R-0003535
2.6.	A piston syringe lever is required for administration	The syringe lever shall comply with the requirements of FDA product code "QBL"	N/A	The specifications for the syringe lever to be used with UGN-101 require that it be FDA cleared under 510(k) for product code QBL Conclusion: The component is 510(k) cleared.	Specifications for devices utilized in support of UGN-101 drug use: PSP-0011950

Index	Requirement or EPR	Description	Applicable Standards, Guidelines,	Results and Conclusions	Applicable Document
		The syringe lever shall enable aseptic use	N/A	The specifications for the syringe lever to be used with UGN-101 require that it enable cleaning and disinfection or sterilization Conclusion: The component can be disinfected and sterilized.	Specifications for devices utilized in support of UGN-101 drug use: PSP-0011950
2.7.	The syringe lever shall enable use with the designated 20 mL syringe for administration	The syringe lever be compatible with the 20 mL syringe	N/A	The specifications for the syringe lever to be used with UGN-101 require that it be compatible with a 20 mL syringe Conclusion: The component is compatible.	Specifications for devices utilized in support of UGN-101 drug use: PSP-0011950

Index	Requirement or EPR	Description	Applicable Standards, Guidelines,	Results and Conclusions	Applicable Document
2.8.	EPR for the syringe lever – the syringe lever shall enable administration of UGN-101 per the approved IFU document	The syringe lever shall enable administration of UGN-101 following the approved IFU – shall be verified and validated per predefined usability specifications	FDA Usability Guidance, 3-Feb-16	The syringe lever enables administration of the UGN-101 drug product following the approved IFU shall be verified and validated per predefined usability specifications The component is verified.	Results for (b) (4) administration validation test by Human Factors MD: VAL-R-0007901
2.9.	EPR for all the administration devices – The defined devices shall enable safe and effective administration of UGN-101 per the approved IFU document and routine processes	The use of the mentioned devices shall be verified and validated for the safe and effective administration of UGN-101 per predefined usability specifications.	FDA Usability Guidance, 3-Feb-16	The mentioned devices were verified and validated to be safe and effective for the administration of UGN-101 per predefined usability specifications. The component is verified.	Results for (b) (4) administration validation test by Human Factors MD: VAL-R-0007901

Closed System (Vial/Syringe Adaptor)

As part of the UGN-101 preparation, a closed system is applied to the mitomycin for solution vial to prevent exposure of the operator to cytotoxin and to allow the introduction of diluent into the vial.

Most studies used the Tevadaptor in the preparation of UGN-101 admixture, including, in-use and robustness study ([rpt-devmgr03-aadmixture](#)), leachable study (refer to section [3.2.P.2.4-admixture](#)) and all of the UGN-101 stability studies (section [3.2.P.8.3-admixture](#)).

Confirmation of the Tevadaptor's ability to act as a barrier to aerosol challenge, to maintain a sterile environment for up to 7 days and resist dry component disconnections are verifications of the acceptability of the Tevadaptor for use as a closed system.

STUDY SUMMARIES

Aerosol Challenge Test

The Tevadaptor was subjected to an aerosol challenge using *Bacillus atrophaeus* spores ([tech-info-tevadaptor-bacterial-aerosol-challenge](#)). The objective of this study was to see whether the Tevadaptor closed system could maintain sterility of the pharmaceutical preparations. This test compared the results of bacterial challenge between test samples and control samples. The challenge solution delivery rate was 20 mL per hour to a nebulizer attached to the aerosol exposure chamber. Test and control samples (first run: 30 sterile empty syringes with plunger half drawn out; second run: 28 sterile tryptic soy broth filled vials mounted with Tevadaptor) were exposed for 60 minutes. Aseptically placed gauze pieces (5 measuring 2 x 2 inches) were inside the chamber to monitor aerosol levels. The gauze pieces were extracted, diluted and plated onto soybean casein digest agar (SCDA) plates. All plates were incubated at 30°C to 35°C for 24 to 48 hours and enumerated. The results of both challenge runs are listed in [Table 3](#). The Tevadaptor provided a barrier to the infiltration of *Bacillus atrophaeus* spores into the exposed vials.

Table 3 Results of Aerosol Challenge of Tevadaptor versus Sterile Syringe

Sample Description	Run 1 Results	Run 2 Results
Test samples	Growth (30/30 syringes)	No growth (28/28 vials with Tevadaptor)
Negative samples	No growth (2/2)	No growth (2/2)
Positive samples	N/A	Growth (2/2)
Compromised jar of SCDB	Growth (1/1)	Growth (1/1)
Media monitor	No growth (1/1)	N/A
Environmental monitor	No growth (1/1)	N/A
Growth promotion	N/A	Growth (1/1)

