

## Memorandum

Food and Drug Administration  
Center for Biologics Evaluation and Research  
Office of Compliance and Biologics Quality  
Division of Manufacturing and Product Quality

**To:** File STN BL 125579/0

**From:** Richard Heath Coats OCBQ, DMPQ

**Subject:** Review of CR Letter Responses 5-10 and addendum to Primary Review Memo for SmartPractice Denmark ApS, BLA STN 125579/0

**Through:** Carolyn Renshaw, Branch Chief BI, OCBQ, DMPQ

**Products:** Rubber Panel Thin-Layer Rapid Use Epicutaneous Patch

**Resubmission  
Action Due  
Date:** **26-Feb-2016** *(Non-PDUFA application – Chair of file determined due date shall be missed based on IR response date of 11 February 2016)*

### Administrative Information

A 10 item Complete Response Letter was sent to the firm for STN BL 125579/0 on January 12, 2015. The firm provided responses to the letter through the gateway on August 25, 2015. The firm's response to items 5 - 10 of the letter are under DMPQ purview. This memorandum reviews the firm's responses to these items.

This memo will also address aspects of DMPQ purview for Quality Systems requirements for the device component of a combination product.

### Recommendation on CR Letter Responses

The firm's responses to complete response items 5 – 10 are adequate and do not prevent approval of the submission.

### CR Letter Deficiencies under DMPQ purview

- 5) Please confirm the manufacturing areas used for the Rubber Panel T.R.U.E. TEST are the same areas as currently licensed for T.R.U.E. TEST panels. Please provide a summary of changes and any testing performed to assess the adequacy of these changes made to the manufacturing areas, equipment, or processes for the Rubber Panel T.R.U.E. TEST since the original submission of this material.**

#### **Firm response:**

It is hereby confirmed that the manufacturing areas for Rubber Panel TRUE Test are the same areas as the currently licensed for TRUE Test panels.

#### **Review of Response:**

The firm's response is acceptable.

- 6) Please indicate if any changes have been made to the process flow diagrams since they were submitted as Attachment 10 in your original submission dated January 5, 2006.**

**Firm response:**

The process flow diagrams have been updated since the original 2006 submission and are included with this submission on Appendix 6 of the enclosed disc.

**Review of Response:**

The firm's response is acceptable. The updated diagrams capture the major aspects of the manufacturing process and are comparable to the original diagrams.

- 7) Please provide the current procedure for the assembly and pouch packing of the Rubber Panel T.R.U.E. TEST. Information originally submitted appears to be for the assembly of the original three panel T.R.U.E. TEST.**

**Firm response:**

The updated draft packing instruction batch journal for the Rubber Panel T.R.U.E. TEST may be found in Appendix 7 of the enclosed disc.

**Review of Response:**

The firm's response is acceptable.

- 8) Please indicate if an assembly automation validation was executed for the Rubber Panel T.R.U.E. TEST. It appears the assembling automation validation provided in the submitted materials is for one of the original T.R.U.E. TEST panels.**

**Firm response:**

The assembly automation works the same way no matter the length of the tapes and the amount of patches to be assembled. Process validation is part of the normal procedure when a different length of (b) (4) is manufactured. This is done to show that the manufacturing done according to the procedure of assembly and relevant SOPs results in a product in accordance with specifications.

**Review of Response:**

The firm's response is acceptable. The previously performed assembly automation validation is adequate for the Rubber Panel TRUE Test assembly. The validation previously executed demonstrated the patch (b) (4) is performed as expected by the equipment.

- 9) Please indicate if purchased (b) (4) water is still utilized in product manufacture.**

**Firm response:**

The type of purchased water in product manufacture has not been changed. The purchased water used has a grade of (b) (4). The water is analyzed according to the (b) (4) except test for sterility as the finished product is not sterile.

**Review of Response:**

The firm's response is acceptable.

- 10) Please provide an environmental assessment or a request for a categorical exclusion according to 21 CFR 25.31.**

**Firm Response:**

We hereby claim a categorical exclusion of Environmental Assessment (EA) of the product(s) under our efficacy supplement STN 103738/5074, as required under 21 CFR 25.15(a). We believe the action requested qualifies for categorical exclusion under 21 CFR 25.31(b) (2) as follows:

"NDAs, abbreviated applications, and supplements to such applications if FDA's approval of the application increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb)."

