Sharing Experience on WHO PQ Approval

(Euvichol, Oral Cholera Vaccine)

29 June 2016

CONTENTS

1. Introduction to EuBiologics

Company overview

EuBiologics Co., Ltd.

A Biopharmaceutical company building a portfolio of vaccines designed to improve global public health, in addition to providing CRMO* service to domestic and international clients

- CEO: Yeong Ok, Baik
- Foundation: March 10, 2010
- Business place: Main Office in Seoul
- Bio-Plant, R&D Center in Chuncheon City

- No. of employees: 85
- Capital : 8.0 Mil. USD
- Sales: 3 Mil. USD (Yr. 2015)

- Website : www.eubiologics.com
- Tel.: 82-2-572-6675 / 82-33-817-4001

- Business area
  - ✓**Vaccine Development** (Development/supply of safe and effective vaccine for global market)
  - ✓**CRMO Service** (Development/supply of advanced manufacturing technology for biopharmaceuticals)

CRMO* (Contract Research and Manufacturing Organization)

Vision & Mission

For health that lasts a lifetime

Vision: To be a global bio-drug company providing safe, healthy and lively future

Business Category

Vaccine Development

- OCV "Tech. Transferred by IVI"
- Typhoid conjugate vaccine
- Pneumonia conjugate vaccine

INTERNATIONAL VACCINE INSTITUTE

CRMO*

- Contract manufacturing service for biopharmaceuticals
- Contract R&D service

(재)춘천바이오산업진흥원 CHUNCHEON BIOINDUSTRY FOUNDATION

*CRMO: Contract R&D and Manufacturing Organization

2. Euvichol®
Development for WHO PQ

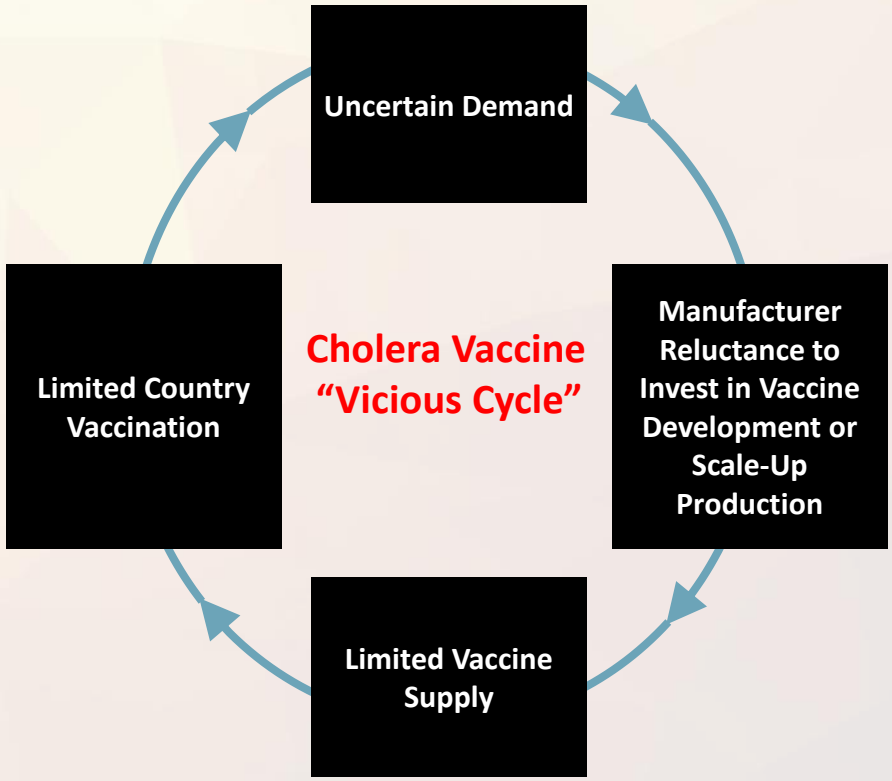
OCV Development background

WHO Stockpile Program

A global stockpile of oral cholera vaccine has been created, as an additional tool to help control cholera epidemics. The stockpile has been available 2 million doses of vaccine.

<Source : BMGF (2012)>

- Inexpensive and effective vaccines are underutilized because of the "vicious cycle" of uncertain demand and inadequate supply
- In order to convert the "vicious cycle" into a "virtuous cycle" of vaccine availability and country adoption, demand and/or supply stimuli are needed
- A cholera vaccine stockpile could break the "vicious cycle" and convert it into a "virtuous cycle"



Euvichol® Development Milestones

2010	Sep. OCV License Agreement with IVI
2011	Apr. Non-clinical Trial for OCV in Korea
2012	Oct. Phase I clinical trial in Korea
2014	Aug. Phase 3 clinical trial in the Philippines
2015	Jan. Approval of Marketing Authorization from MFDS (28 Jan.)
	Jan. Dossier submission to the WHO-PQ (30 Jan.)
	Aug. WHO Inspection (24 ~ 28 Aug.)
	Dec. WHO PQ Approval (23 Dec.)
2016	May. Approval for Variation(Scale-up & removal of thiomersal) from MFDS (28 May)

Euvichol® Profile

Description	*V. cholerae* O1 and O139 bivalent inactivated vaccine	
Indication	Prevention of Cholera caused by *Vibrio cholerae*	
 Composition in 1.5mL	**Composition**	**Quantity**
	V. cholerae O1 Inaba Cairo 48, Heat Inactivated	300 L.E.U*
	V. cholerae O1 Inaba Phil 6973 El Tor, Formalin inactivated	600 L.E.U
	V. cholerae O1 Ogawa Cairo 50, Formalin inactivated	300 L.E.U
	V. cholerae O1 Ogawa Cairo 50, Heat Inactivated	300 L.E.U
	V. cholerae O139 4260B, Formalin inactivated	600 L.E.U
	Phosphate buffered saline (pH7.3)	20 mM
	Thimerosal	0.15 mg
Recommended age	1 year and older	
Doses	Two(2) dose vaccines given with 2 week interval	
Storage temperature	2 to 8 ℃	
Shelf life	24 months	
Primary Packaging	Single dose 1.5 ml/ glass vial	
Packaging Unit	10 single doses /carton (5 vials*2 lines)	
VVM	VVM 30	

90mm*35mm*35m =110cm^3/10 vials

*** LEU : Lipopolysaccharide ELISA Units**

Euvichol ® is the 2nd OCV which was developed by technology transfer from IVI, and equivalent to Shanchol™ (Shantha Biotechnics, India) in terms of quality, safety and effectiveness.

