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Business, Consumer Services and Housing Agency
Department of Consumer Affairs
Gavin Newsom, Governor

To: Board Members

Subject: Agenda Item V. Discussion and Consideration of Requests to Waive Pharmacy Law Provisions Consistent with the Authority of Business and Professions Code section 4062

Consideration of Site-Specific Waiver, Exela Pharmacy Sciences, BPC 4129.8 Temporary License

Background

In light of Governor Gavin Newsom's declaration of emergency and the national declaration of emergency, and consistent with Business and Professions Code (BPC) section 4062, the California State Board of Pharmacy (Board) or the Board president through delegated authority has been issuing waivers of Pharmacy Law or its regulations adopted pursuant to it, if in the board's opinion the waiver will add in the protection of public health or the provisions of care. In general, waivers are limited in duration as determined by the Board, or by the Board president as delegated by the Board, unless the waiver resulted in the issuance or renewal of a license.

Since that time the Board approved several waivers and has delegated authority to the Board's to issue waivers for up to 90-days and further to grant up to two extensions, for an addition 90 days per extension.

Specific to this agenda item, on June 23, 2020, the Board issued temporary licenses to Exela Pharma Sciences LLC, NSF 136 and NSF 137, after approval of a limited waiver to BPC 4129.2(c) to allow for such issuance without an inspection. Consistent with the provisions of a temporary license, these licenses will expire on December 15, 2020.

Multiple data points and documents were reviewed by the inspectors and discussed with the quality staff and other personnel in advance of the approval of the waiver including the following:

- Floor plan of the facility
- Organizational chart, Staff list, staff duties as appropriate, resumes for new staff
- Appropriate and any updated Standards of Practice (SOP), table of contents for all SOPs
- FDA, DEA and/or accreditation inspections
- List of products and expiry dates and new processes, stability studies as appropriate
- Products, formulations, validations and stability studies and method suitability
- IOPQ of equipment
- Vendor qualifications and quality agreements for vendors done in the last 12 months
- Compounding area certification and all appropriate Lumacs for manufacturing
- Quality assurance reports, micro trending

- Adverse drugs events within the last 12 months and FDA reporting
- Any recalls in the last 12 months and the FDA reporting
- Annual Product reviews

Further, as part of the approval process, Board staff requested quarterly reporting of batches produced and sent into California along with information on batches rejected. October 12, the Board received the first quarterly report. Exela reports that during the reporting period, July 1 – September 30, 2020, it has shipped 60 vials of midazolam into California. Further, Exela reports that none of the batches of the various products produced during the reporting period have been rejected.

<u>For Board Discussion and Consideration</u>
As current law prevents the issuance of a temporary license for a period greater than 180 days, during this meeting, members will have the opportunity to consider a waiver from BPC section 4129.8 related to temporary licenses. With restrictions on travel outside of California remain, Board staff cannot complete the necessary inspection until conditions improve.

Because of the timing of the Board meeting in December, this issue is being brought to the Board for consideration during this meeting. Board staff is recommending that the Board consider an extension of the temporary license for an additional 180 days from the current date of expiration, unless public protection issues are identified. Staff note the potential need for COVID related products if there is a shortage for patients on ventilators. Alternatively, the Board may wish to delegate to the Board's president the authority to extend a temporary license for 180 days as appropriate.

Following this memo is the quarterly report provided by Exela.

EXELA
PHARMA SCIENCES

Quarterly Report Card

3nd Quarter: July 1st through September 30th 2020

STERILE INJECTABLE MANUFACTURER

Licensed 503B Outsourcing Facility

Exela Pharma Sciences, LLC
1245 Blowing Rock Blvd
Lenoir, NC 28645
(828) 758-5474

I. Brief Introduction To Exela

Exela is an award-winning fast-growing FDA-registered cGMP manufacturer with over ten years of commercial manufacturing of sterile injectable products (both NDAs and ANDAs). We have over 350 employees and our operations encompass four buildings totaling over 450,000 sqft of state-of-the-art manufacturing, analytical laboratories, warehousing, inspection, labeling, packaging, and shipping activities. Over 30 FDA Approved SKUs for the US, Canada, and Australian markets are manufactured with additional pending NDAs and ANDAs. Exela is the sole supplier of seven NDA drug products in the country today. Exela employs flexible manufacturing practices to commercially produce cGMP product on short notice.