To our knowledge, no extraordinary circumstances exist as described in (21 CFR 25.15(d)). We herewith submit additional information and calculations demonstrating that the allergens meet the quantitative criteria of 21 CFR 25.31(b) (one part per billion) for the Expected Environmental Concentration (EEC).

Name: Rubber Panel T.R.U.E. TEST	Preferred Substance Name	UNII	Ingredient Type	Label pr patch in gram	% of each component in patch	total kg in 5 year maximum( (b) (4) patches) sold annually	EIC one year
<b>Carba Mix</b>	CARBA MIX		ACTIVE	0 0002025		(b) (4)	(4)
	diphenylguanadine	6MRZ85RNHQ	ACTIVE		33 33		
	zincdiethyldithiocarbamate	ICW4708Z8G	ACTIVE		33 33		
	zincdibutylthiocarbamate	HNM5J934VP	ACTIVE		33 33		
<b>Black Rubber Mix</b>	BLACK RUBBER MIX		ACTIVE	0 0000607			
	N-isopropyl-N'-phenyl paraphenylenediamine	0M7PSL4100	ACTIVE		16 8		
	N-cyclohexyl-N'-phenyl paraphenylene- diamine	T29JGK5V4R	ACTIVE		41 58		
	N, N'-diphenyl paraphenylenediamine	DD517SCM92	ACTIVE		41 58		
<b>Mercapto mix</b>	MERCAPTO MIX			0 0000607	100		
	N-cyclohexylbenzothiazyl-sulfenamide	UCA53G94EV	ACTIVE		33 33		
	dibenzothiazyl disulfide	6OK753033Z	ACTIVE		33 33		
	morpholinylmercaptobenzothiazole	VCD7623F3K	ACTIVE		33 33		
<b>Thiuram Mix</b>	THIURAM MIX		ACTIVE	0 0000202	100		
	tetramethylthiuram monosulfide	01W430XXSQ	ACTIVE		25		
	tetramethylthiuram disulfide	0D771IS0FH	ACTIVE		25		
	tetraethylthiuram disulfide	TR3MLJ1UAI	ACTIVE		25		
	dipentamethylenethiuram disulfide	CR113982E5	ACTIVE		25		
<b>Mercaptobenzothiazole</b>	MERCAPTOBENZOTHAZOLE	5RLR54Z22K	ACTIVE	0 000075	100		

#### Review of Response:

Based on the submitted information the firm's request is justified.

#### Addendum to Primary Review Memo

The firm submitted a meeting request for a proposed (b) (4) in summer of 2015 that prompted the review committee to focus on the combination products compliance status of the current Rubber Panel application. Discussions between the committee and the firm led to the issuing of the following Information Requests in order to assess the firm's ability to come into compliance with the combination product requirements. My initial review memo did not address combination product specifics and so this addendum will serve to summarize the information requests pertaining to combination products and additional topics reviewed.

A surveillance inspection was performed by Team Biologics at the SmartPractice facility at the end of January 2016. DMPQ and product reviewers made requests to the inspection team to assess the firm's progress on working toward compliance with Quality Systems regulations regarding combination products. Additional topics such as humidity control and product yield were also forwarded to the inspection team for consideration during the inspection. These topics are also noted in the summaries of the information requests that follow.

#### Information Request September 30, 2015:

**Please describe your procedures and other documentation utilized for evaluating, approving, and controlling suppliers as per 21 CFR Part 820.50 for the device component.**

#### Firm Response

*We currently have procedures in place for the evaluation, approval and management of our suppliers. We*

*are assessing the updates necessary to the procedures and documentation utilized for evaluating, approving, and controlling suppliers as per 21 CFR Part 820.50 for the device component. We expect to have this detailed in our Project Plan that will be completed in November 2015.*

#### **Review of Response**

The firm provided the GAP analysis and Project Plan in response to an Information Request submitted December 11, 2015. This information request is summarized in this memo on Page 4.