Timeline for Licensure

Task force team was organized in July 2014 and every activities to be performed for WHO-PQ approval were listed up.

	2014												2015											
	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
Licensure in Korea																								
Quality(CMC) approval																								
Non-clinical & Clinical results approval																								
GMP approval																								
WHO PQ																								
Pre-meeting																								
Dossier preparation																								
PQ application																								
Screening of the PSF(1month)																								
PSF evaluation (7months)																								
Sample testing (3months)																								
Site visiting (2months)																								
Report and outcome of the ass essment																								

*** Above table is the real one set up on June 2014**

2.1 Clinical Studies

Development Studies

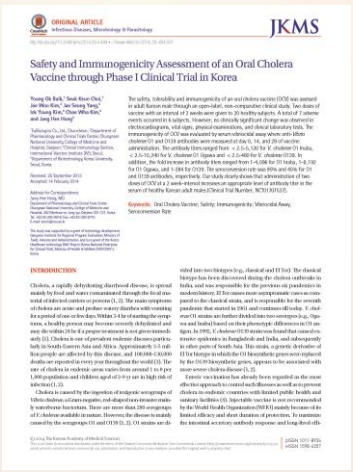
Pre-Clinical Study Apr. 2011	A 6-Week Oral Toxicity Study of Oral Cholera Vaccine in Sprague-Dawley Rats. (http://dx.doi.org/10.5487/TR.2012.28.4.225)
Phase 1 Clinical Study Oct. 2012	Safety and Immunogenicity Assessment of an Oral Cholera Vaccine through Phase I Clinical Trial in Korea. (http://synapse.koreamed.org/DOIx.php?id=10.3346/jkms.2014.29.4.494)
Phase 3 Clinical Study* Aug. 2014	A Randomized, Non-inferiority Trial Comparing Two Bivalent Killed, Whole Cell, Oral Cholera Vaccine (Euvichol vs Shanchol) in the Philippines (http://linkinghub.elsevier.com/retrieve/pii/S0264-410X(15)01228-1)

"The safety and the immunogenicity of Euvichol® were proved to demonstrate non-inferiority to Shanchol"

Pre-Clinical Study

A 6-Week Oral Toxicity Study of Oral Cholera Vaccine in Sprague-Dawley Rats

Phase 1 Clinical Study



JKMS

Safety and Immunogenicity Assessment of an Oral Cholera Vaccine through Phase I Clinical Trial in Korea

Phase 3 Clinical Study

Vaccine

A randomized, non-inferiority trial comparing two bivalent killed, whole cell, oral cholera vaccines (Euvichol vs Shanchol) in the Philippines

Summary of Phase 3 Clinical Trial

Title	A randomized, single blind, multicenter, therapeutic confirmatory study to assess the efficacy (immunogenicity) and safety of Euvichol in healthy adults and children
Objectives	This study is to assess the efficacy(immunogenicity) and safety of Euvichol in healthy adult and children subjects.
Investigational product	▪ Test drug: Euvichol ▪ Comparator drug: Shanchol
Study population	Number of subjects included in analysis: (1) Pivotal study - ITT group: 1,228 subjects (Test group: 614 subjects, comparator group 614 subjects) - PP group: 1,224 subjects (Test group: 610 subjects, comparator group 614 subjects) (2) Safety study - Safety group: 3,632 Subjects (Test group: 2,999 subjects, comparator group: 633 subjects
Conclusion	It was confirmed that the efficacy and safety of Euvichol are non-inferior compared to the comparator drug Shanchol in healthy child and adult subjects.

1) ITT (Intention To Treat) — The ITT set includes subjects who had at least one measurement of anti-V. cholera O1 antibody titer after investigational product dosing.

2) PP (Per Protocol) — The PP set includes ITT subjects who completed this study per protocol (2 drop outs)

3) Safety — The safety set includes all subjects who participated in the study and had at least one dose of the Investigational product.

Summary of Phase 3 Clinical Trial

❖ Vibriocidal antibody titers and proportion of ≥ 4 fold rise from baseline GMT to *V. cholerae* (O1 Inaba, O1 Ogawa, and O139) : Adults

ADULTS (≥18 years old)		O1 Inaba			O1 Ogawa			O139		
		Euvichol (n=377)	Shanchol (n=376)	*p* value	Euvichol (n=377)	Shanchol (n=376)	*p* value	Euvichol (n=377)	Shanchol (n=376)	*p* value
DAY 0	Baseline GMT[a]	35.8	35.8	0.99	76.8	73.8	0.82	4.3	3.4	0.08
DAY 14	GMT[a]	1140	1086	0.68	1718	1280	0.01	16.1	17.9	0.52
	GMFr[b]	31.9	30.3	0.77	22.4	17.4	0.09	3.8	5.3	0.02
	# seroconversion (%)[c]	317 (84.1)	315 (83.8)	0.91	322 (85.4)	295 (78.5)	0.01	127(33.7)	157(41.8)	0.02
	95% CI lower boundary[d]	-4.94%			1.48%			-14.97%		
DAY 28	GMT[a]	773	732	0.59	1238	962	0.01	12.4	14.0	0.42
	GMFr[b]	21.6	20.5	0.73	16.1	13.0	0.15	2.9	4.2	0.01
	# seroconversion (%)[c]	308 (81.7)	287 (76.3)	0.07	302 (80.1)	278 (73.9)	0.04	108(28.6)	142(37.8)	0.01
	95% CI lower boundary[d]	-0.44%			0.18%			-15.82%		

[a]Geometric mean reciprocal titres

[b]Geometric mean-fold rise from baseline to 14 days after first dose or from baseline to 14 days after second dose

[c]# with ≥4 fold rise in titres from baseline to 14 days after first dose or from baseline to 14 days after second dose

[d] 95% lower confidence intervals for Noninferiority analysis of the difference and the margin is 10%. Difference is seroconversion rate of (Euvichol-Shanchol).

