FINAL REPORT

Sino-implant (II) Initiative: 2016 Quality Assurance Evaluation

November 15, 2016

Submitted by:

FHI 360

Markus Steiner, Ph.D.
Contraceptive Technology Innovation
359 Blackwell Street, Suite 200
Durham, NC 27701
E-mail: msteiner@fhi360.org
Telephone: 919-544-7040 ext. 11346
Fax: 919-544-7261

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Markus Steiner, Ph.D.
Sino-implant (II) Project Director
Contraceptive Technology Innovation
359 Blackwell Street, Suite 200
Durham, NC 27701
E-mail: msteiner@fhi360.org
Telephone: 919-544-7040 ext. 11346
Fax: 919-544-7261

Derek H. Owen, Ph.D.
Scientist I
Contraceptive Technology Innovation
359 Blackwell Street, Suite 200
Durham, NC 27701
E-mail: dowen@fhi360.org
Telephone: 919-544-7040 ext. 11168
Fax: 919-544-7261

Xian Zhong, Ph.D.
Research Associate
Contraceptive Technology Innovation
359 Blackwell Street, Suite 200
Durham, NC 27701
E-mail: xzhong@fhi360.org
Phone: 919-544-7040 ext. 11192
Fax: 919-544-5849

David W. Jenkins, Ph.D.
Associate Director
Product Quality and Compliance Department
2810 Meridian Parkway, Suite 160
Durham, NC 27713
E-mail: djenkins@fhi360.org
Phone: 919-544-7040 ext. 11617
Fax: 919-544-5849

Haizhen Meng
Research Associate
Contraceptive Technology Innovation
359 Blackwell Street, Suite 200
Durham, NC 27701
E-mail: hmeng@fhi360.org
Phone: 919-544-7040 ext. 11491
Fax: 919-544-5849

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List of Abbreviations

API	Active Pharmaceutical Ingredient
ASTM	American Society for Testing and Materials
BLD	Below Limit of Detection
BRL	Below Reporting Limit
BP	British Pharmacopeia
CFDA	China Food and Drug Administration
CP	China Pharmacopeia
Dahua	Dahua Pharmaceutical Co., Ltd
DMF	Dimethylformamide
ECH	Ethylene Chlorohydrin
EG	Ethylene Glycol
EO	Ethylene Oxide
EP	European Pharmacopeia
FPP	Finished Pharmaceutical Product
GC	Gas Chromatography
NMT	No More Than
ICH	International Conference on Harmonisation
ISO	International Organization for Standardization
LAL	Limulus Amebocyte Lysate
LNG	Levonorgestrel
PDE	Permitted Daily Dose
QA	Quality Assurance
TLC	Thin Layer Chromatography
US FDA	U.S. Food and Drug Administration
USP	United States Pharmacopeia
WHO	World Health Organization
Yangzhou	Yangzhou Pharmaceutical Co., Ltd.
ZiZhu	China Resources ZiZhu Pharmaceutical Co., Ltd.

Executive Summary

A Quality Assurance (QA) Evaluation and Monitoring program was implemented by FHI 360 to verify that Sino-implant (II) meets lot release specifications for the product. This report presents the 2016 results of the QA evaluation and monitoring program that has been conducted since 2008.

Commercial lot release testing verification was conducted for two (2) lots of Sino-implant (II), containing Active Pharmaceutical Ingredient (API) Levonorgestrel (LNG) supplied by Yangzhou Pharmaceutical Co. Ltd., (Yangzhou) that were shipped to countries as part of Sino-implant (II) introduction activities in developing countries. In all instances results were in compliance with Sino-implant (II) lot release specifications (Table 1).

A more extensive battery of tests was conducted to evaluate if Sino-implant (II) meets international quality standards. The tests selected were based on standards from the United States Pharmacopeia (USP), European Pharmacopeia (EP), International Organization for Standardization (ISO), and the American Society for Testing and Materials (ASTM), recognized by World Health Organization (WHO) Prequalification (PQ) program.

From 2008 to 2012, LNG test results concluded that the Yangzhou API was capable of meeting all LNG standards tested, including China Pharmacopeias (CP), USP and British Pharmacopeias (BP). In 2013, the LNG BP monograph was harmonized with the LNG EP monograph (EP 7.4), which resulted in a new specification for related substance with a slightly different impurity profile and limits to allowable levels. In 2014, the LNG EP monograph (EP 8.0) again revised the impurity profile and limits to allowable levels. Fortunately, these new impurity profiles and limits on allowable levels do not affect the official impurity specification of the finished pharmaceutical product.