N/A = not applicable

Sterility Maintenance

The ability of the Tevadaptor system to maintain sterility of pharmaceutical operations was assessed with 5 Tevadaptors mounted onto a 20-mL vial of sterile water. Each day, 1 mL of sterile water was aseptically transferred using a Tevadaptor syringe adaptor from each of the assemblies into a test tube containing 30 mL of tryptic soy broth (TSB) medium, and 1 mL was transferred into fluid thioglycollate medium (FTM). After each sampling, the assemblies were capped and maintained in a nonsterile area. The TSB tubes were incubated at $24^{\circ}\text{C} \pm 1^{\circ}\text{C}$ for 14 days and the FTM tubes were incubated at $31^{\circ}\text{C} \pm 1^{\circ}\text{C}$ for 14 days. A control sample was a sterile needle inserted into a 20-mL vial of sterile water. The negative control for each of the sterile media was a test tube without any manipulation, incubated along with the other treated samples.

The broth media (TSB) used for the sterility test was evaluated for the ability of specific organisms to use it as growth media. TSB was found to support growth of *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*, and *Aspergillus niger*. FTM was found to support *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Clostridium sporogenes*.

Samples were examined daily for 7 days for turbidity. No growth was observed in any of the test samples or the negative control ([tech-info-tevadaptor-sterility](#)).

Dry Disconnections

The Tevadaptor was tested for its ability to minimize the risk of exposure to potentially hazardous drugs using 10 vials each, containing 10 mL of pH 1 distilled water. The Tevadaptor was mounted on each vial. One mL of water was removed using a syringe assembly connected to the Tevadaptor assembly. Following the removal of water, litmus paper was used to wipe the surfaces of the vial adaptor and syringe adaptor septa for each of the 10 vials. All of the Tevadaptor assemblies tested showed no color change when wiped with litmus paper ([tech-info-closed-system-risk-test](#)).

Delivery Chain Validation

Delivery chains used for instillation of UGN-101 as listed in [Table 2](#), were used in the UT-001 study (formerly known TC-UT-P-03). Instillation procedure is detailed in the Physician Instructions for Use, ([IFU](#)).

To validate the delivery chains a DOE (Design of Experiment) model was used:

The first study supported a delivery chain composed of accessories listed in [Table 2](#) including UroGen **Ureteral 7Fr catheter** using sterile hydrogel¹. The tests were performed under a range of controlled hydrogel temperatures and injection speeds. The model shows that:

- (i) The delivery chain does not leak and remains structurally intact even at Peak Plunger Initiation and Average Expulsion Forces up to (b) (4)

- (ii) The DOE model predicts that no forces above (b) (4) will occur over the entire range of the injection process parameters, provided that the injection speed does not exceed 108 mm/min at a temperature not higher than 21°C.

The temperature and injection speeds selected for these DOE model tests ranged from lower than normal injection speed and temperature indicated for use, to higher than indicated injection speed and temperature (conditions in which the UGN-101 viscosity is at its semi-solid state for delivering 15 mL of UGN-101). Therefore, all other tested parameter combinations of lower injection speed or temperature will result in lower and safer injection forces. For further details refer to report [\(rpt-dev-rt-gel-del\)](#).

A similar DOE model was developed for the delivery chain tests with 20 mL Medallion® COP syringe and a representative **Ureteral 5Fr Catheter**. In this case, the model shows:

- iii. The delivery chain does not leak and remains structurally intact even at Peak Plunger Initiation and Average Expulsion Forces of up to (b) (4)
- iv. The DOE model predicts that no forces above (b) (4) will occur over the entire range of the injection process parameters, provided that the injection speed does not exceed 66 mm/min at a temperature not higher than 6°C.

For further details refer to evaluation report [rpt-verr-0003719](#).

The chemical compatibility of the delivery chain in contact with the UGN-101, i.e., the Medallion COP® syringe, UroGen Ureteral catheter 7 Fr (UC0001), and 5 Fr representative catheter was evaluated in [rpt-devmgr06-admixture](#), [rpt-devmgr05-admixture](#), and [rpt-devr-0003535](#), respectively. The syringe compatibility was evaluated by comparing the assay and impurities of UGN-101 (at worst case storage condition, following incubation of 9 hrs at 30°C) before and after 15-minute storage in the syringe. ¹ Hydrogel was chosen as the model in this study since it has “worst case” properties in terms of viscosity and liquid-gel transition temperature (~14°C) in comparison to the properties of UGN-101 (~16°C).

The catheter compatibility was evaluated by comparing the UGN-101 assay and impurities before and after injection through the catheter (admixture was delivered using the delivery chain at the end of its in-use holding period). Assay results from the compatibility studies of UGN-101 with delivery chain items are depicted at Table 4. The syringe and the catheters were found compatible, showing no effect on the UGN-101 assay and impurities level.