Summary of Phase 3 Clinical Trial

❖ Vibriocidal antibody titers and proportion of ≥ 4 fold rise from baseline GMT to *V. cholerae* (O1 Inaba, O1 Ogawa, and O139) : Children

CHILDREN (1-17 years old)		O1 Inaba			O1 Ogawa			O139		
		Euvichol (n=231)	Shanchol (n=235)	*p* value	Euvichol (n=231)	Shanchol (n=235)	*p* value	Euvichol (n=231)	Shanchol (n=235)	*p* value
DAY 0	Baseline GMT[a]	12.3	11.9	0.88	12.8	12.9	0.96	4.0	3.0	0.09
DAY 14	GMT[a]	680	609	0.63	780	636	0.35	60.1	65.7	0.62
	GMFr[b]	55.1	51.0	0.75	61.0	49.2	0.39	15.1	22.0	0.07
	# seroconversion (%)[c]	198 (85.7)	198 (84.3)	0.66	200 (86.6)	197 (83.8)	0.40	148(64.1)	158(67.2)	0.47
	95% CI lower boundary[d]	-5.03%			-3.69%			-11.78%		
DAY 28	GMT[a]	625	621	0.98	838	733	0.42	40.0	43.2	0.68
	GMFr[b]	50.6	52.1	0.90	65.6	56.7	0.51	10.0	14.5	0.07
	# seroconversion (%)[c]	202 (87.4)	209 (88.9)	0.62	209 (90.5)	207 (88.1)	0.40	131(56.7)	146(62.1)	0.23
	95% CI lower boundary[d]	-7.35%			-3.22%			-14.32%		

[a]Geometric mean reciprocal titres
[b]Geometric mean-fold rise from baseline to 14 days after first dose or from baseline to 14 days after second dose
[c] # with ≥4 fold rise in titres from baseline to 14 days after first dose or from baseline to 14 days after second dose
[d] 95% lower confidence intervals for Noninferiority analysis of the difference and the margin is 10%.
Difference is seroconversion rate of (Euvichol-Shanchol).

Summary of Phase 3 Clinical Trial

❖ **Solicited systematic adverse events (AEs) among adults**

	Euvichol (n=388)	Shanchol (n=389)	p value
ADULTS			
Within 6 days of first dose			
Nausea/Vomiting	0	0	
Diarrhea	1	2	1.00
Headache	9	14	0.29
Fatigue	0	0	
Myalgia	2	1	0.62
Fever[a]	2	6	0.29
Loss of appetite	0	0	
Within 6 days of second dose	**(n=382)**	**(n=377)**	
Nausea/Vomiting	0	1	0.50
Diarrhea	0	1	0.50
Headache	6	7	0.79
Fatigue	0	0	
Myalgia	0	1	0.50
Fever[a]	2	1	1.00
Loss of appetite	0	0	
Number (%) of participants with ≥ 1 AEs within 14 days[b] of either dose	17(4.4)	27(6.9)	0.12
Number (%) of participants with SAEs within 14 days of either dose	0	0	

[a] Temperature ≥ 38.0°C.

[b] Number of participants of 6 days is the same as that of 14days.

Summary of Phase 3 Clinical Trial

❖ **Solicited systematic adverse events (AEs) among children**

	Euvichol (n=240)	Shanchol (n=244)	p value
CHILDREN			
Within 6 days of first dose			
Nausea/Vomiting	1	0	0.50
Diarrhea	1	1	1.00
Headache	0	3	0.25
Fatigue	0	0	
Myalgia	0	0	
Fever[a]	3	5	0.72
Loss of appetite	0	0	
Within 6 days of second dose	**(n=235)**	**(n=237)**	
Nausea/Vomiting	2	2	1.00
Diarrhea	0	2	0.50
Headache	2	3	1.00
Fatigue	0	0	
Myalgia	0	0	
Fever[a]	5	9	0.29
Loss of appetite	0	0	
Number (%) of participants with ≥ 1 AEs within 14 days[b] of either dose	12(5.0)	17(7.0)	0.36
Number (%) of participants with SAEs within 14 days of either dose	0	0	

[a] Temperature ≥ 38.0°C.

[b] Number of participants of 6 days is the same as that of 14days.

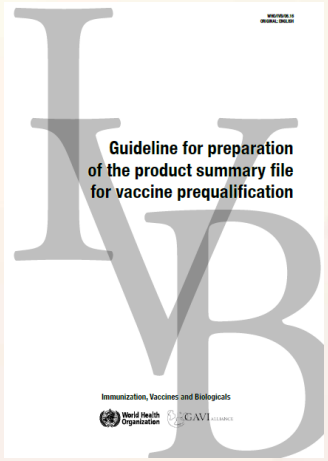
2.2 Dossier Preparation

Dossier Preparation

Basically, Dossiers were prepared according to the WHO guideline

1. Product Summary File :

Guideline for preparation of the product summary file for vaccine prequalification



Chapter 1: General Information

Chapter 2: Personnel

Chapter 3: Premises and Equipment

Chapter 4: Vaccine composition, presentations and schedules

Chapter 5: Production

Chapter 6: Quality Control

Chapter 7: Stability

Chapter 8: Clinical experience

Chapter 9: Production and distribution data

Chapter 10: Update of Regulatory Authority Actions Relevant to the Product

Dossier Preparation

Product Summary File :

Guideline for preparation of the product summary file for vaccine prequalification

Example;

Chapter 1: General Information:

1.1 Brief information on the firm (including name and address of the site, including telephone, fax and 24-hour telephone numbers, and the principal contacts of the Company), relation to other sites where steps of the process or testing activities may be conducted.