**Please describe your procedures for implementation of corrective and preventive actions as per 21 CFR Part 820.100 for device component.**

#### **Firm Response**

*Corrective and Preventive Action (CAPA) Procedures are in place at SmartPractice Denmark now. We are assessing the updates necessary to the procedures and documentation as per 21 CFR Part 820.100 for the device component. We expect to have this detailed in our Project Plan that will be completed in November 2015. We have made changes to the (b) (4) used in the production of the Rubber Panel T.R.U.E. TEST. (b) (4) tests according to the supplier CoA, microbiology assessments, (b) (4) studies, clinical data, customer feedback will all be reviewed and included retrospectively in the Design History File.*

#### **Review of Response**

CAPA was assessed by ORA during the surveillance inspection conducted in January 2016. This is summarized in the section of this memo discussing the Information Request submitted on December 11, 2015. Refer to Page 4 in this memo.

**If any of the preceding items have not been performed by your organization, please provide your gap analysis in your response showing the topics that need to be addressed. Please also include in your response a plan and timeline for completion of each of the above requirements.**

#### **Firm Response**

*Our Gap Analysis and Project Plan will be completed in November 2015 and full implementation is expected by April 2016 which will fully cover the stated requirements.*

#### **Review of Response**

The firm was asked to provide the GAP analysis and Project Plan in an Information Request submitted December 11, 2015. This is discussed on the bottom of this page.

**Please provide legible copies of executed batch records for the manufacture and assembly of Rubber Panel T.R.U.E. TEST.**

#### **Firm Response**

*The firm provided the following batch records:*

- *Packing Instruction Batch Journal for Rubber Panel T.R.U.E. TEST*
- *Batch Records- Manufacture and Assembly of Rubber Panel T.R.U.E. TEST.*

#### **Review of Response**

The firm's response is adequate. Additional information requests regarding review of executed batch record are in the Information Request December 11, 2015 that follows.

#### **Information Request December 11, 2015**

**In your submission you provided a completion date of November 2015 for the gap analysis and your plan to address the quality system regulations related to the device component of your combination product. Please provide your completed gap analysis and project plan to address the following regulations:**

- **§ 820.20.- Management responsibility**

its response to the 483 observations that an effectiveness check requirement has been added to the CAPA SOP as of January 22, 2016.

The firm was contacted in March 2016 and asked to provide SOPs pertaining to Purchasing Controls mentioned in the GAP analysis. The following SOPs were submitted by the firm in response to the request for SOPs regarding Purchasing Controls:

SOP 199 Purchasing of Raw Materials and Packaging Materials

SOP 343 Contract Work and Contract Work Agreements including Service Agreements

SOP 357 Audit of Contract Laboratories and Manufacturers of APIs and Packaging Materials

The SOPs supplied by the firm provide an overview of the purchasing controls in place for raw materials and services provided.

Raw materials are classified as being ordered to support commercial or clinical manufacture. Purchasing of raw materials for commercial use is based on inventory data contained in a raw material purchasing list maintained by the firm's Logistics Department. This list is compiled from information in the purchasing system, and contains expiration dates of raw materials purchased and identifies materials to be ordered. This list is updated every (b) (4) months and material orders appear to be placed when this list is updated.

Commercial raw materials are assigned to a production batch when ordered. The order process includes a review of previous purchases of the specific material for the supplier and quantity. The supplier is verified to be an approved supplier from a list maintained by the firm. The order is then placed with the approved supplier, and the supplier is requested to indicate any changes to the manufacturing process or specifications for the material during placement of the order.

Suppliers of APIs are approved through audits performed by SmartPractice. The audit interval for API suppliers is (b) (4) years, and the following are evaluated prior to subsequent audits:

- (b) (4)
- (b) (4)
- (b) (4)

The firm also indicates that 'For-cause' audits may occur depending on issues with the supplied material or possible events at the manufacturer.

