For Health that lasts a lifetime!

eubiologics

OCV in Plastic Tube Container
Euvichol-Plus

I. EuBiologics_Company Overview

Company Profile

Establishment	10th March, 2010
Business Place	HQ: Seoul, South Korea Facility - 2 Manufacturing sites in Chuncheon - R&D Center in Chuncheon
No. of Employee	Over 300
Market Capital	USD 60M Listed in KOSDAQ since Jan 2017
Business Area	- Vaccine Development, Manufacturing & Supply - CRMO(Contract R&D and Manufacturing Organization)

CEO Profile

Dr YEONGOK BAIK

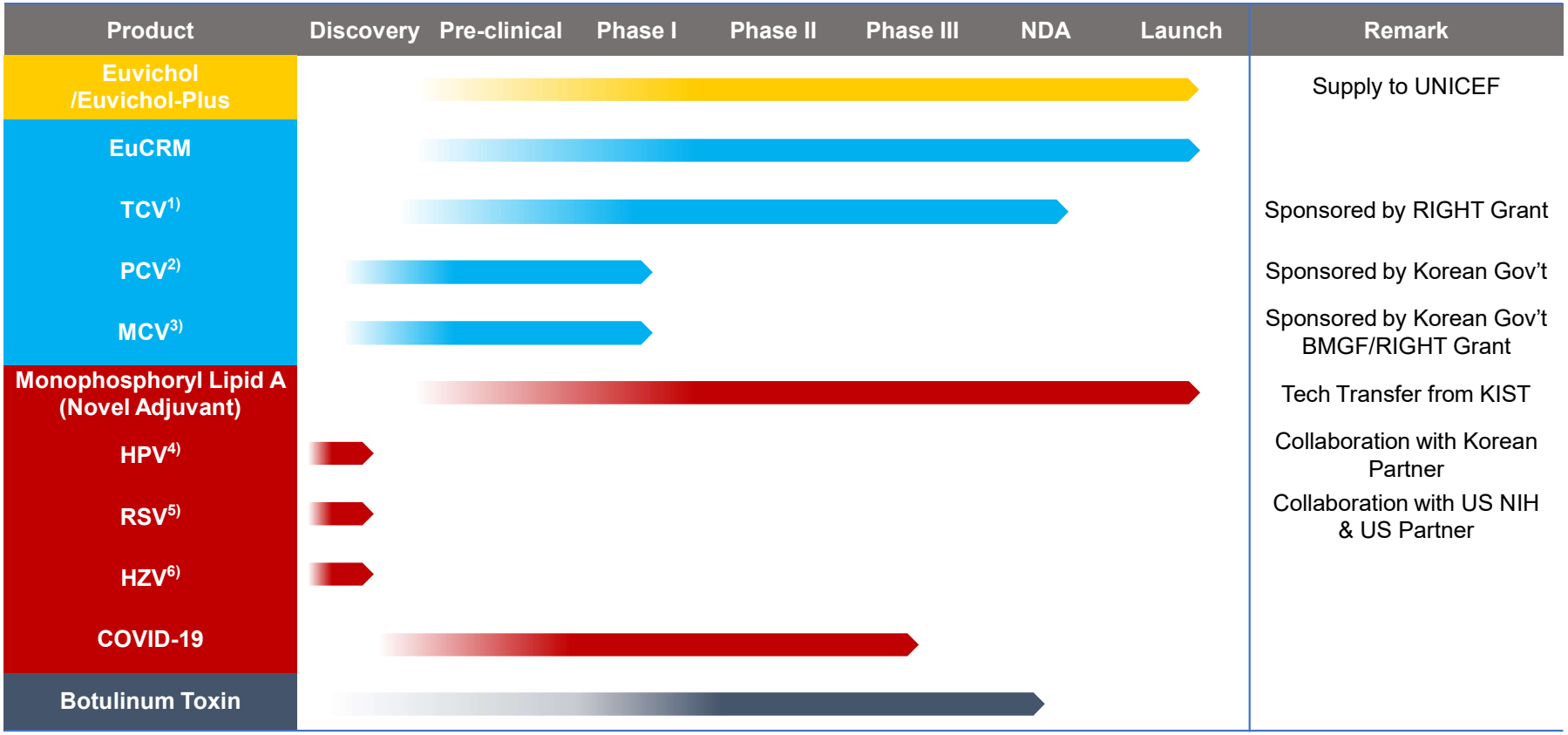
- Bachelor, Master in Veterinary Medicine, Seoul National Univ.
- Ph.D. in Life Science, Korea Univ.
- CJ Corporation
- Director, Korea Institute of Industrial Technology

