

Quality Assurance Evaluation of Sino-implant (II): a low-cost safe and effective contraceptive implant

David Jenkins, PhD

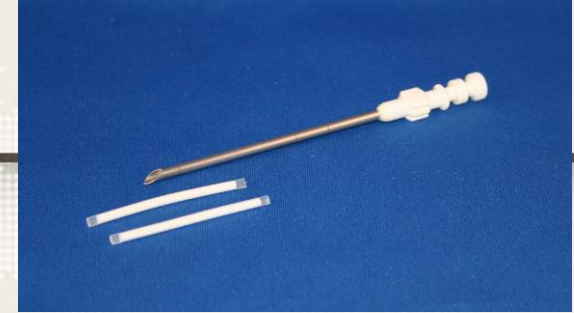
Aida Cancel, PhD

Markus Steiner, PhD



IMPROVING LIVES
WORLDWIDE

Sino-implant (II)



- Two rod system with 75 mg levonorgestrel in each rod
- Made of medical grade silastic
- Dimensions: 2.4 mm x 44 mm
- Shelf-life: up to 4 years
- Manufactured by Shanghai Dahua Pharmaceutical Co., Ltd.
- Registered in China (1994), Indonesia (2002), Sierra Leone (2008) and Kenya (2009)
- Tradename: *Zarin*[®], *Trust*[®], *Femplant*[®]

Sino-implant (II) Activities

- Quality Assurance
- Registration
- Introduction Activities

E02-2: Steiner et. al. Increasing access by introducing a low-cost contraceptive implant in resource constrained countries

Research Purpose

The purpose of this research was to conduct an independent evaluation of Sino-implant (II) to provide assurance of the product quality and verify that it meets international quality standards.



Quality Assurance Evaluation Team

FHI Team

Markus Steiner, PhD	Sino-implant (II) Program Director
David Jenkins, PhD	Laboratory Manager, Product Quality and Compliance
Aida M. Cancel, PhD	Director, Regulatory Affairs and Quality Assurance
Eli Carter	Director, Product Quality and Compliance Division (PQC)

Consultants

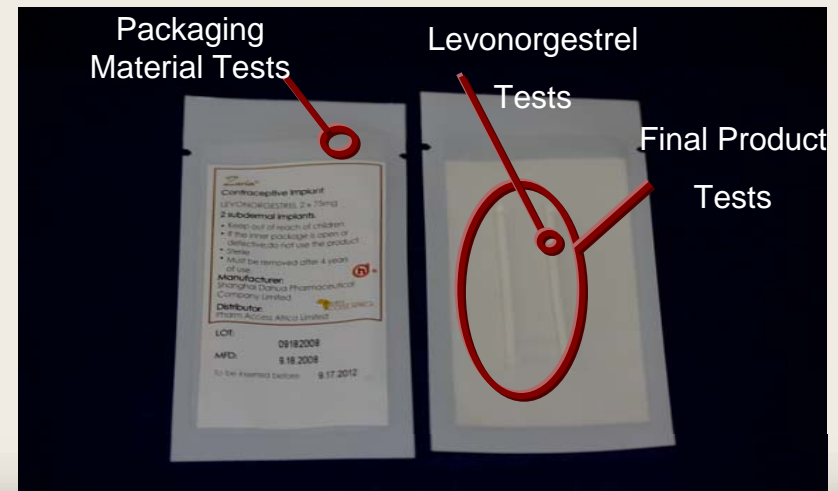
Eric Weichert, PhD	President, Applications Specialists International
Gary Gammerman, MS, JD	President, Seraphim Life Sciences Consulting

Partner Laboratories

SGS	Shanghai, China
Nelson Laboratories	Salt Lake City, UT
Cyanta Analytical Laboratories	Maryland Heights, MO
Irvine Pharmaceutical Sciences	Irvine, CA