Raw materials ordered that constitute the APIs of the drug substances of Rubber Panel each have a Quality Specification Substance sheet. These sheets specify the material name and the article number for the material. The supplier is not identified but makes a reference to the approved supplier list. The firm provided the Quality Specification Substance sheets for materials used to manufacture the drug substances in the original submission. These sheets specify the supplier agreement of supplying a certificate of analysis for each batch of material delivered. The sheets also specify the firm's re-test period and tests to be performed. A reference Certificate of Analysis is included with the Quality Specification Substance sheet for each material. The Certificate of Analysis reports the testing performed by the vendor at release of the material.

An example of this is a summary of the Quality Specification Substance sheet for N-isopropyl-N'-phenyl paraphenylenediamine. This material is one of the constituents of the Black Rubber Mix allergen in the Rubber Panel. The article number ((b) (4)) for the material is specified on the sheet as is the storage temperature of (b) (4) °C. The supplier agreement is to provide a Certificate of Analysis on each batch. The Certificate of Analysis lists the following tests performed, results obtained for the lot in question, and the specification for each test:

- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

- **§ 820.30.- Design controls**
- **§ 820.50.- Purchasing controls**
- **§ 820.100.- Corrective and preventive action**

**Firm Response:**

*The firm provided the following document: GAP Analysis Between the Quality System in SmartPractice Denmark ApS and 21CFR, Part 4 Current Good Manufacturing Practice Requirements for Combination Products.*

*The GAP analysis provided the identification of activities the firm will implement for demonstration of compliance with the Quality System Regulations for Medical Devices.*

**Management Responsibilities**

*The firm committed to creating a Quality Manual from existing SOPs #002 Quality Assurance System and SOP #353 Quality Management Review that will contain the following identified items:*

- *Processes for Quality Objectives and Quality Planning*
- *Identification of the current Director of Quality Assurance as Management Representative, and updating the Director's job description*
- *Description of an improved and updated process for Management Review.*

**Design Controls**

- *A new SOP for Design Control shall be created*
- *Creation of a Design History File for Rubber Panel T.R.U.E. Test*
- *Creation of a Device Master Record for Rubber Panel T.R.U.E. Test*
- *Creation of a Risk Management Plan and product and process FMEA for Rubber Panel T.R.U.E. Test*

**Purchasing Controls**

- *SOP #343 for Suppliers of Services (Contract Laboratories, Calibration and Maintenance, etc.) and SOP #199 for Purchasing of raw materials and packaging materials shall be updated to include consultants in SOP #343 and change notice requirements for vendors in SOP#199.*
- *SOP #357 Supplier Audits will be created to improve the supplier evaluation process*

**Corrective and Preventive Action**

- *Current SOPs addressing deviations, out of specification, internal audits, complaints, adverse reactions, and recalls have been reviewed and subjected to minor updates*
- *SOP #331 Corrective and Preventive Actions will be updated to include a planned evaluation of the effectiveness of the implemented CAPA*

**Review of Response:**

The GAP analysis provided addressed both the existing licensed T.R.U.E. Test and the proposed Rubber Panel. The firm had communicated a target date of April 2016 for completion of the action items identified in the GAP analysis. A surveillance inspection was performed by ORA at SmartPractice January 25-29, 2016 and assessed the firm's progress in coming into compliance with Quality Systems Regulations regarding combination products. The inspector's assessment was that the firm was making adequate progress on coming into compliance with the combination product requirements.

Review of the EIR for the January 2016 surveillance inspection indicates that Management Responsibilities were assessed during the inspection. No observations were noted in the 483 issued at the end of the inspection.

I defer to the Product Reviewer to assess the adequacy of GAP analysis items regarding Design Control.