Table 4 The effect of representative delivery chain items on UGN-101 assay

Delivery chain item in contact with the UGN-101	Preparation number	UGN-101 assay (%)	
		Before contact with the delivery chain item	After contact with the delivery chain item
Medallion COP® syringe	P1	92	93
	P2	94	93
Medallion COP® syringe+ UroGen Ureteral catheter 7 Fr (UC0001)	P1	96	96
	P2		97
Medallion COP® syringe+5 Fr representative catheter	P1	98	100
	P2		102

Mixing and Instillation Instructions Validation (Human Factor Studies)

1. Human Factor Validation Study for Pharmaceutical Preparation:

A human factor validation study for pharmaceutical preparation was conducted according to Protocol VAL-P-0002270. The objective of the study was to conduct a simulated-use test in order to assess if the intended users (pharmacy professionals) could safely and effectively prepare the UGN-101 admixture in the expected-use environment, without risk of serious harm to the patient or themselves. Critical tasks such as review of known use problems and a use-related hazards analysis were evaluated. Each known use problem and use-related hazard was assessed to determine if a potential for harm to the user or the patient could or would occur. As stated in the FDA Guidance *Issued Feb 03, 2016: "Applying Human Factors and Usability Engineering to Medical Devices"*, harm included compromised medical care as well as harm to the user during the preparation. After reviewing each task involved in preparing the UGN-101 admixture, and any known use problems and use-related hazards associated with that task, all tasks that, if performed incorrectly or not performed at all, would or could cause serious harm to the user or the patient were included in the test. UGN-101 single-use carton and its associated IFP and devices, as listed in [Table 1](#), were received by 15 pharmacy professionals, each participant performed a UGN-101 preparation. During the preparation of UGN-101, a moderator observed and recorded all points of interaction between the participants and the UGN-101 admixture components, focusing on evidence of use-related issues on safety-critical tasks. Following completion of the preparation, the moderator engaged the participant in a post-simulation interview. The interview included questions designed to evaluate the participant's understanding of other critical aspects of use that could not be assessed through observations of simulated-use.

Performance in preparing a dose of the UGN-101 admixture was very strong, with 14 of 15 participants preparing a full and efficacious dose of 15 mL or more of

UGN-101. The human factors study protocol ([hf-ifp-protocol-val0002270](#)) and report ([hf-ifp-report-valr0005188](#)) are provided in section 5.3.5.4.

2. **Human Factor Validation Study for UGN-101 Instillation:**

A human factor validation study for UGN-101 instillation was conducted according to protocol DEV-P-0007253. The objective of the study was to assess if the intended users (urologists, nurses, and technicians) could safely and effectively instill UGN-101 in the expected-use environment, without risk of serious harm to the patient or themselves. A comprehensive use-related risk assessment to identify and analyze the potential use-related issues that might occur when the intended users instill UGN-101 was performed. The use-related risk analysis for the instillation of UGN-101 was built around the perception, cognition, and action task analysis methodology. The potential use-related risks associated with each task required to instill UGN-101 were considered. Each use-related risk was analyzed to determine the extent, if any, of the potential harm to the user or patient, the possible root causes of those hazards, and the potential risk controls that could be implemented to mitigate those hazards. The study included 45 representative UGN-101 users (15 urologists and 15 dyads (n = 30) of non-sterile nurses, and sterile nurses or technicians). The intended users in the study received a UGN-101 admixture vial, Physician Instructions for Use, (IFU) and devices, as listed in Table 2. Assistants participated in dyad sessions, where they prepared a syringe of UGN-101 that would later be instilled by the urologists. Urologists participated in individual sessions, where they instilled prepared UGN-101 into a manikin. After completing their respective tasks related to preparation or instillation, both user groups were asked a series of knowledge-based questions designed to evaluate their understanding of other critical aspects of use. There were no safety-related use issues experienced on any simulated-use task or knowledge-based task during this validation test. All 15 assistant dyads were successful in preparing a dose of UGN-101 for instillation, and all 15 urologists were successful in instilling the dose into the manikin. The study protocol and report ([hf-ifu-protocol-dev0007253](#) and [hf-ifu-report-valr0007901](#)) are also provided in section 5.3.5.4.

[Vol 002, Module 3.2r](#) – Reg. Info

Container closure system information for UGN-101 admixture (single-use carton) is provided in [Table 7](#).

Table 7 Container/Closure System for the UGN-101 Single-use Carton

Materials	Quantity Required
Sterile Hydrogel vial (20 mL of material in 30-mL clear vial)	1
Mitomycin for Solution vial (40 mg mitomycin in 100-mL amber vial)	2
1 x UGN-101 vial label	1
1 x Instructions for Pharmacy (*IFP) (section 1.14 - Labeling)	1
1 x Instructions for Use (*IFU) (for instillation only) (section 1.14 - Labeling)	1
1 x US Package Insert (*USPI)	1

Carton box	1
------------	---

*USPI + IFP + IFU are three separate documents included within the box.