Sino-implant (II) Quality Evaluation Activities

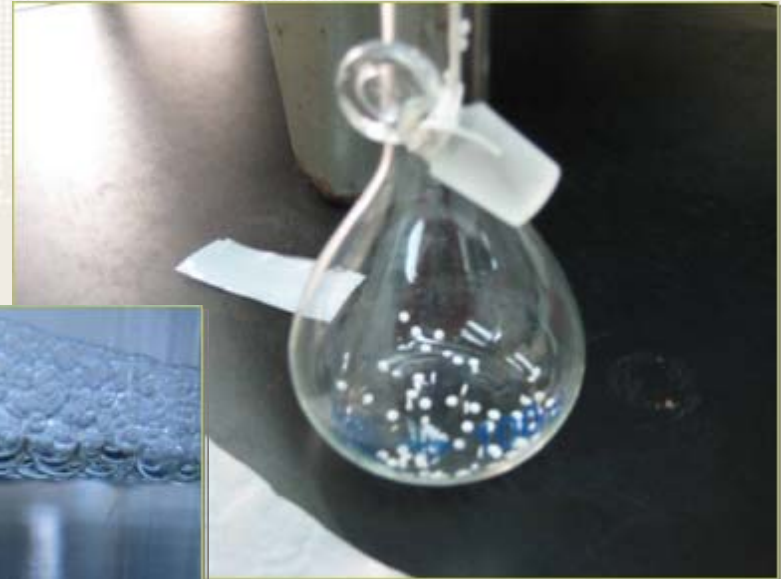
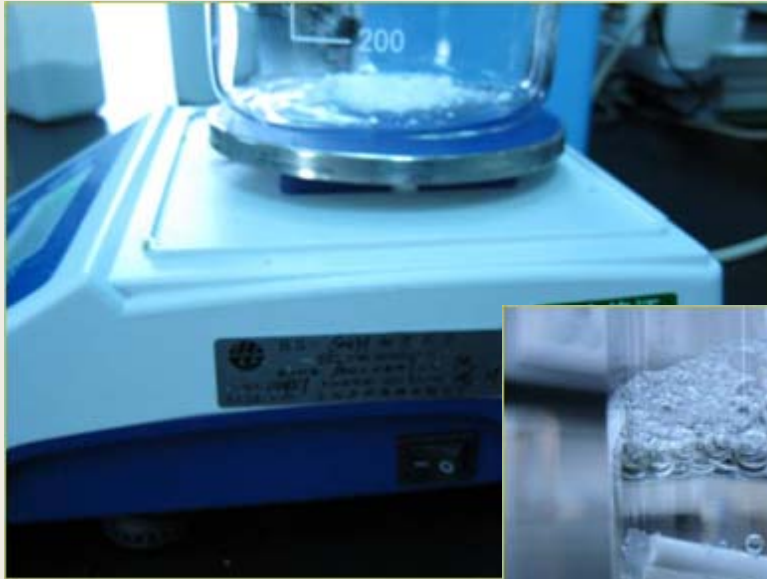
- Active ingredient (levonorgestrel)
- Final product (Sino-implant II rods)
- Packaging material



Standards and Specifications

- **Based on international or stringent regulatory authority standards**
 - International Standards Organization (ISO)
 - United States Pharmacopeia (USP)
 - United States Food and Drug Administration (USFDA)
 - European Agency for the Evaluation of Medicinal Products (EMA)/Committee for Proprietary Medicinal Products (CPMP)
 - American National Standards Institute (ANSI)/ Association for the Advancement of Medical Instrumentation (AAMI)

Tests and Results

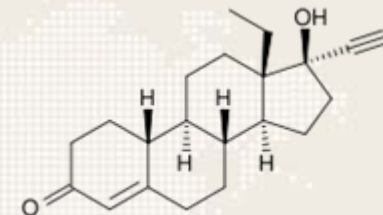


Lot Release Verification

- WS1-(X-281)-2004Z Levonorgestrel Silastic Implants (II) approved by the State Pharmacopoeia Commission, China
- Independently conducted by FHI (PQC, NC) and SGS (Shanghai)
- 10 lots of Sino-implant (II) analyzed
- All 10 lots of Sino-implant (II) met lot release testing requirements
- Independent commercial lot release testing of all commercial lots (except China and Indonesia) at SGS until 2013

Standard: WS1-(X-281)-2004Z	
Test	Specification
Identification	Thin Layer Chromatography spot identification
Assay (mg/set)	92.0-108.0%
Dissolution (Release Rate)	80-120 ug/set/24 h
Sterility	No evidence of growth

Levonorgestrel



- 3 lots tested from API manufacturer
- All 3 lots met requirements for the USP Levonorgestrel specification

Standard: USP Levonorgestrel	
Test	Specification
Identification A USP<197K>(IR)	Infrared absorption spectrum is consistent with that of the standard
Identification B	Meets requirements for Specific Rotation and Melting range
Melting range USP<741>	232 – 239 °C
Specific rotation USP<781S>	-30° to -35°
Loss on drying USP<731>	<0.5%
Residue on ignition USP<281>	<0.3%
Limit of ethynyl group- Titration	7.81 – 8.18%
Chromatographic purity USP<621> (TLC)	Sum of the impurities in the test <2.0% and no single impurity > 0.5%
Assay- UV	98.0 – 102.0% calculated on dried basis
Residual solvents (Ethanol, Ethyl acetate, Methanol)	Ethanol <5000 ppm
	Ethyl acetate <5000 ppm
	Methanol <3000 ppm

Ethylene Oxide Residuals

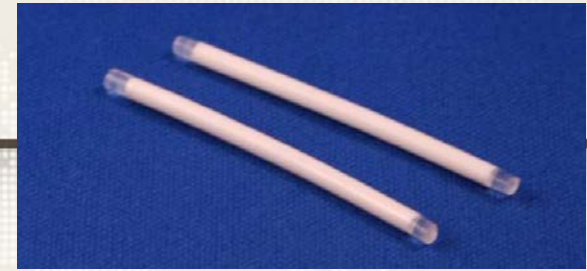


- Test to determine the concentration of ethylene oxide sterilization residues.