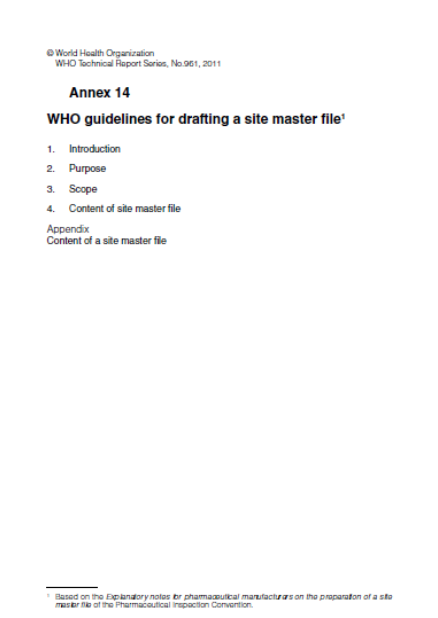
It is expected that the name of the company applying for PQ is listed first. The full address of the head office and contact person with his/her title/position, and the contact numbers should be given. This should be followed by a listing of other sites or other companies involved in any phase of production or testing, (parent company, other sites for the company, any contract manufacturers or testing laboratories, subcontracted warehousing, etc) and their addresses.

The relationship between sites is a request for an indication of generally how the product is transported between the various sites for production, testing and storage.

Dossier Preparation

2. Site Master File :

WHO guidelines for drafting a site master file (Annex 14, WHO TRS, No.961, 2011)



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WHO Technical Report Series, No.961, 2011

Annex 14

WHO guidelines for drafting a site master file[1]

1. Introduction
2. Purpose
3. Scope
4. Content of site master file

Appendix
Content of a site master file

[1] Based on the *Explanatory notes for pharmaceutical manufacturers on the preparation of a site master file* of the Pharmaceutical Inspection Convention.

1. General information on the manufacturer
2. Quality Management
3. Personnel
4. Premises and Equipment
5. Documentation
6. Production
7. Quality Control
8. Distribution, Complaints, Product defects and Recalls
9. Self-inspections

- ***SMF can be useful in the planning and undertaking of GMP inspections***
- ***25~30 pages plus appendices,***
- ***Simple plan, outline drawings or schematic layouts are preferred.***