14.3.1.3 – JELMYTO™ Instructions for Use (IFU)

The instructions specify that the drug is for use (i.e., to be mixed prior to injections) with specific devices. Those devices are not labeled for use to mix drug components. The drug is time dependent with a 4-minute limit total use life to include mixing and no more than 1 of those minutes to inject the mixture (Part D).

- You cannot instill JELMYTO without the Uroject12

[K180345/S001 Uroject12 Syringe Lever](#) [is cleared](#) for use in the administration of sterile materials under aseptic conditions, in a clinical urology setting, by a clinician and in accordance with the best judgment of a physician. This is a general indication.
- Do Not substitute any of these components (TEVADAPTOR® Syringe Adaptor HF; COP MEDALLION® 20 mL Luer Lock syringe; Ureteral Catheter with molded Luer lock port (5 Fr or 7 Fr); UroGen Pharma Uroject12 Syringe Lever; ice bath to chill the vial of JELMYTO prior to instillation) – The IFU directs the user to specific devices and those are not specifically for mixing liquids to form a gel.

Recommendation:

No additional deficiencies. The response provided 03/30/2020 adequately addressed the interactive review deficiencies. The devices are not supplied by the drug maker but are provided by the pharmacy mixing the drug preparation and the devices are used according to their indications for use. The devices can not be considered a combination product because the devices are not supplied with the drug and there is no cross labeling needed.

Digital Signature Concurrence Table	
Reviewer Sign-Off	
Team Sign-Off	

Appendix – Emails during Review

03.26.2020 Alan Stevens Email

From: Stevens, Alan M
Sent: Thursday, March 26, 2020 5:58 PM
To: Patel, Sapana; Young, Rumi; Seiler, Jim
Subject: Re: Related - Devices used according to their indications for use.

The use of these devices to transfer and administer drugs is within their indications. As Sapana mentions, the performance testing should have been conducted during review of the copackage. I can tell you that the 510k for these devices did not assess a product with the viscosity of this drug.

From: Patel, Sapana <Sapana.Patel@fda.hhs.gov>
Date: March 25, 2020 at 4:55:54 PM EDT
To: Stevens, Alan M <Alan.Stevens@fda.hhs.gov>, Young, Rumi <Rumi.Young@fda.hhs.gov>, Seiler, Jim <James.Seiler@fda.hhs.gov>
Subject: FW: Related - Devices used according to their indications for use.

Hi Jim,

I've copied Rumi and Alan for the Team 1 device which is the syringe. They can assist with the syringe IFU. I had one additional question that will help. You referenced an NDA, is there a way to determine if these devices were reviewed as part of the NDA [REDACTED] (b) (4), they are reviewed as part of the NDA prior to approval. I'm not certain if it was in this case.

Thanks

Regards,

Sapana Patel, PharmD., RAC
General Hospital Devices Team Lead

General Hospital Devices Team
DHT3C: Division of Drug Delivery and General Hospital Devices, and Human Factors| OHT3: Office of Gastrorenal, ObGyn, General Hospital and Urology Devices
Office of Product Evaluation and Quality

CDRH | Food and Drug Administration
White Oak, Bldg. 66, Rm. 2468|10903 New Hampshire Avenue | Silver Spring, MD 20993
Ph: (240) 402-4968
Sapana.patel@fda.hhs.gov



Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

<https://www.research.net/s/cdrhcustomerservice?ID=1533&S=E>

THIS MESSAGE IS INTENDED FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by email or telephone found above. This communication is consistent with 21 CFR 10.85(k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the view expressed.

From: Seiler, Jim
Sent: Wednesday, March 25, 2020 4:33 PM
To: Patel, Sapana <Sapana.Patel@fda.hhs.gov>
Subject: Related - Devices used according to their indications for use.

Sapana,

I need your help on confirmation of something I said in a review about devices being used according to their indications for use. This was for an Intercenter consult about a urology drug review.

First, from the email the other day, you were correct about the chilling block (a Physical Medicine device) and I talked with Vivek Pinto about that and his advice lead me to research that category and decide the chilling unit is a tool used in the preparation of the drug.

Second – Indications for use.

There are 4 other devices used to: a) prepare/mix/reconstitute the components of the drug and b) to administer/instill/place the product. I am trying to only confirm that the firm’s statement is correct – that the devices are used according to their indications for use.

- Two are urological – ureteral catheter and the UroJect 12 Syringe Lever - I reviewed those and I believe they are used according to their indication for use.
- The remaining two devices are General Hospital devices: **Tevadaptor Syringe Adaptor, and the COP Medallion 20 ml Luer Lock Syringe.**

I also looked up in CTS the following review numbers and lead reviewers (follow the links in the table below):

510k in CTS	Reviewer	Public Database Indication for use
K152783/S001	Janice Ferguson	K152783 ; Indication - https://www.accessdata.fda.gov/cdrh_docs/pdf15/K152783.pdf
K141448/S001	Ryan McGowan	K141448 ; Indication – https://www.accessdata.fda.gov/cdrh_docs/pdf14/K141448.pdf

So my question is whether you, or someone on your staff could read over the attached instructions and confirm that the Tevadaptor Syringe Adaptor, and the COP Medallion 20 ml Luer Lock Syringe are used in accordance with their indication for use? They are also available at this location: ([\CDSESUB1\evsprod\NDA211728\0002\m1\us\114-labeling\114a-draft-label](#))

Here is some background on the drug that is being mixed.