CEO Profile

SEUKKEUN CHOI

- Bachelor in Microbiology, Seoul National Univ.
- Green Cross Corporation
- CJ Corporation
- LG Life Sciences
- Plant head, Meditox

I. EuBiologics_Pipeline



1) TCV: Typhoid Conjugate Vaccine 2) PCV: Pneumococcal Conjugate Vaccine 3) MCV: Multivalent Meningococcal Conjugate Vaccine
4) HPV: Human Papilloma Virus 5) RSV: Respiratory Syncytial Virus 6) HZV: Herpes Zoster Virus

II. Cholera Overview

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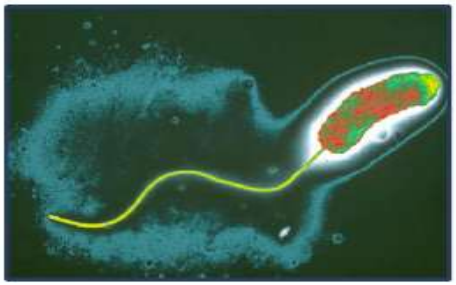
• Vibrio cholerae, highly pathogenic waterborne bacterium, causes outbreaks of acute diarrheal disease
; 3 million cases per year, mainly in Africa and Southeast Asia, 100,000 deaths

• Two types of oral cholera vaccine (OCV) available;
- Killed (inactivated) bacterial cells
- Live attenuated bacteria
; Reluctance to invest in vaccine development and scale-up



• A global stockpile of OCV created in 2013, to control cholera epidemics.
; 2~3 million doses in Stockpile, to convert the "vicious cycle" into "virtuous cycle" of vaccine availability and country adoption, as demand and/or supply stimuli are needed

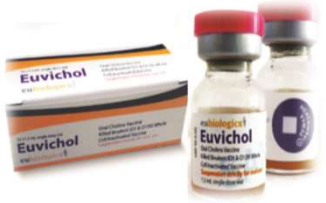
• GAVI Investment Decision in 2013
; Initial Support for global stockpile up to USD 115M over 2014-2018 to trigger vaccine demand/supply

III. OCV_Development History

- EuBiologics, chosen as the 2nd manufacturer of OCV through the Cholera Vaccine Initiative (CHOVI) program sponsored by Bill and Melinda Gates Foundation (BMGF), and has technology transferred by International Vaccine Institute in 2010.

<Targets for OCV Development>

- ✓ A low-cost vaccine;
  → Process optimization, Yield increase (fed-batch fermentation)
- ✓ High quality vaccine in compliance with global standards;
  → In compliance with Korea GMP and WHO GMP
  → Thimerosal free formulation
- ✓ Sufficient capacity more than 6 Million doses per year targeted to global public market
  → from 100L to 600L scale (up to 25 M per year)
  → Easier administration (Plastic Tube Presentation)



III. OCV_Development History

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

  - Sep 2010 OCV License Agreement with IVI

  - Apr 2011 Non-clinical Trial for OCV in Korea (http://dx.doi.org/10.5487/TR.2012.28.4.225)

  - Oct 2012 Phase I Clinical Trial in Korea (http://synapse.koreamed.org/DOIx.php?id=10.3346/jkms.2014.29.4.494)

  - Aug 2014. Non-inferiority trial "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)