Our cGMP compliance record is one of the best in the industry. We have been inspected by the FDA fourteen times in the past 9+ years. Such inspections resulted in no findings. All the observations when found have been addressed promptly and completely. There are no outstanding 483 responses. The last FDA inspection was in October 2019 which ended with no findings.

In addition to being a cGMP manufacturer, Exela is also an FDA-registered 503B facility. Exela in fact was the first cGMP manufacturer to register with the FDA as a 503B facility, having done so **solely** to provide cGMP manufactured drug product on a commercial scale in cases of national drug shortages such as now.

Exela manufactures its compounded products in its currently approved cGMP facilities, using cGMP processes, and cGMP trained personnel, in the same way as we manufacture approved NDA and ANDA products, and under the supervision of a registered pharmacist.

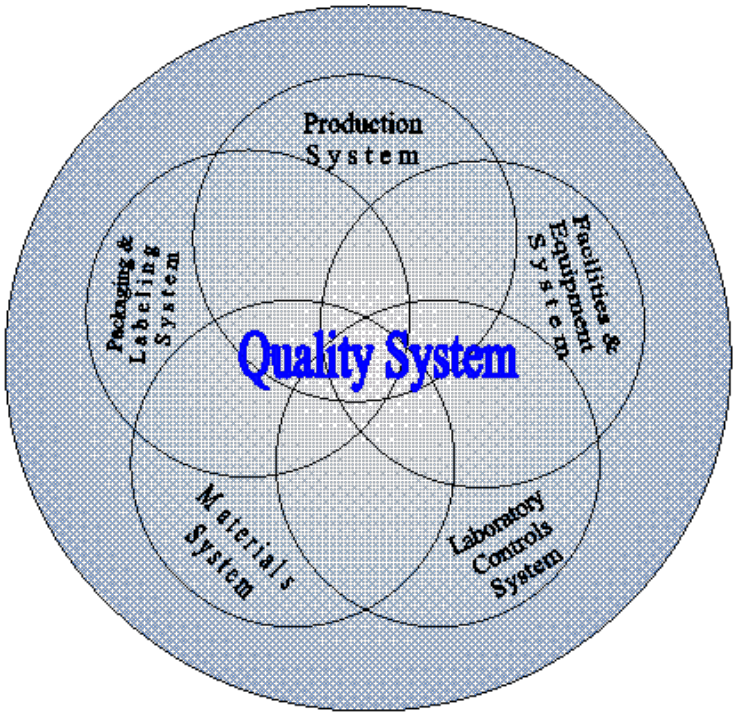
II. Exela Pharma Sciences Quality Systems

Exela's Quality System follows the FDA 6 System approach endorsed by FDA as part of cGMP operations. Primarily a provider of cGMP NDA/ANDA products, Exela is in the unique position of having superior quality systems to support 503b manufacturing. These systems govern our approach to the procedures, practices and behaviors we execute each day. Following best practices and FDA requirements our processes and products are designed from the start with quality and compliance in mind. Like FDA, our overarching quality philosophy is:

III. Quality should be built into the product, and testing alone cannot be relied on to ensure product quality

Exela manufactures product in compliance with 21 CFR Parts 210 and 211. We follow strict cGMP that exceeds the requirements of routine 503b production. Our 503b manufacturing represents less than 1% of our overall volume, the rest being approved NDA's and ANDA's. We only perform 503B services during times of severe drug shortages to help alleviate that shortage. Our facilities have been inspected 14 times by the FDA, of which six times we had no 483 observations. Our latest inspection in October 2019 resulted in no 483 findings.