With the aim of obtaining WHO Prequalification (PQ) approval for Sino-implant (II), Shanghai Dahua Pharmaceutical Co., (Dahua), the finished pharmaceutical product (FPP) manufacturer, switched API supplier from Yangzhou Pharmaceutical to China Resources Zizhu Pharmaceutical Co., Ltd. (ZiZhu) in their WHO PQ application submitted May 2015. The ZiZhu LNG API has been prequalified by WHO (Ref: APIMF172) and is capable of meeting the latest EP standards (EP 8.0) requested by WHO. The testing results are presented in this report.

However, since the currently registered product contains the Yangzhou API in all marketed countries, Dahua will continue using the Yangzhou API for commercial lots of Sino-implant (II) until the dossier referencing the ZiZhu API obtains WHO PQ and is subsequently approved at the country level. During this transitional period, two lots of LNG manufactured by ZiZhu, and one lot of LNG manufactured by Yangzhou and used in FPP commercial lots, were selected and evaluated according to the LNG CP monograph (CP 2015) and LNG EP monograph (EP 8.0) as part of the 2016 QA Evaluation program.

Test results concluded that the ZiZhu API was capable of meeting all specifications for the LNG CP 2010 and EP 8.0 monographs. The Yangzhou API continues to meet specifications for the LNG CP 2010 monograph, the legal standard for LNG in China (Table 1).

Additionally, three (3) FPP lots, two made with the Zizhu API (as described in the WHO PQ submission) and one made with the Yangzhou API (for current markets) were obtained from Dahua. Dahua performed an internal manufacture qualification test that includes the same battery of tests historically conducted as part of the Sino-implant (II) QA program as well as new tests suggested by WHO PQ. The upgraded identification, assay, related substances, content uniformity, and dissolution tests are conducted using HPLC technology. Test results concluded that for both formulations (Yangzhou API and Zizhu API) Sino-implant (II) is capable of meeting the quality requirements specified for WHO-PQ.

In addition, an independent laboratory (SGS) performed the lot characterization verification for all three batches. The results of the lot characterization verification activities for samples tested in the Annual Product QA Evaluation are summarized in Table 1. In all instances, results were in compliance with Sino-implant (II) lot characterization specifications.

With the ultimate goal of transferring all QA testing to China, efforts were made to move all QA testing activities to SGS in Shanghai, including all official test methods used or adopted at Dahua.

Table 1. Summary of 2016 QA Monitoring and Evaluation of Sino-implant (II)

Test Item		Lot No.	Result
Annual QA Monitoring of Sino-implant (II)			
Sino-implant (II): Commercial Lot Release Verification		Lot 20150604 Lot YZ20151006	Met requirements
Annual QA Evaluation of Sino-implant (II)			
Levonorgestrel (LNG): API QA Evaluation	CP 2015 Evaluation	ZiZhu Pharmaceutical Co., Ltd. Lot S1370801504002	Met requirements
		Yangzhou Pharmaceutical Co., Ltd. Lot S01ZQ20150013	Met requirements
	EP 8.0 Evaluation	ZiZhu Pharmaceutical Co., Ltd. Lot S1370801504002	Met requirements
		Yangzhou Pharmaceutical Co., Ltd. Lot S01ZQ20150013	Met requirements
Sino-implant (II) :	QA Commercial Lot Release Verification	Lot YZ 20160101 Lot ZZ 20160202 Lot ZZ 20160203	Met requirements
Sino-implant (II) : FPP QA Evaluation	QA WHO-PQ Lot Characterization Verification	Lot YZ 20160101 Lot ZZ 20160202 Lot ZZ 20160203	Met requirements
	Assay, Related Substance, and Content Uniformity, Sterility Evaluation		Met requirements
	Ethylene Oxide (EO) Residuals Evaluation		Met requirements
	Inorganic Impurities Evaluation		Met requirements
	Residual Solvents Evaluation		Met requirements
	Bacterial Endotoxin Evaluation		Met requirements
	Cytotoxicity Evaluation		Met requirements
	Dissolution		Met requirements
Sino-implant (II) : Packaging QA Evaluation	Package Integrity Evaluation	Lot YZ 20160101 Lot ZZ 20160202 Lot ZZ 20160203	Met requirements