  - Jan 2015 Approval of Marketing Authorization from Korea MFDS

  - Dec 2015 Euvichol Prequalification from WHO (6M doses per annum)

  - Sep 2016 PQ variation approval (600L scale up allowing 25M doses & removal of thimerosal)

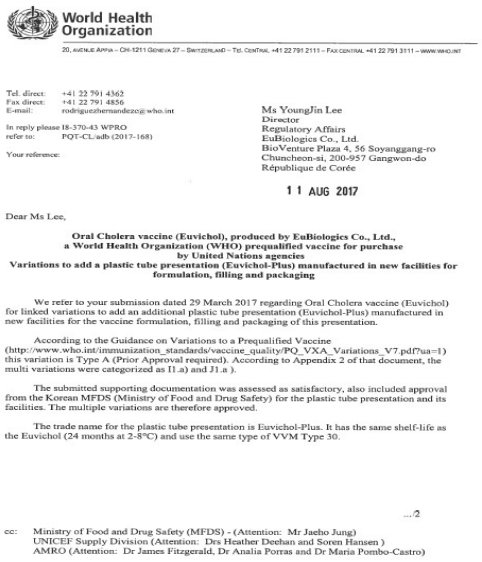
  - Aug 2017 PQ variation approval (Plastic Tube)

IV. Euvichol-Plus_Milestone

Euvichol-Plus Development Milestone

- Aug 2014: GHIF* Investment (USD 5M) for establishment of fill seal facility
- Aug 2016: Mock Inspection for F/F line sponsored by Kobia**
- Sep 2016: Dossier submission to KMFDS*** for Euvichol-Plus
- Dec 2016: Site inspection by KMFDS
- Jan 2017: Mock inspection sponsored by DCVMN
- Mar 2017: Approved by KMFDS and a dossier submission for variation to WHO
- May 2017: Began the production of Euvichol-Plus
- Aug 2017: Approved by WHO PQ

*GHIF: Global Health Investment Fund
**Kobia: Korea Biomedicine Industry Association
***KMFDS: Korea Ministry of Food and Drug Safety



World Health Organization

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL. CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

Tel. direct: +41 22 791 4362
Fax direct: +41 22 791 4856
E-mail: rodriguezhernandezc@who.int

In reply please IE-370-43 WPRO
refer to: PQT-CL/adb (2017-168)

Your reference:

Ms YoungJin Lee
Director
Regulatory Affairs
EuBiologics Co., Ltd.
BioVenture Plaza 4, 56 Soyanggang-ro
Chuncheon-si, 200-957 Gangwon-do
République de Corée

11 AUG 2017

Dear Ms Lee,

Oral Cholera vaccine (Euvichol), produced by EuBiologics Co., Ltd., a World Health Organization (WHO) prequalified vaccine for purchase by United Nations agencies
Variations to add a plastic tube presentation (Euvichol-Plus) manufactured in new facilities for formulation, filling and packaging

We refer to your submission dated 29 March 2017 regarding Oral Cholera vaccine (Euvichol) for linked variations to add an additional plastic tube presentation (Euvichol-Plus) manufactured in new facilities for the vaccine formulation, filling and packaging of this presentation.

According to the Guidance on Variations to a Prequalified Vaccine (http://www.who.int/immunization_standards/vaccine_quality/PQ_VXA_Variations_V7.pdf?ua=1) this variation is Type A (Prior Approval required). According to Appendix 2 of that document, the multi variations were categorized as I1.a) and J1.a).

The submitted supporting documentation was assessed as satisfactory, also included approval from the Korean MFDS (Ministry of Food and Drug Safety) for the plastic tube presentation and its facilities. The multiple variations are therefore approved.

The trade name for the plastic tube presentation is Euvichol-Plus. It has the same shelf-life as the Euvichol (24 months at 2-8°C) and use the same type of VVM Type 30.