Exela Pharma Sciences System Elements



Key Elements	Details
Quality System	Includes the management system, QA and Compliance, Documentation/GDP, Training, Deviation/CAPA, Internal Audit, Annual Product Reviews (APRs), Complaints
Documentation and Training	Routine GMP training for all personnel, Qualification of personnel to role designed training plans, routine periodic training evaluation/supplementation, competency assessment for key processes.
Material Control	Sourcing, Vendor Management, Supplier Qualification and Auditing, Material Controls, Quarantine/Release of materials
Validation	Aseptic Validation/Simulations (Media Fills), Equipment Qualification (IOPQ), Process Validation, Cleaning Validation, Risk Assessments, Part 11 and Data Integrity Compliance
Environmental Monitoring	Consistent with FDA and EU regulations, continuous monitoring of GMP activities, routine EM sampling and personnel monitoring, Disinfectant Efficacy Studies, Gowning Qualification
Production System and Controls	Fully compliant batch records with QA oversight, pharmacist oversight of critical operations, in process testing and monitoring, Routine EM controls, Continuous room monitoring, Hold Times,
Packaging/Labeling	Label Compliance and Control, Cleaning and Clearance of lines, AQL Inspection of finished goods, Package Design
Laboratory and Stability	State of the art laboratory, USP testing, Method qualification/validation, Specification Controls, Strict sample management, Stability Studies/Storage all conducted in house

Exela Pharma Sciences

Environmental/Facility Monitoring

Q3-2020

Particulate					
Non-Viable Particulates			Viable Particulate		
Class	Limit	Result	Class	Limit	Result
A	ISO 14644-1	Acceptable	A	<1 CFU/m^3	Acceptable
B		Acceptable	B	<10 CFU/m^3	Acceptable
C		Acceptable	C	<100 CFU/m^3	Acceptable
D		Acceptable	D	<200 CFU/m^3	Acceptable

Surfaces and Personnel					
Surface Monitoring			Personnel		
Class	Limit	Result	Class	Limit	Result
A	<1 CFU	Acceptable	A/100	<1 CFU	Acceptable
B	<5 CFU	Acceptable			
C	<25 CFU	Acceptable	B/10,000	<5 CFU	Acceptable
D	<50 CFU	Acceptable			

Utilities					
Water for Injection			Clean Compressed Air		
TOC	≤500 ppb	Acceptable	NV Particulate	ISO 14644-1	Acceptable
Conductivity	Conforms to USP	Acceptable	Viable Particulate		Acceptable
Bioburden	<10 CFU/100 mL	Acceptable	Chemical Quality	Oil/Water Free	Acceptable
Endotoxin	<0.25 EU/mL	Acceptable			

EXELA PHARMA SCIENCES

FINISHED PRODUCT CERTIFICATE OF ANALYSIS

PRODUCT: Midazolam Injection (1 mg/mL), 100 mg/ 100 mL, 100 mL Vial	CATALOG NUMBER: 10020TS005	CORE LOT NUMBER: PACKAGED LOT NUMBER:

Test	Methods[1]	Specifications	Results
Physical Appearance and Description A: Solution Description B: Container / Closure Appearance C: Visual Particulate Matter	QCTM-216	A. Clear colorless to red/brown solution. B. No visible leak, precipitate, or other C. Essentially free of visible particulate matter.	A: Conforms B: Conforms C: Conforms
Identification A: HPLC Retention Time B: UV Spectrum (200 - 400 nm)	 A.RDTM-000197 B.RDTM-000197	 A. The retention time of the peak in the Sample solution corresponds to that of the Reference Standard solution, as obtained in the test for Assay. B. The UV Spectrum of the Sample solution corresponds to that of the Reference Standard Solution, as obtained in the test for Assay.	 A: Conforms B: Conforms
pH	USP <791> QCTM-215	3.0 - 4.0	3.5
Assay	RDTM-000197	90.0 - 110.0% Label Claim of Midazolam	99.7%
Fill Volume	USP <697> QCTM-217	NLT 100 mL	104 mL
Osmolality	USP <785>	240 - 290 mOsm/kg	262 mOsm/kg
Container Closure Integrity, Helium Leak	USP <1207>	NMT 6 x 10^{-6} std cc/sec	Conforms
Particulate Matter, per Container: A. ≥10µm B. ≥25µm	USP <788>, Method I USP <1788> QCTM-000083	 A: NMT 6,000 B: NMT 600	 A: 273 B: 11
Related Substances: A. Reduce Midazolam (EP Inpurity I)[3] B. Reduced Midazolam (EP Impurity J)[4] C. Amino Compound (EP Impurity E)[5] D. Oxide Midazolam (EP Impurity D)[6] E. Nitromethylene Compound[7] F. Dihyromidazolam (EP Impurity A)[8] G. Desfluoromidazolam (EP Impurity G)[9] H. 6*H*-Isomer (EP Impurity B)[10] I. EP Inpurity H[11] J. Glycol Ether[12] K. Individual Unspecified Impurity L. Total Impurities	RDTM-000197	 A. NMT 0.5% B. NMT 0.5% C. NMT 0.5% D. NMT 0.5% E. NMT 0.5% F. NMT 0.5% G. NMT 0.5% H. NMT 0.5% I. NMT 0.5% J. NMT 0.5% K. Report Value L. NMT 1.0%	 A. ND B. ND C. ND D. ND E. ND F. ND G. ND H. ND I. ND J. ND K. ND L. 0.0%