UGN-101 (mitomycin gel) for instillation, 0.4% (UGN-101) is intended for the treatment of low-grade Upper Tract Urothelial Cancer (UTUC). The UGN-101 drug-product is provided in a single-use carton which contains sterile hydrogel and mitomycin for solution that need to be mixed together (reconstituted) by a healthcare professional prior to administration (instillation). Once reconstituted, it has a special characteristic that makes it liquid at cold temperatures and gel at around room temperature, so it needs to be chilled in order to instill the admixture. Once instilled into the patient's upper urinary tract, it forms a gel, thereby exposing the tissue to mitomycin over a prolonged period of time. UGN-101 is viscous, even when it is a liquid in a chilled state.

The UGN-101 preparation (mixing) and administration processes require several devices utilized in support of drug use, as detailed below:

Preparation Devices

CSTD system comprising of a vial adaptor and a syringe adaptor

Female to Female Luer-lock connector 10 mL sterile Luer-lock syringes (x2) 20 mL sterile Luer-lock syringe

Syringe needle Chilling Device

Administration Devices CSTD syringe adaptor 20 mL Luer-lock syringe

Ureteral Catheter (5 Fr or 7 Fr) Syringe Lever

Use of the mentioned devices for preparation and administration of UGN-101 would be in accordance with the *Indications for Use* of each respective medical device (pharmacy supplies listed above). The labeling for each medical device is consistent with the mixing, preparation and administration of UGN- 101, without alteration. These devices commercially available in the USA, are supplied separately to the Pharmacy and are not currently provided with UGN-101.

Ancillary Supplies

(to be provided by your facility):

⚠ Do not substitute any of these components.

- TEVADAPTOR® Syringe Adaptor HF
- COP MEDALLION® 20 mL Luer Lock syringe
- Ureteral Catheter with molded Luer lock port (5 Fr or 7 Fr)
- UroGen Pharma Uroject12 Syringe Lever

Note: The Uroject12 Syringe Lever is a multi-use device and must be sterilized or disinfected before use. Please follow the sterilization or disinfection instructions detailed in the Uroject12 Syringe Lever Instructions for Use.

- An ice bath to chill the vial of JELMYTO prior to instillation.



TEVADAPTOR® Syringe
Adaptor HF

COP MEDALLION® 20 mL Luer
Lock syringe

Ureteral Catheter with molded
Luer lock port



Thanks,

Jim Seiler
240-205-2495

From: Seiler, Jim
Sent: Monday, March 23, 2020 1:08 PM
To: Patel, Sapana <Sapana.Patel@fda.hhs.gov>
Cc: Kiang, Tina <Tina.Kiang@fda.hhs.gov>; Betz, Martha <Martha.Betz@fda.hhs.gov>
Subject: RE: 890.5940 - Chilling unit

Sapana,

Maybe I have the wrong branch?

You re right that 890.5940 is a Physical Medicine classification – do you know who currently works in that section?

I could not find it in the new org chart
(<http://inside.fda.gov:9003/downloads/CDRH/OfficeoftheDirector/UCM608756.pdf>).

I am following this lead only because the component which does not have a 510k is the “Chilling Unit” which I think the company believes falls under that cited regulation.

Thank you,

Jim Seiler

From: Patel, Sapana <Sapana.Patel@fda.hhs.gov>
Sent: Monday, March 23, 2020 1:01 PM
To: Seiler, Jim <James.Seiler@fda.hhs.gov>
Cc: Kiang, Tina <Tina.Kiang@fda.hhs.gov>; Betz, Martha <Martha.Betz@fda.hhs.gov>
Subject: RE: 890.5940 - Chilling unit

Hi Jim,

Just want to clarify are you asking if the cold packs are what is intended to be chilled by the chilling units? Or asking if the urogen pharma that you have pictured is under this classification. I would need additional info, as I don't believe the 890.5940 is a GH regulation.

Regards,

Sapana Patel, PharmD., RAC
General Hospital Devices Team Lead

General Hospital Devices Team
DHT3C: Division of Drug Delivery and General Hospital Devices, and Human Factors| OHT3: Office of Gastrorenal, ObGyn, General Hospital and Urology Devices
Office of Product Evaluation and Quality

CDRH | Food and Drug Administration
White Oak, Bldg. 66, Rm. 2468|10903 New Hampshire Avenue | Silver Spring, MD 20993
Ph: (240) 402-4968
Sapana.patel@fda.hhs.gov



Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

<https://www.research.net/s/cdrhcustomerservice?ID=1533&S=E>

THIS MESSAGE IS INTENDED FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this

document in error, please immediately notify us by email or telephone found above.
This communication is consistent with 21 CFR 10.85(k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the view expressed.