Dossier Preparation

The progress of dossier preparation was checked on biweekly meeting

	작업 이름	담당부서	시작	완료	완료
임상	유비콜 임상시험연구	Eub > Eub, ADM	13-11-19 (화)	14-11-28 (금)	6
	Pivotal_Database locking	ADM		14-09-25 (목)	
	Pivotal_Statistical analysis	ADM		14-10-02 (목)	
	Safety_Database locking	ADM		14-09-30 (화)	
	Safety_Statistical analysis	ADM		14-10-08 (수)	
	CSR(국문) development	ADM		14-10-22 (수)	
	CSR(국문) review	EuB>RA		14-10-24 (금)	
	CSR translation (Eng)	ADM		14-1	
	CSR(영문) Finalization	JVI		14-1	
	Site closing Visiting	ADM, GCRC	14-10-06 (월)	14-10-24 (금)	
Quality	유비콜 제조		13-12-02 (월)	14-03-28 (금)	5
	DS 제조 원료시험	Eub>QC	13-12-02 (월)	13-12-09 (월)	1
	DS 제조 및 성적서	EUB>QA	13-12-09 (월)	14-02-14 (금)	1
	DP 제조 및 성적서	EUB>QA,QC,N서	14-03-03 (월)	14-03-28 (금)	1
	DS 장기 안정성(냉장, 36개월)_3개월	EUB>QC	14-02-10(월)	14-08-29 (금)	5
	DS 장기 안정성(냉장, 36개월)_6개월	EUB>QC		14-09-17 (수)	
	DS 장기 안정성(냉장, 36개월)_9개월	EUB>QC		14-12-12 (금)	
	DP 가속 안정성(25도, 2개월)	EUB>QC	14-04-21(월)	14-08-29 (금)	5
	DP 가속 안정성(25도, 4개월)	EUB>QC	14-04-21(월)	14-09-19 (금)	5
	DP 가속 안정성(25도, 6개월)	EUB>QC		14-11-07 (금)	
	DP 가속 안정성(25도, 8개월)	EUB>QC		15-01-10 (금)	
	DP 가속 안정성(37도, 6주)	EUB>QC		14-10-31 (금)	
	DP 장기 안정성(냉장, 36개월)_3개월	EUB>QC	14-04-01(화)	14-08-22 (금)	5
	DP 장기 안정성(냉장, 36개월)_6개월	EUB>QC		14-10-31 (금)	
	DP 장기 안정성(냉장, 36개월)_9개월	EUB>QC		15-01-09 (금)	
	DP(1 lot) 장기 24개월 보고서 작성	EUB>QC		14-08-29 (금)	10
	DP(1 lot) 가속 안정성(37도, 8주)	EUB>QC		14-07-18 (금)	10
	DS 제조 공정 밸리데이션	EUB>QA		14-07-18 (금)	10
	DP 제조 공정 밸리데이션	EUB>QA>GCC		14-07-18 (금)	10
	포장기록서 작성	EUB>QA>GCC		14-08-14 (목)	
	DS 운송 SOP 작성	EUB>PD		14-07-31 (목)	
	DS 제조기록서 개정	EUB>PD		14-09-30 (화)	
	불활화 검정(Verification) 보고서 개정	EUB>PD		14-08-25 (월)	
	DP Release SOP 작성	EUB>QA		14-08-29 (금)	
	LPS함량시험법 MV(Ogawa, O139)	EUB>QC	14-07-28 (월)	14-08-14 (목)	5
	표준품 확립	EUB>QC		14-07-31 (목)	10
	MCB 안정성 보고서(3년)	EUB>QC		14-07-31 (목)	10
	WCB 제조	EUB>PD		14-08-29 (금)	
	2차 포장재(라벨, 카톤, 설명서) 규격서 설정	EUB>마케팅		14-07-31 (목)	
	Shipper 및 configuration 결정			14-09-30 (화)	
	Shipping validation			14-10-31 (금)	
	VVM 포장 절차 확립			14-09-30 (화)	
	CTC study	EUB>QC	15-02-02(화)	15-04-17(금)	
	Stability indicating study	EUB>QC		14-08-29 (금)	5
	벤처프라자 입주 업체 조사 및 위험 평가	EUB>경영>QA		14-09-30 (화)	
	제품 표준서 업데이트	EuB>QA		14-08-27 (tn)	
	MFDS	MFDS 수출용 허가 획득	Eub>RA		
		등록 CRO 계약	EUB>RA	14-06-30 (월)	14-07-11
		CMO 계약(w/GCC)	Eub>QA	14-07-07 (월)	14-08-29
		DP 제조업 허가 변경	Eub>QA		14-08-29
		전시설심사(MFDS)	EUB>RA	14-08-18 (월)	14-11-0
		GMP실사(MFDS)	Eub>RA	14-09-22 (월)	14-11-0
		품목 허가 신청(기시, 안유, GMP)	Eub>RA	14-08-29 (금)	15-01-09
		GMP Audit(이정길 자문관)	Eub>QA	14-09-15 (월)	14-09-19
		GMP Audit(해외)	Eub>QA	15-03-09 (월)	15-03-13
	WHO	WHO PQ approval			
		DP(SMF 등) 자료 확보	Eub>RA>GCC	14-07-07 (월)	14-07-31
		WHO 3rd Meeting	Eub>RA	14-11-10 (월)	14-11-14
		Clinical expert evaluation report	Eub>RA	14-11-24 (월)	14-12-19
		Application letter 발송	Eub>RA	14-12-22 (월)	14-12-26
		Product summary file submission to WHO	EUB>RA	15-01-19 (월)	15-01-30
		1. General information			
		1.1 회사 정보(Eub & 녹십자)	EUB>QA		14-09-12
		1.2 Pharmaceutical & non-pharmaceutical activity	EUB>QA		14-09-12
		1.3 Short description of site	EUB>QA		14-09-12
		1.4 Structure of organization	EUB>QA		14-09-12
		1.5 List of outside assistance (GCC)	EUB>QA		14-09-12
		1.6 Quality management system	EUB>QA		14-09-12
		1) Manual 작성	EUB>QA		14-09-12
		2) Policy 작성	EUB>QA		14-09-12
		3) Quality management review	EUB>QA		14-09-12
		4) Risk Management	EUB>QA		14-09-12
		1.7 Internal audit system	EUB>QA		14-09-12
		2. Personnel			
		2.1 Organizational chart(QA, QC, 생산)	EUB>QA		14-09-12
		2.2 Training 이력(QA, QC, 생산)	EUB>QA		14-09-12
		영문 CV 작성(QA, QC, 생산, 보관)	EuB>QA		14-09-12
		2.3 교육프로그램	EUB>QA		14-09-12
		2.4 생산 직원 health requirement	EUB>QA		14-09-12
		듀코랄 접종	EuB>마케팅		14-09-26
		3. Premises and equipment		14-08-01 (금)	14-08-29
		3.1 제조 및 QC의 평면도와 설명	EUB>QA		14-09-12
		3.2 제조 및 QC 구역의 construction and finishes 의 natur & 설명	EUB>QA		14-09-12
		3.3 제조 및 QC의 ventilation system	EUB>QA		14-09-12
		환경모니터링 프로그램에 대한 설명	EUB>QC		14-09-12
		3.4 위험구역에 대한 정보	EUB>경영>QA		14-09-12
		3.5 Water system(위생절차 및 스케줄 포함)	EUB>QA		14-09-12
		3.6 Maintenance system	EUB>QA		14-09-12
		3.7 생산에 사용되는 장비목록(위치포함)	EUB>QA		14-09-12 (금)
		3.8 Separate facility에 대한 여부?	EUB>QA		14-09-12 (금)
		3.9 Qualification and validation procedure(컴퓨터와 controller에 해당)	EUB>QA		14-09-12 (금)
		Validation master plan	EUB>QA		14-09-12 (금)
		3.10 Procedure for cleaning manufacturing area	EUB>QA		14-09-12 (금)
		각종 도면 영문화	EUB>PD>Eng		14-09-12 (금)
		4. Vaccine composition, presentations and schedules		14-08-01 (금)	14-08-29 (금)
		4.1 Product 의 조성	EUB>RA		14-08-29 (금)
		4.2 UN기구에서 이용할 수 있는 Presentation	EUB>RA		14-08-29 (금)
		4.3 접종주기, 접종 루트	EUB>RA		14-08-29 (금)
		4.3 1차포장제 및 박스 sample, insert(다국어)	EUB>RA		14-08-29 (금)
		4.4 Lot summary protocol(WHO format사용)	EUB>QA		14-08-29 (금)
		5. Production		14-07-01 (화)	14-07-31 (목)
		5.1 DP의 Manufacturing formulae	EUB>QA		14-08-29 (금)
		DP의 batching formula	EUB>QA		14-08-29 (금)
		충진 size에 대한 vials 및 dose 의 수량	EUB>QA		14-08-29 (금)
		반제품 및 제품에 대한 lot numbering system	EUB>QA		14-08-29 (금)
		5.2 제조 과정(Flowcharts) 및 제품의 Characterization	EUB>PD		14-08-04 (금)
		5.3 PV에 대한 general policy, 수행한 PV 목록	EUB>QA		14-08-29 (금)
		5.4 원료, 포장재, DS, DP의 Handling 에 대한 요약서	EUB>QA		14-08-29 (금)
		5.5 반품 원료 및 제품에 대한 Handling 요약서 및 폐기절차	EUB>QA		14-08-29 (금)
		UDP 제조기록서 영역	EUB>PD		14-08-29 (금)
		DSP 제조기록서 영역	EUB>PD		14-08-29 (금)
		DP 제조기록서 영역	EUB>PD		14-08-29 (금)
		DS PV 보고서 영역	EUB>PD		14-08-29 (금)
		DP PV 보고서 영역	EUB>PD		14-08-29 (금)
		DS 불활화 PV 보고서 영역	EUB>PD		14-08-29 (금)
		DP 무균공정밸리데이션 보고서 영역	EUB>PD		14-08-29 (금)
		DP shipping validation 보고서 영역			14-09-26 (금)
		6. Quality control		14-07-01 (화)	14-08-29 (금)
		6.1.1 원자재 규격서	EUB>QC		14-08-29 (금)
		생물 유래 원료의 justification	EUB>QA		14-08-29 (금)
		6.1.2 1차 및 2차 포장재, 라벨에 대한 cotrol test 목록	EUB>QA		14-08-29 (금)

*** Above table is the real one set up on June 2014**

Dossier Preparation

Dossier was submitted on 30th Jan. 2015. After WHO PQ team's screening, A letter was received on 12th Mar. 2015, mentioning that the PQ team like to undergo PSF review.

World Health Organization

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Tel. direct: +41 22 791 4362
Fax direct: +41 22 791 4384
E-mail : rodriguezhernandezc@who.int

In reply please refer to: IR-370-43 WPRO
PQT-DMI/rs (2015-086)

Your reference:

Mr Seuk Keum Choi
EuBiologics Co., Ltd
BioVenture Plaza 4,
56 Soyanggang-ro, Chuncheon-si
200-957 Gangwon-do
République de Corée

12 MAR 2015

Dear Mr Choi,

Acceptability, in principle, of Euvichol (Oral Cholera vaccine) produced by EuBiologics for purchase by United Nations agencies

Reference is made to the Product Summary File (PSF) pertaining to Euvichol (Oral Cholera vaccine) vaccine produced by EuBiologics Co. Ltd, submitted to WHO in your letter received on 3 February 2015. After screening of the dossier, we are pleased to inform you that it has been found acceptable to undergo the PSF review.

During the screening it was noted that the following additional information was required. This information was transmitted to you via email and we acknowledge receipt of the additional information on 10 March 2015.

- Section 5.3 Please provide the report of validation of the methods of inactivation (TTR-14025)
- Section 7.1a Please provide information on the containers used for storage of intermediates
- Section 10.1a It is acknowledged that you provided by email on 29 January a document indicated to be the marketing authorisation from MFDS. The document was in Korean and you indicated you would send the English translation. Please do so.
- Section 10.1.c The only GMP certificate included was for the Green Cross formulation and filling site. Please provide GMP certification for the Eubiologics site.

The process for evaluation will follow the document "Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations Agencies" (**WHO TRS 978, Annex 6**).

.../2

cc: EuBiologics Co., Ltd, Chuncheon-si (Attention: Dr Sue-nie Park)
Ministry of Food and Drug Safety (Attention: Mr Tae-Kyun Nam)
UNICEF Supply Division, Nordhavn (Attention: Dr H. Deehan and Ms K. Dorgan)

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Dossier Preparation

After WHO PQ team's PSF review, LoQ(List of Questions) were received on 1st Jul. 2015, and EuBiologics responded to each question immediately.

Example;

Chapter 1: A risk assessment regarding the potential impact on Euvichol of other activities taking place at both EuB and GCC

Chapter 4: Multilingual versions of the insert

Chapter 5: Is all of seed Culture 2 is used to inoculate the main culture?

⋮

2.3 Sample Testing

Sample Testing

As per WHO PQ team's request, Euvichol samples were sent to 2 different laboratory for testing on June 2015, and test results were received on 14th Oct. 2015

3 sets of samples, Standards, Reagents and SOP

Lab 1

NIBSC
Confidence in Biological Medicines

Results

Lab 2

ansm
Agence nationale de sécurité du médicament et des produits de santé

Results

2.4 GMP Inspection

Mock Inspection

Before WHO Inspection, the GMP status of EuBiologics was evaluated by 3 different external Inspection teams.