EXELA PHARMA SCIENCES

FINISHED PRODUCT CERTIFICATE OF ANALYSIS

PRODUCT: Midazolam Injection (1 mg/mL), 100 mg/ 100 mL, 100 mL Vial	CATALOG NUMBER: 10020TS005	CORE LOT NUMBER: PACKAGED LOT NUMBER:

Test	Methods[1]	Specifications	Results
Bacterial Endotoxin	USP <85>	NMT 8.33 EU/mL (equivalent to 8.33 EU/mg Midazolam)	< 0.10 EU/mL
Sterility	USP <71>	No growth is observed	Testing In Progress[13]
USP <1> Injectabled and Implanted Drug Products	USP <1>	Conformance to all applicable tests in USP <1>	Conforms

1-Where Compendial methods are stated, the latest revision is used.
2-When released by QA, this document is the "Certificate of Analysis".
3-Reduced Midazolam, also kown as EP Impurity I, is chemically known as 8-Chloro-3a,4-dihydro-6-(2-fluorophenyl)-1-methyl-3*H*-inidazo[1,5-a] [1,4]-benzodiazepine.
4-Reduced Reduced Midazolam, also known as EP Impurity J, is chemically known as 8-Chloro-6-(2-fluorophenyl)-3a,4,5,6-tetrahydro-1-methyl-3*H*-imidazo [1,5-a] [1,4]-benzodiazepine.
5-Amino Compound, also known as EP Impurity E, is chemically known as 2-Aminomethyl-7-chloro-2,3-dihydro-5-(2-fluorophenyl)-1*H*-1,4-benzodiazepine.
6-Oxide Midazolam, also know as EP Impurity D, is chemically known as 8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-a] [1,4]-benzodiazepine-5-oxide.
7-Nitromethylene Compound is chemically known as 7-Chloro-1,3-dihydro-2-nitromethylene-5-(2-fluorophenyl)-2*H*-benzodiazepine-4-oxide.
8-Dihydromidazolam, also known as EP Impurity A, is chemically known as 8-Chloro-6-(2-fluorophenyl)-5,6-dihydro-1-methyl-4*H*-imidazo [1,5-a] [1,4]-benzodiazepine.
9-Desfluoromidazolam, also know as EP Impurity G, is chemically known as 8-Chloro-6-phenyl-1-methyl-4*H*-imidizo [1,5-a] [1,4]-benzodiazepine.
10-6*H*-isomer, also known as EP Impurity B, is chemically known as 8-Chloro-6-(2-fluorophenyl)-1-methyl-6*H*-imidazo [1,5-a] [1,4]-benzodiazepine.
11-EP Impurity H is chemically known as 6-Chloro-4-(2-fluorophenyl)-2-methylquinazoline.
12-Glycol Ether is chemically known as 8-Chloro-6-[2-(2-hydroxyethoxy)ethyoxyphenyl]-1-methyl-4*H*-imidiazolo [1,5-a] [1,4]-benzodiazepine.
13-Reference DEV-01683.
USP – United Stated Pharmacopeia, NMT - Not More Than, NLT - Not Less Than, ND - Not Detected, QL - Quantitation Limit

Document Version 1.0

Lot Expiration Date: 04/16/2021	
Quality Assurance Released By[2]:	Date Approved: