FINAL REPORT

Sino-implant (II) Initiative: 2014 Quality Assurance Evaluation

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Submitted by:

FHI 360

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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	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 expands on the results obtained after the QA evaluation and monitoring program conducted from 2008 to 2013.

Commercial lot release testing verification was conducted for one (1) lot of Sino-implant (II), with Active Pharmaceutical Ingredient (API) Levonorgestrel (LNG) supplied by Yangzhou Pharmaceutical Co. Ltd., (Yangzhou), that was shipped to countries as part of the Sino-implant (II) introduction 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 battery of tests selected was based on standards from the United States Pharmacopeia (USP), EP 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 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, which resulted in more stringent specifications. The Yangzhou API was unable to meet these more stringent specifications in 2013.

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 to China Resources Zizhu Pharmaceutical Co., Ltd. (ZiZhu) in their WHO PQ application in mid-2013. The ZiZhu LNG API has been prequalified by WHO (Ref: APIMF172) and is capable of meeting the latest EP standards requested by WHO.

However, since it is the Yangzhou not ZiZhu API currently registered as the API of Sino-implant (II) in all marketed countries, the company will continue using the Yangzhou API for making commercial lots of Sino-implant (II), until the product with the ZiZhu API obtains the WHO PQ approval and is approved at the country level. Therefore, during this transitional period, three (3) lots of the ZiZhu API, made for the three (3) FPP lots for WHO PQ submission, and one (1) lot of the Yangzhou API, made for the FPP commercial lots, were selected and evaluated according to the CP 2010 and EP 8.0 LNG monograph in 2014 QA Evaluation program.

Test results concluded that the ZiZhu API was capable of meeting all specifications of LNG CP 2010 and EP 8.0 monograph, but that the Yangzhou API failed the assay and related substance test in the recently revised EP standards. The Yangzhou API is continuously capable of meeting specifications of LNG CP 2010 monograph, the legal standard for LNG in China (Table 1).

Additionally, the three (3) FPP lots with ZiZhu API, made by Dahua for WHO PQ submission purpose, were selected and tested for not only the same battery of QA evaluation tests previously conducted, but also some new tests requested by WHO in Dahua's PQ application, including assay and related substances test (HPLC) and content uniformity test. Test results concluded that Sino-implant (II), made of ZiZhu API, are capable of meeting quality requirements for all tests conducted (Table 1).

Furthermore, with an ultimate goal of performing all QA testing in China by the end of the 2nd grant of Sino-implant (II) Initiative, an effort was made this year to move some of the QA testing conducted in US to China. In 2014, the following testing were transferred to China, and all test methods were validated by receiving labs prior to the sample testing:

- Ethylene Oxide (EO) Residuals Evaluation, from Nelson to SGS Shanghai
- Residual Solvents Evaluation, from Irvine to SGS Shanghai
- Bacterial Endotoxin Evaluation, from Nelson to SGS Shanghai

Table 1. Summary of 2014 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 (SGS, Shanghai, China)		Lot 10072013 (with Yangzhou API)	Met requirements
Annual QA Evaluation of Sino-implant (II)			
Levonorgestrel (LNG): API QA Evaluation	CP 2010 Evaluation (SGS, Shanghai, China)	ZiZhu Pharmaceutical Co., Ltd. (ZiZhu) Lot 27801305001 Lot 27801305002 Lot 27801305003	Met requirements
		Yangzhou Pharmaceutical Co., Ltd. (Yangzhou) ZQ20130012	Met requirements
	EP 8.0 Evaluation (Lancaster, Lancaster, PA, USA)	ZiZhu Pharmaceutical Co., Ltd. (ZiZhu) Lot 27801305001 Lot 27801305002 Lot 27801305003	Met requirements
		Yangzhou Pharmaceutical Co., Ltd. (Yangzhou) ZQ20130012	Met all requirements except for assay and related substances
Sino-implant (II) : FPP QA Evaluation	QA Lot Release Verification (SGS, Shanghai, China)	Lot 12112013 (10 rods/pouch) Lot 25112013 (10 rods/pouch Lot 26112013 (10 rods/pouch) (with ZiZhu API)	Met requirements
	Assay, Related Substance and Content Uniformity Evaluation (Frontage, Shanghai, China)		Met requirements
	Ethylene Oxide (EO) Residuals Evaluation (Switched from Nelson to SGS Shanghai)		Met requirements
	Inorganic Impurities Evaluation (SGS, Lincolnshire, IL, USA)		Met requirements
	Residual Solvents Evaluation (Switched from Irvine to SGS Shanghai)		Met requirements
	Bacterial Endotoxin Evaluation (Switched from Nelson to SGS Shanghai)		Met requirements
	Cytotoxicity Evaluation (Nelson, Salt Lake City, UT, USA)		Met requirements
Sino-implant (II) : Packaging Material QA Evaluation	Packaging Physicochemical Evaluation (Nelson Salt Lake City, UT, USA)	Trust: Lot# (11-0719)-11-8-23-1 Trust: Lot # 13-01-06-(11-0719A-1)-11-9-22-1 Trust: Lot # B-01-06-(13-0251)-13-3-20-1	Met requirements
	Package Integrity Evaluation (Nelson Salt Lake City, UT, USA)	Lot 12112013 (10 rods/pouch) Lot 25112013 (10 rods/pouch) Lot 26112013 (10 rods/pouch) (with ZiZhu API)	Met requirements