Inspection Team	Date	No. of Inspectors	Major Issue
KoBIA	4 ~ 5 Dec. 2014 (2 days)	3	Layout
MFDS	15 ~ 17 Dec. 2014 (3 days)	4	Validation
Chimera Gentec. (India)	15 ~ 20 Jun. 2015 (6 days)	4	Quality Risk Management, Shipping Validation, Control of AHU

KoBIA : Korea Biomedicine Industry Association

WHO Inspection

☞ Date : 24 ~ 28 Aug. 2015 (5 days)

☞ Inspectors : Mr. Mustapha Chafai (GMP Inspector WHO)

Dr. Mohammed Alali (Vaccines Assessor WHO)

☞ Summary of activities

Facilities	Purpose
Clean Utilities	Purified water, WFI generator, Clean steam generator, AHU
Warehouse	Quarantine for testing, Sampling, Raw material and drug product storage
Packaging Room	Visual inspection, Labelling and Packaging
Microbial Production	OCV DS production (Seed culture, main culture, recovery, cold storage, and CIP room)
QC Lab	Sterility testing, Microbial/Physicochemical testing

WHO Inspection

☞ **Documents should be available without delay at any time during the inspection**

- Copy of the PSF with associated updates and annexes
- General layout of the site
- Manufacturing formula and master batch record
- Detailed manufacturing process flow chart
- Specification for starting material
- Packaging material specification
- Organization chart
- Job description of key personnel
- Index of controlled documents
- Batch numbering system SOP
- Number of lots
- Product Quality Review
- Environmental monitoring / Water sampling SOP and records
- Validation Master Plan
- Preventive maintenance SOP and records
- Cleaning Procedures…

WHO Inspection

☞ **Inspection Schedule**

Date	Activities	Remarks
24 Aug	Opening meeting	Instructions and registration Company Presentation
	QMS review	
	Tour : warehouse & Personnel review	
25 Aug	Site plan review	
	Tour: production	Process Simulation
	QC review & BPR review	
26 Aug	Tour: production & QC lab	
	VMP, Qualification and PM review	
	Tour: utilities & Utilities review	
27 Aug	Tour: production	
	Document review	
28 Aug	Document review	
	Internal discussion	
	Wrap-up meeting	Issuing draft report

WHO Inspection

WHO Inspection

After wrap-up meeting, Inspection report(draft) was issued.

☞ **No Critical, but some observations…..**

- Bulk Fill & aseptic inoculation should be performed ..

- Bio welding process should be validated…..

- Inactivation Process should be considered the worst conditions

- Supplier of disposable bag and filters were not audited

…

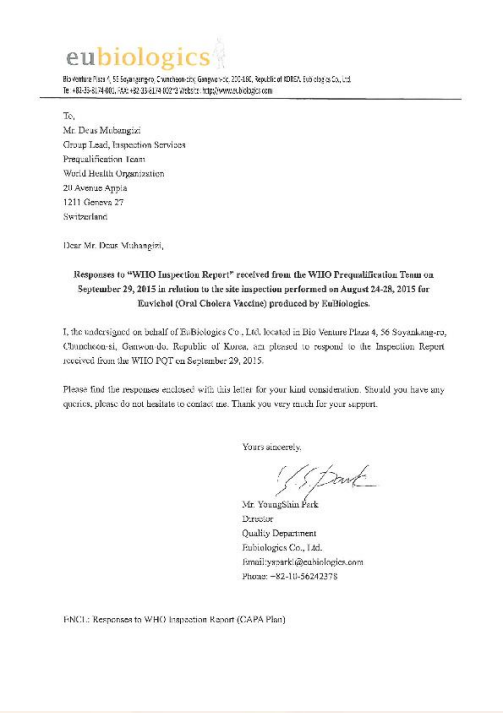
WHO Inspection

It was requested to submit a response to the inspection report detailing the root cause analysis and proposed CAPAs for all observations .

	Observations	***Root cause analysis*** *(Additional information may be attached as annexes)*	***Correction and proposed corrective action*** *(Additional information may be attached as annexes)*	***The steps that have or will be taken for the demonstration of effectiveness of the actions taken***	***Timeline***	***Assessment by inspector***
	Major					
1	*a)*	*a)*				
2	*a)*	*a)*				
	Others					
3	*a)*	*a)*				
4	*a)*	*a)*				

WHO Inspection

2 times of formal responses to the inspection report were submitted to the WHO PQ team.



eubiologics

To,
Mr. Deus Mubangizi
Group Lead, Inspection Services
Prequalification Team
World Health Organization
20 Avenue Appia
1211 Geneva 27
Switzerland

Dear Mr. Deus Mubangizi,

Responses to "WHO Inspection Report" received from the WHO Prequalification Team on September 29, 2015 in relation to the site inspection performed on August 24-28, 2015 for Euvichol (Oral Cholera Vaccine) produced by EuBiologics.

I, the undersigned on behalf of EuBiologics Co., Ltd. located in Bio Venture Plaza 4, 56 Soyanggang-ro, Chuncheon-si, Gangwon-do, Republic of Korea, am pleased to respond to the Inspection Report received from the WHO PQT on September 29, 2015.

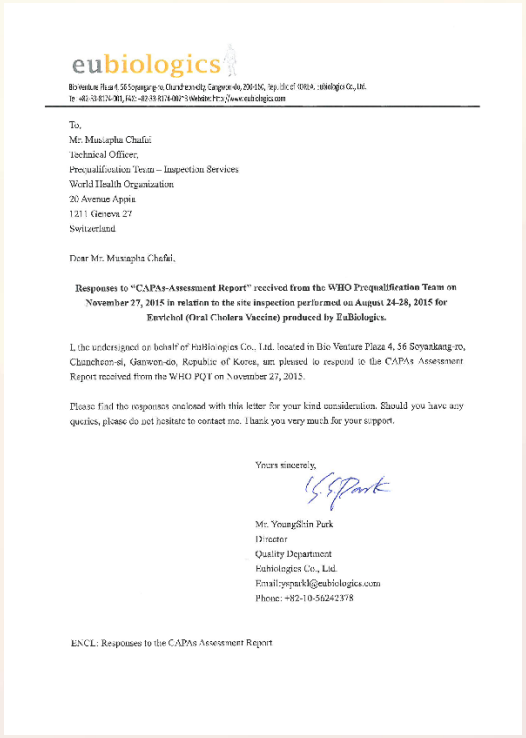
Please find the responses enclosed with this letter for your kind consideration. Should you have any queries, please do not hesitate to contact me. Thank you very much for your support.