Corrective and Preventive Action was assessed during the inspection and one observation was noted for lack of an effectiveness check requirement to assure that corrective actions adequately address issues. This was noted by the firm in the provided GAP analysis as an outstanding issue, and the firm reported in

The re-test period for N-isopropyl-N'-phenyl paraphenylenediamine is listed as (b) (4) years. Tests performed by SmartPractice during the re-test are as follows with the specifications listed:

- (b) (4)
- (b) (4)
- (b) (4)

**An information request was sent to the firm on April 22, 2016 to provide purchasing control information for the device component for the Rubber Panel T.R.U.E. Test.**

**Please provide the following information regarding the polyester sheet used as backing for the allergen gel (b) (4):**

- **The material specification sheet for the polyester sheet**
- **A description of the process of receiving shipments of polyester sheets. Please include any inspections or testing performed and the frequency of these tests during the receipt, inspection, and release of material for use in commercial manufacturing**

#### **Firm Response**

*The firm responded by providing the specification sheet for the polyester sheet QSC 50-8841-00 and a certificate of analysis for (b) (4) polyester film. The firm also provided the following summary of the receipt process:*

*Each batch (shipment) is received according to SOP 356 where labeling are checked against order document (receiving batch journal), and checked for damage on containers. Each batch is labeled, samples are taken, analyzed by the Quality Control laboratory and released by Quality Assurance according to SOP 139 and specification QSC 50-8841-00.*

#### **Review of Response**

The purchasing control information for the polyester sheet appears acceptable. The polyester sheet has an appearance specification of an (b) (4) film. A (b) (4) specification of (b) (4) per (b) (4) is also listed. In addition to visual appearance and (b) (4), the (b) (4), (b) (4), and (b) (4) of the sheets are specified. The physical testing of measurements appears to be performed for (b) (4) received. The provided Certificate of Analysis lists the following tests performed and results obtained for the lot in question:

- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

**Please describe the vendor qualification process for the vendor(s) of the polyester sheet. Please include what periodic reassessment or requalification of the vendor(s) is planned.**

#### **Firm Response**

*The firm responded by indicating the original vendor qualification was performed a long time ago and prior to the firm's implementation of purchasing controls for device components of combination products. The firm stated the vendor is requalified every (b) (4) year according to SOP 329 by reviewing questionnaire, ISO certificate and any deviations since last qualification.*

#### **Review of Response**

The firm's inclusion of the vendor into the vendor requalification program appears adequate.

The 2016 inspection included one observation that noted the use of (b) (4) batches of raw materials for commercial production of T.R.U.E. Test. This is documented as Observation 6 on page 26 of the 2016

EIR. The EIR discussed the firm's procedure that allowed materials to be used prior to release under certain conditions. The firm's response to this observation is that SOP 339 Dispensation from Quarantine that described this practice has been abolished and this practice is immediately terminated.

An observation from the 2014 surveillance inspection involved the incomplete requalification of a raw material supplier. The 2016 inspection team assessed the implemented corrective action for the observation as adequate in the EIR.

Other topics discussed during the 2016 inspection involve the utilization of change control for changes to material manufacturers and SOP 890 Preparation of Packaging Material Specifications, Raw Material Specifications and Standard Substance Specifications.

The firm's response to this request is acceptable. I agree with the Team Biologics inspector's assessment that the firm is making progress in achieving compliance with QS requirements for combination products. As mentioned earlier, the firm is planning introduction (b) (4)

**Please provide a detailed description of the process of (b) (4) patches from the Rubber Panel (b) (4), the placement of the patches on the tape, and the pouch packaging of the test strip. Please include details, such as whether the individual Rubber Panel T.R.U.E. TEST allergen (b) (4) are (b) (4) independently or simultaneously and whether test strips are assembled one at a time or in multiples.**

**Firm Response: (Response provided by firm on February 11, 2016)**

*The firm provided a diagram of the assembly apparatus utilized in the cutting and placing of allergen patches on the surgical tape. The firm also provided a narrative describing the process of (b) (4) and placing of the patches. The narrative also included a description of process of placing foil over the tape loaded with patches, and the pouch packaging process.*

**Review of Response:**

The firm adequately communicated the process of assembling the surgical tape containing the six allergen patches.

This assembly machine utilizes the same process as used for the existing licensed TRUE panel. The assembly machine is (b) (4)

(b) (4)

This description provided an adequate understanding of the process.

