SUMMARY REVIEW MEMO TEMPLATE

DATE: **JULY 15, 2011**

FROM:

SUBJECT: **P040024/S052**
RESTYLANE INJECTABLE GEL

CONTACT: **FRAN WORKMAN**

TO: **THE RECORD**

BACKGROUND/ REASON FOR SUPPLEMENT

P040024/S052 is a 180 Day Supplement that requests an extension to the expiration date of the lidocaine hydrochloride raw material from 12 months to 24 months. The supplement also requests approval of the stability protocol to further extend the shelf life to 36 months upon satisfactory stability test results.

REVIEW TEAM

Table 1 below lists the participants in this review team and their role in the review of the supplement:

Reviewer	Role
CDRH/ODE/DSORD	Lead Reviewer
CDER/OPS/ONDQA/DNDQA III/BRANCH VII	Lidocaine Information Reviewer

Table 1: Review team for P040024/S052

INDICATIONS FOR USE

Restylane® is indicated for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds.

Perlane® is indicated for implantation into the deep dermis to superficial subcutis for the correction of moderate to severe facial folds and wrinkles, such as nasolabial folds.

DEVICE DESCRIPTION

Restylane L is a gel of hyaluronic acid generated by *Streptococcus* species of bacteria, chemically crosslinked with BDDE and suspended in phosphate buffered saline at pH=7 and concentration of 20mg/mL with 0.3% lidocaine.

Perlane L is a sterile gel of hyaluronic acid generated by *Streptococcus* species of bacteria, chemically cross-linked with BDDE and suspended in phosphate buffered saline at pH=7 and concentration of 20 mg/mL with 0.3% lidocaine. The median particles size is between 750 and 1000 microns.

PRECLINICAL/BENCH

Stability Data

The lidocaine hydrochloride (lidocaine) raw material used in Restylane L and Perlane L are manufactured by Cambrex Karlskoga AB located in Farlskoga, Sweden. This drug source is documented in DMF (b) (4), which was previously reviewed by (b) (4) and found to be adequate as a source for the Restylane and Perlane injectable products. The injectable products are manufactured at the Q-Med AB facility in Uppsala, Sweden. The quality systems and manufacturing procedures will not change with the extension of shelf life.

In order to support the extension of shelf life from 12 months to 24 months, data from stability studies conducted at both Cambrex and Q-Med are presented in the supplement.

Data from the Cambrex study included a stability study on the lidocaine when stored in double polyethylene bags in fibre drums stored at (b) (4)°C. The results verified that the lidocaine is stable for at least 60 months using this packaging method. When the lidocaine is delivered to Q-Med, it is repackaged in 250ml amber glass bottles. As a result of the packaging change, a stability study was initiated at Q-Med on the lidocaine when stored in the amber glass bottles to verify the test results from Cambrex.

Data from the Q-Med study included a stability study that was initiated in February 2008. The repackaged lidocaine provided by Cambrex is stored at (b) (4)°C/(b) (4)% RH for (b) (4)months. Assay for lidocaine as well as tests for related substances, water content and microbial contamination are performed at predetermined intervals. The acceptance limits for the parameters are identical to the acceptance limits in the specifications for incoming raw material. The sponsor provided the raw data at the 0, 6, 12, 14, 18 and 24 month shelf life intervals in the supplement.

The results of the stability study show that the lidocaine is within specification limits. The sponsor concludes that the quality of lidocaine after long term storage for 24 months at (b) (4)°C/(b) (4)% RH is equivalent to the quality when manufactured.

In his review memo, Dr. Carver states that based upon the stability data submitted, a 24-month shelf life, from the date of testing upon receipt by the drug product manufacturer, is appropriate for the lidocaine hydrochloride drug substance repackaged in amber glass bottles.

The Q-Med study is assessing the lidocaine stored in 250ml amber glass bottles for a period of 36 months. The sponsor states that if approval is granted for the protocol, upon completion of the study, the shelf life will be extended up to 36 months if test results are satisfactory and within limits.

Dr. Carver states that the protocol is adequate for the proposed stability study through 36 months, however, the results of the stability testing should be submitted to the FDA for review.

CONCLUSION

Based on the stability data presented in the supplement, a shelf life of 24 months is acceptable for the lidocaine hydrochloride raw material when stored at up to 25˚C in the 250ml amber glass bottles used at Q-Med AB. The protocol is acceptable for the proposed stability study through 36 months, but the data should be submitted to FDA for review.

RECOMMENDATION - I recommend that the supplement be **Approved**.

Reviewer name Date

Name, Chief, Branch Date