Yours sincerely,

Mr. YoungSkin Park
Director
Quality Department
EuBiologics Co., Ltd.
Email:yspark@eubiologics.com
Phone: +82-10-56242378

ENCL: Responses to WHO Inspection Report (CAPA Plan)

21 Oct. 2015



eubiologics

To,
Mr. Mustapha Chafai
Technical Officer,
Prequalification Team – Inspection Services
World Health Organization
20 Avenue Appia
1211 Geneva 27
Switzerland

Dear Mr. Mustapha Chafai,

Responses to "CAPAs-Assessment Report" received from the WHO Prequalification Team on November 27, 2015 in relation to the site inspection performed on August 24-28, 2015 for Euvichol (Oral Cholera Vaccine) produced by EuBiologics.

I, the undersigned on behalf of EuBiologics Co., Ltd. located in Bio Venture Plaza 4, 56 Soyanggang-ro, Chuncheon-si, Gangwon-do, Republic of Korea, am pleased to respond to the CAPAs Assessment Report received from the WHO PQT on November 27, 2015.

Please find the responses enclosed with this letter for your kind consideration. Should you have any queries, please do not hesitate to contact me. Thank you very much for your support.

Yours sincerely,

Mr. YoungSkin Park
Director
Quality Department
EuBiologics Co., Ltd.
Email:yspark@eubiologics.com
Phone: +82-10-56242378

ENCL: Responses to the CAPAs Assessment Report

7 Dec. 2015

WHO Inspection

Finally…

World Health Organization

Tel. direct: +41 22 791 4162
Fax direct: +41 22 791 4856
E-mail: rodriguezhernandezo@who.int

In reply please refer to: 18 370 43 WPRO
PQT-DMrs (2015-460)

Your reference:

Ms Shanelle Hall
Director, Supply Division
UNICEF
Oestervej 10 12
2150 Nordhavn
Denmark

23 DEC 2015

Dear Ms Hall,

Acceptability, in principle, of Euvichol [(oral cholera vaccine (inactivated)] produced by Eubiologics, Co. Ltd, Republic of Korea for purchase by United Nations agencies

We are pleased to inform you of the positive decision on the acceptability, in principle, of the Euvichol [(oral cholera vaccine (inactivated)] for purchase by United Nations agencies. This product was assessed using the procedure as described in WHO TRS 978 (Annex 6).

This decision is based on the review of the information submitted to WHO by Eubiologics, Co. Ltd, site inspection of the manufacturing facility and results of testing of samples in WHO contract laboratories.

Product Characteristics:

Euvichol [(oral cholera vaccine (inactivated)] is a liquid vaccine presented in a type I colourless borosilicate glass vial with 2 ml capacity, with a chlorobutyl rubber stopper, with an aluminium flip off seal. The vial bears a Vaccine Vial Monitor (VVM) type 30 as part of the label.

The shelf-life of the Euvichol is 24 months at 2 – 8°C.

../2

cc: UNICEF Supply Division (Attention: Dr JL Deehen and Ms K. Dorgan).
Eubiologics Co., Ltd (Attention: Mr Seuk-Keun Cho.)
Ministry of Food and Drug Safety (MFDS) (Attention: Dr Eun-u Kim)
AMRO (Attention: Dr M. Pomho and Dr J. Fitzgerald)
WHO/CPS (Attention: Ms H. Scarumuzzi)

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Regional Food & Drug Administration
#212, Mokdongjungang-ro, Yangcheon-gu, Seoul, Korea
Tel: 82-2-2640-1307, Fax: 82-2-2640-1360

ertificate of Good Manufacturing Practice

YeongOk Baik	Name Of Manufacturer	Eubiologics CO., LTD.
3-2~3, 4 BioVenture plaza 56, Soyanggang-ro, Chuncheon-si, Gangwon-do, Republic of Korea		
KyeongHo Min	Registered Quality Control Manager	Youngshin Park
Approved Dosage Forms		Approval Date
vichol (Oral Cholera Vaccine)		28 January 2015

fied that the above manufacturing plant in which the products are ject to inspections at suitable intervals and the manufacturer P(Good Manufacturing Practice) as recommended by PIC/S and

Issued date :Feb. 02, 2015 2015-B1-0061

Certified by

Seoul Regional Commissioner Food and Drug Administration

eubiologics

WHO Inspection

Finally…

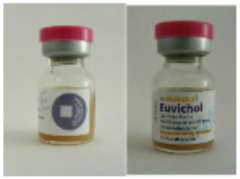
World Health Organization

cholera: inactivated oral

Euvichol

Product Overview:

Type:	cholera: inactivated oral
Commercial Name:	Euvichol
Manufacturer:	Eubiologics Co., Ltd.
Country:	Republic of Korea
URL:	http://www.eubiologics.com/ENG/eng_info/info.php
Responsible NRA:	Ministry of Food and Drug Safety
Country:	Republic of Korea
URL:	
Bulk Supllier:	



Prequalification:

Prequalification Status:	Current
Effective Date (dd/mm/yyyy):	23/12/2015

Product Description:

Pharaceutical Form:	Liquid: ready to use
Presentation:	Vial
Number of Doses:	1
Diluent:	
Route of Administration:	Oral

eubiologics

3. Lesson Learned

Lesson Learned

WHO PQ approval of Euvichol was achieved based on the following elements

- **For completion to OCV project successfully**
  - **All staffs' strong belief to make this possible**
  - **GMP compliance, GMP education and training**
  - **Leadership and followership**

- **For satisfactory development as a small bio-venture, the following external factors were too much influential**
  - **IVI's, the technology developer of OCV, full technical support**
  - **Guidance and suggestion in advance from the regulatory experts of WHO PQ team and MFDS to avoid trial and error**
  - **Pre-communication with many non-profitable organizations i.e., BMGF, GAVI, WHO, UNICEF**

Thank you very much!