**On page 6 of the batch record it appears that (b) (4) specifications were not met when production started on January 5 and 6, 2015. The specification for (b) (4) is listed as (b) (4) and (b) (4) should be between (b) (4). The (b) (4) result is documented as (b) (4) and (b) (4) on January 5 and 6, 2015, and the (b) (4) values for both days are all at or (b) (4). Please clarify what affect these conditions had on the operations performed on these specific days, and if any deviations or corrective actions were associated with these events.**

**Firm Response: (Response provided by firm on February 11, 2016)**



(b) (4) do not have any effect on the allergens used for Rubber Panel T.R.U.E. Test or on the operations performed to assemble the test strips.

No deviations or corrective actions were associated with these events. (b) (4) limit is (b) (4) and the recorded (b) (4) are rounded off to (b) (4). As the (b) (4) does not affect the operations, our current practice is to have the production manager sign off on deviations from the limit in the batch record. We are currently evaluating this practice and assessing the current limits based on scientific rationale.

#### **Review of Response:**

It is unclear why the batch record would have a (b) (4) specification documented if there is no effect of (b) (4) on the Rubber Panel allergens or the assembly process. An observation regarding (b) (4) specifications was noted in the surveillance inspection performed in January 2016. This observation led to the firm's response indicating (b) (4)

The firm committed in their response to conduct a study justifying (b) (4) levels for the process. The firm targets a completion date of October 2016. The firm's response to the observation and commitment to assess the (b) (4) levels appears acceptable.

**On page 7 of 26, the table associated with the (b) (4) test of the vision system is lined out and the test appears to not have been performed. Please describe how (b) (4) testing of the vision system is performed and indicate how acceptability of testing is documented.**

#### **Firm Response: (Response provided by firm on February 11, 2016)**

*As we have not yet manufactured this product for commercial use yet, we have not yet implemented and validated a master for Rubber Panel T.R.U.E. Test. This has to be implemented before the first production of commercial product.*

*The batch in question is only used for batch release samples and is manufactured without vision system in place, but with a 100% check of test panels.*

(b) (4) there will be performed a challenge test: (b) (4). This test will be documented in the table on page 7 of the batch record.

#### **Review of Response:**

I initially expected the vision system to have been validated for Rubber Panel in order to support the process validation lots for this submission. I will accept this response since the appearance of the Rubber Panel Patch Test is similar to the currently licensed TRUE Test.

**Pages 24 and 25 of the executed batch record appear to document reconciliation of used foil and calculation of yield. The written notes are barely legible, however it appears a 97% deviation is noted for the pouches when the limit is specified as (b) (4)%. It also appears that of the (b) (4) pouches manufactured, (b) (4) of the pouches were rejected, (b) (4) were sampled, (b) (4) pouches were considered the yield, and the total number of pouches produced was below the specified mean. Please elaborate on the following items:**

- a. Please confirm a pouch at this step contains a test strip
- b. Calculations regarding the deviation of the number of pouches manufactured and whether 'Double pouches – empty' are retained or discarded
- c. Any investigations performed assessing the documented low yield

#### **Firm Response:**

- a. Not all pouches contain a test strip at this step

- b. *Double pouches – empty are discarded*  
*The deviation is 0.7%: calculated as:*  
*(b) (4) = 0.7% or -7 pouches*  
*For batches (b) (4) the limit is (b) (4) pouches and for batches (b) (4) pouches the limit is (b) (4).*
- c. *A formal investigation of the low yield has not been done, as on page 21 it is stated that 35 tests have been rejected in conjunction with pouch packing, where they were not placed correctly in the pouch, so the reason for the low yield is known.*

**Review of Response:**

The firm's response allows me to understand the calculation performed in the batch record. The yield apparently refers only to the finished Patch Tests, and not the assembled pouches. The calculation performed for the pouches appears to be for reconciliation only, and the firm does not appear concerned with the high number (b) (4) of rejected pouches or provide a reason for the high number. This topic was forwarded to the inspectors prior to the inspection in January and it that yield and reconciliation were addressed in some fashion through review of the EIR. A discussion item is noted regarding the accuracy of the pouch counter on the assembly unit.

The firm communicated in a follow up information request on April 22, 2016 that the (b) (4) rejected pouches are produced during the adjustment of the pouch packing machine to obtain a correct pouch prior to packaging. This is an acceptable response, although (b) (4) pouches appear to be a high number for setup activities.