From: Seiler, Jim
Sent: Monday, March 23, 2020 12:50 PM
To: Patel, Sapana <Sapana.Patel@fda.hhs.gov>
Cc: Kiang, Tina <Tina.Kiang@fda.hhs.gov>; Betz, Martha <Martha.Betz@fda.hhs.gov>
Subject: 890.5940 - Chilling unit

Hi Sapana:

I have a question about a General Hospital classification.

A classification exists in the [Physical Medicine](#) device panel ([890.5940](#) - Chilling unit) that is classified as Class I, Exempt from 510(k). The limits of exemption (from 510(k)) are based on the classification of the device, and under 21 CFR [890.5940](#) a chilling unit is a refrigerative device intended for medical purposes to chill and maintain cold packs at a reduced temperature.

1. Those cold packs are things like the “Blue Gel” packs or similar?

I have a reference to a chilling unit mentioned in a CDER review, but it is not for maintaining “blue ice” cold packs at a reduced temperature, instead it is to provide a cooling environment for drug components before they are mixed.



2. Would you say a unit like this could be either: a) part of the [890.5940](#) classification because its just cooling something, or b) should be classified as something else – and if you recommend this – do you know what this would be part of? The only “chill” anything in the device classification database is 890.5940.

James Seiler

Electrical Engineer | MDR Analyst
THT3B3: Urological Devices Team
DHT3B: Division of Reproductive, Gynecology and Urology Devices
OHT 3: Office of Gastro, ObGyn, General Hospital and Urology Devices

CDRH | Food and Drug Administration
White Oak, Bldg. 66 | Room 2623 | 10903 New Hampshire Avenue | Silver Spring, MD 20993

Ph: (301) 796-6558
James.Seiler@fda.hhs.gov



Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: <https://www.research.net/s/cdrhcustomerservice?ID=1523&S=E>
THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by email or telephone.

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

03.24.2020 Sarah Mollo Email

From: Mollo, Sarah
Sent: Tuesday, March 24, 2020 6:22 PM
To: Seiler, Jim; Bertram, James
Cc: CDRH Product Jurisdiction
Subject: RE: followup after email

Hi Jim,

The device components that are used to used to prepare and administer the drug product appear to be provided by the facility and are not included (e.g. co-packaged or pre-filled) with the drug product, which is provided in a vial (see below); if that is the case, then I don't think the product would be considered a combination product.

I think in your previous email strings you were concerned if the products were being used consistent with their clearance? If that is not clear from your review of the submission, you could ask the CDRH review group who cleared the products, if they believe use is inconsistent with the labeling. If you plan to do that, I would at least include 1) the indications for the drug, 2) how the devices will be used, and 3) what specifically appears to be inconsistent based on the cleared use.

Ancillary Supplies

(to be provided by your facility):

 **Do not substitute any of these components.**

- TEVADAPTOR® Syringe Adaptor HF
- COP MEDALLION® 20 mL Luer Lock syringe
- Ureteral Catheter with molded Luer lock port (5 Fr or 7 Fr)
- UroGen Pharma Uroject12 Syringe Lever

Note: The Uroject12 Syringe Lever is a multi-use device and must be sterilized or disinfected before use. Please follow the sterilization or disinfection instructions detailed in the Uroject12 Syringe Lever Instructions for Use.

- An ice bath to chill the vial of JELMYTO prior to instillation.



TEVADAPTOR® Syringe
Adaptor HF

COP MEDALLION® 20 mL Luer
Lock syringe

Ureteral Catheter with molded
Luer lock port



Hope this helps. Please let me know if you have additional questions.

Thank you,

Sarah

Sarah Mollo, Ph.D, RAC
Combination Product Policy Analyst (Detail)

Combination Products and OHT Regulatory Support Team 2
Regulations, Policy, and Guidance Staff
Office of Product Evaluation and Quality (OPEQ)

CDRH | Food and Drug Administration
White Oak, Bldg. 66, Rm. 1643 | 10903 New Hampshire Avenue | Silver Spring, MD 20993
Phone: (301) 796-5517
Sarah.mollo@fda.hhs.gov



Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: <https://www.research.net/s/cdrhcustomerservice?ID=1042&S=E>



From: Seiler, Jim <James.Seiler@fda.hhs.gov>
Sent: Tuesday, March 24, 2020 1:33 PM
To: Mollo, Sarah <Sarah.Mollo@fda.hhs.gov>; Bertram, James <James.Bertram@fda.hhs.gov>
Subject: RE: followup after email

Hi Sarah and James.

I finished an Intercenter consult (Attached).

To spare you from reading most of that, pages 2 to 4 have my comments about combination products.

I believe that based on <https://www.fda.gov/combination-products/about-combination-products/combination-product-definition-combination-product-types> I think the devices used in preparation of the drug are group #3, type 7 or 8.

I saw in the emails that there was a statement from CDERs CMC group that they believed this was not a combination product. Was that a message that went to the company?

Also, when devices appear to be used in accordance with their own indications for use, is there still a combination product? Or does the combo criteria only activate if the labeling needs to change in the drug or in the device?

Thanks,

Jim

-----Original Appointment-----

From: Mokhtarzadeh, Maryam <Maryam.Mokhtarzadeh@fda.hhs.gov>
Sent: Tuesday, March 24, 2020 12:09 PM
To: Seiler, Jim; Chang, Cherryn; Mollo, Sarah
Subject: Canceled: followup after email
When: Tuesday, March 24, 2020 4:00 PM-4:30 PM (UTC-05:00) Eastern Time (US & Canada).
Where: webex
Importance: High

As mentioned in a separate email, I am recommending that Jim followup with James or Sarah at this time. They can let me know if additional support is needed. Thanks, everyone, for all your hard work on this. I realize it's a tough time and hope you are all doing well.

M

Jim,
Please let me know if this is a good time to talk.

M

03.23.2020 Vivek Pinto Email

From: Seiler, Jim
Sent: Monday, March 23, 2020 6:11 PM
To: Pinto, Vivek
Cc: Betz, Martha; Ballard, Amber
Subject: RE: 890.5940 - Chilling unit

Vivek,

It is part of a CDER intercenter consult and I should have been at this point much earlier in the review.

- Jim

From: Pinto, Vivek <Vivek.Pinto@fda.hhs.gov>
Sent: Monday, March 23, 2020 6:09 PM
To: Seiler, Jim <James.Seiler@fda.hhs.gov>
Cc: Betz, Martha <Martha.Betz@fda.hhs.gov>; Ballard, Amber <Amber.Ballard@fda.hhs.gov>
Subject: RE: 890.5940 - Chilling unit

Hi Jim,

I'm just cc'ing Amber Ballard, acting Team Lead for the Neurodegenerative Devices team to take a look. Question – is this for a (b) (4) or just a general inquiry?

Thanks,

Vivek

Vivek Pinto, PhD

Director, DHT5B: Division of Neuromodulation and Physical Medicine Devices

OHT5: Office of Neurological and Physical Medicine Devices | Office of Product Evaluation and Quality
CDRH | Food and Drug Administration
White Oak, Bldg. 66, Rm. 4108 | 10903 New Hampshire Avenue | Silver Spring, MD 20993
Ph: (301) 796-1136

Vivek.Pinto@fda.hhs.gov



Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

<https://www.research.net/s/cdrhcustomerservice?ID=1723&S=E>

From: Seiler, Jim <James.Seiler@fda.hhs.gov>
Sent: Monday, March 23, 2020 5:31 PM
To: Pinto, Vivek <Vivek.Pinto@fda.hhs.gov>
Cc: Betz, Martha <Martha.Betz@fda.hhs.gov>
Subject: RE: 890.5940 - Chilling unit

Vivek,

Thanks for your council by messenger. I did what you said to look up 890.5470 under IMF and the two

devices are not like the regulation description. I am adding this into my memo to capture my research

There is no 510(k) for a UroGen Chilling Block, yet the chilling block does not appear to fit its nearest classification category.

A classification exists in the [Physical Medicine](#) device panel ([890.5940](#) - Chilling unit) that is classified as Class I, Exempt from 510(k). The limits of exemption (from 510(k)) are based on the classification of the device, and under 21 CFR [890.5940](#) a chilling unit is a refrigerative device intended for medical purposes to chill and maintain cold packs at a reduced temperature.

I chatted with Viviek Pinto, a supervisor in the Physical Medicines team. He has never seen a submission for this type of device and he suggested to investigate the two devices under 890.5940 (see IMF product code). The two devices ([K871112](#) and K900419), reviewed over 30 years ago where both from the same company and used to deliver a cooling type therapy to the device. The Chiller Unit is not used to deliver treatment to a patient. Therefore, I agree that the chiller unit is a tool and not a device as it is not intended to treat a disease and is not labelled that way.

The chilling unit described in this 510(k) is not for maintaining cold packs at a reduced temperature, however its not labelled for treating any disease, the Physical Medicine review group should concur with this analysis.

Thanks,

Jim Seiler

From: Kiang, Tina <Tina.Kiang@fda.hhs.gov>

Sent: Monday, March 23, 2020 1:19 PM

To: Seiler, Jim <James.Seiler@fda.hhs.gov>; Patel, Sapana <Sapana.Patel@fda.hhs.gov>; Pinto, Vivek <Vivek.Pinto@fda.hhs.gov>

Cc: Betz, Martha <Martha.Betz@fda.hhs.gov>

Subject: RE: 890.5940 - Chilling unit

Hi,

Physical medicine is under Vivek Pinto. I have copied him on this email. Thanks.