Standard ISO-10993-7: Ethylene Oxide Residuals			
	Ethylene Oxide	Ethylene Chlorohydrin	Ethylene Glycol
ISO - (prolonged /permanent) - 30 days	60 mg	60 mg	N/A
ISO - (lifetime)	2.5 mg	50 mg	N/A
FDA – Devices (ppm)	250 mg	250 mg	5000 mg

- All 3 lots met requirements for the ethylene oxide residuals test specifications

Inorganic Impurities



- Evaluated implants for the presence of 63 trace elements
- The entire rod content was evaluated

Based on USP <231>USP General Chapter on Inorganic Impurities: Heavy Metals	
Test	Acceptance Criteria
Inductively Coupled Plasma Spectroscopy (ICP) with Mass Spectroscopy (MS)	Inorganic impurities: heavy metal stimuli article (USP/NF 2008-04)
	EMEA specification limits for residues of metal analysis (CPMP/SWP/QWP/4446/00 corr Jan 2007)

- All 3 lots met requirements for the inorganic impurities acceptance criteria

Residual Solvents



- Measures the amount of organic volatile chemicals that are present in the final product.

Standard: Based on USP <467> Organic Volatile Impurities		
Solvent Classification	Specification	
Class 3: Solvents that should be used when practical	Ethanol	50 mg or less per day
	Ethyl acetate	50 mg or less per day
Class 2: Solvents to be limited	Hexane	2.9 mg or less per day
Class 1: Solvents to be avoided	None	None

- All 3 lots met requirements for the residual solvents test specifications

Endotoxin and Cytotoxicity



- Tests to (1) evaluate the presence of bacterial endotoxins and (2) evaluate biological reactivity

Test	Standard	Specification
Pyrogenicity	ANSI/AAMI ST72:2002/ USP 85 Limulus amoebocyte lysate (LAL) endotoxin detection test - device immersion	Less than 20 EU per device
Cytotoxicity	AAMI/ISO10993-5 Tests for cytotoxicity – in vitro methods/USP 87 Biological Reactivity Tests, In Vitro	Not greater than mildly reactive (Grade 2)

- All 3 lots met requirements for the Endotoxin and Cytotoxicity test specifications

Packaging Evaluation



	Standard	Test	Specification
Package Integrity	ASTM F2096 Bubble emission test	Bubble emission	Absence of leakage
Package Impurities	USP <661> Containers: Physicochemical tests- plastics	Buffering Capacity	≤ 10.0 mL
		Nonvolatile Residue	≤ 15 mg
		Residue on Ignition	≤ 5 mg
		Heavy Metals	≤ 1 ppm

- All 3 lots met requirements for the package integrity test specifications
- One lot of the package material was evaluated and met requirements for the package impurities test specifications

Summary of Quality Evaluation Activities

Year 1

Test	# Lots	Results
Quality Monitoring Activities		
Sino-implant (II) : Lot release verification	10	Met requirements
Annual Quality Evaluation		
Levonorgestrel Lot release verification	3	Met requirements
Ethylene Oxide Residuals Evaluation	3	Met requirements
Metal Impurities Evaluation	3	Met requirements
Residual Solvents Evaluation	3	Met requirements
Bacterial Endotoxin Testing	3	Met requirements
Cytotoxicity	3	Met requirements
Package Integrity Evaluation	3	Met requirements
Package Impurities Evaluation	1	Met requirements

Summary of Quality Evaluation Activities

Year 2

Test	# Lots	Results
Quality Monitoring Activities		
Sino-implant (II) : Lot release verification	3	Met requirements
Annual Quality Evaluation		
Levonorgestrel Lot release verification	3	Met requirements
Sino-implant (II): Lot release verification	3*	Met requirements
Ethylene Oxide Residuals Evaluation	3	Met requirements
Metal Impurities Evaluation	3	Met requirements
Residual Solvents Evaluation	3	Met requirements
Bacterial Endotoxin Testing	3	Met requirements
Cytotoxicity	3	Met requirements
Package Integrity Evaluation	3	Met requirements
Package Impurities Evaluation	1	Met requirements

* Lot release verification for one of these lots was conducted a part of the quality monitoring activities

Conclusion

- Dahua Pharmaceutical Co., Ltd. is capable of consistently producing an implant that meets international quality standards
- A baseline has been established on Sino-implant (II) that can be used to evaluate the continued quality of the product
- A quality assurance program for Sino-implant (II) has been established and will continue until 2013