Tina Kiang, Ph.D.

Director

DHT3C: Division of Drug Delivery and General Hospital Devices and Human Factors |
OHT3: Office of Gastrorenal, OB/GYN, General Hospital, and Urology Devices |
Office of Product Evaluation and Quality

CDRH | Food and Drug Administration

White Oak, Bldg. 66, Rm. 2516 | 10903 New Hampshire Avenue | Silver Spring, MD 20993

Ph: 301-796-7030 | Fax: 301-847-8109

tina.kiang@fda.hhs.gov



Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: <https://www.research.net/s/cdrhcustomerservice?ID=1530&S=E>

From: Seiler, Jim <James.Seiler@fda.hhs.gov>

Sent: Monday, March 23, 2020 1:08 PM
To: Patel, Sapana <Sapana.Patel@fda.hhs.gov>
Cc: Kiang, Tina <Tina.Kiang@fda.hhs.gov>; Betz, Martha <Martha.Betz@fda.hhs.gov>
Subject: RE: 890.5940 - Chilling unit

Sapana,

Maybe I have the wrong branch?

You re right that 890.5940 is a Physical Medicine classification – do you know who currently works in that section?

I could not find it in the new org chart

(<http://inside.fda.gov:9003/downloads/CDRH/OfficeoftheDirector/UCM608756.pdf>).

I am following this lead only because the component which does not have a 510k is the “Chilling Unit” which I think the company believes falls under that cited regulation.

Thank you,

Jim Seiler

From: Patel, Sapana <Sapana.Patel@fda.hhs.gov>
Sent: Monday, March 23, 2020 1:01 PM
To: Seiler, Jim <James.Seiler@fda.hhs.gov>
Cc: Kiang, Tina <Tina.Kiang@fda.hhs.gov>; Betz, Martha <Martha.Betz@fda.hhs.gov>
Subject: RE: 890.5940 - Chilling unit

Hi Jim,

Just want to clarify are you asking if the cold packs are what is intended to be chilled by the chilling units? Or asking if the urogen pharma that you have pictured is under this classification. I would need additional info, as I don't believe the 890.5940 is a GH regulation.

Regards,

Sapana Patel, PharmD., RAC
General Hospital Devices Team Lead

General Hospital Devices Team
DHT3C: Division of Drug Delivery and General Hospital Devices, and Human Factors| OHT3: Office of Gastrorenal, ObGyn, General Hospital and Urology Devices
Office of Product Evaluation and Quality

CDRH | Food and Drug Administration
White Oak, Bldg. 66, Rm. 2468|10903 New Hampshire Avenue | Silver Spring, MD 20993
Ph: (240) 402-4968
Sapana.patel@fda.hhs.gov





Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

<https://www.research.net/s/cdrhcustomerservice?ID=1533&S=E>

THIS MESSAGE IS INTENDED FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by email or telephone found above.

This communication is consistent with 21 CFR 10.85(k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the view expressed.

From: Seiler, Jim

Sent: Monday, March 23, 2020 12:50 PM

To: Patel, Sapana <Sapana.Patel@fda.hhs.gov>

Cc: Kiang, Tina <Tina.Kiang@fda.hhs.gov>; Betz, Martha <Martha.Betz@fda.hhs.gov>

Subject: 890.5940 - Chilling unit

Hi Sapana:

I have a question about a General Hospital classification.

A classification exists in the [Physical Medicine](#) device panel ([890.5940](#) - Chilling unit) that is classified as Class I, Exempt from 510(k). The limits of exemption (from 510(k)) are based on the classification of the device, and under 21 CFR [890.5940](#) a chilling unit is a refrigerative device intended for medical purposes to chill and maintain cold packs at a reduced temperature.

1. Those cold packs are things like the “Blue Gel” packs or similar?

I have a reference to a chilling unit mentioned in a CDER review, but it is not for maintaining “blue ice” cold packs at a reduced temperature, instead it is to provide a cooling environment for drug components before they are mixed.



1 x UroGen Pharma
Chilling Block

2. Would you say a unit like this could be either: a) part of the [890.5940](#) classification because its just cooling something, or b) should be classified as something else – and if you recommend this – do you know what this would be part of? The only “chill” anything in the device classification database is

890.5940.

James Seiler

Electrical Engineer | MDR Analyst

THT3B3: Urological Devices Team

DHT3B: Division of Reproductive, Gynecology and Urology Devices

OHT 3: Office of Gastro, ObGyn, General Hospital and Urology Devices

CDRH | Food and Drug Administration

White Oak, Bldg. 66 | Room 2623 | 10903 New Hampshire Avenue | Silver Spring, MD 20993

Ph: (301) 796-6558

James.Seiler@fda.hhs.gov



Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: <https://www.research.net/s/cdrhcustomerservice?ID=1523&S=E>
THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by email or telephone.

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.