.../2

cc: Ministry of Food and Drug Safety (MFDS) - (Attention: Mr Jaeho Jung)
UNICEF Supply Division (Attention: Drs Heather Deehan and Soren Hansen)
AMRO (Attention: Dr James Fitzgerald, Dr Analia Porras and Dr Maria Pombo-Castro)

IV. Euvichol-Plus_Drivers for decision-making

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- **In-house FF facility needed for OCV**
  - Outsourced DP production limiting a total capacity of OCV (DS Capa: 25M, Outsourced DP capa: 12M)
  - High cost associated

- **Differentiation from existing product needed as a late comer**
  - The competitor has the same formulation transferred from IVI
  - Plastic tube presentation can make a difference

- **Plastic tube offers a number of benefits over glass vial, lower production cost, easy administration, storage and transportation**
  - 30% reduction in volume, more than 50% reduction in weight
  - Pricing offered to UNICEF decreased by 23% in the first year attributed to the CoGs decline (Glass vial: USD 1.7, Plastic Tube: USD 1.3)

- **External funding available for FS facility**
  - Global Health Investment Fund (GHIF) led investment for FS facility together with Korean investors
  - Leachable/Extractable study was partly funded by DCVMN

IV. Euvichol-Plus_Layout & Process

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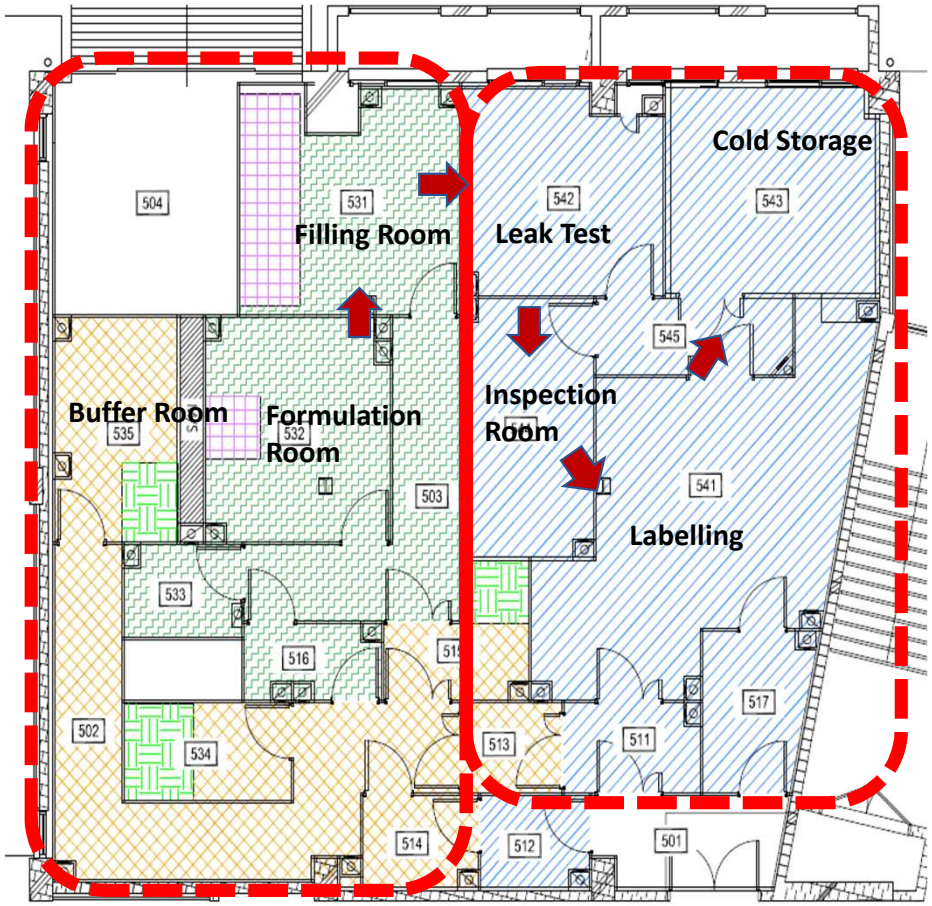
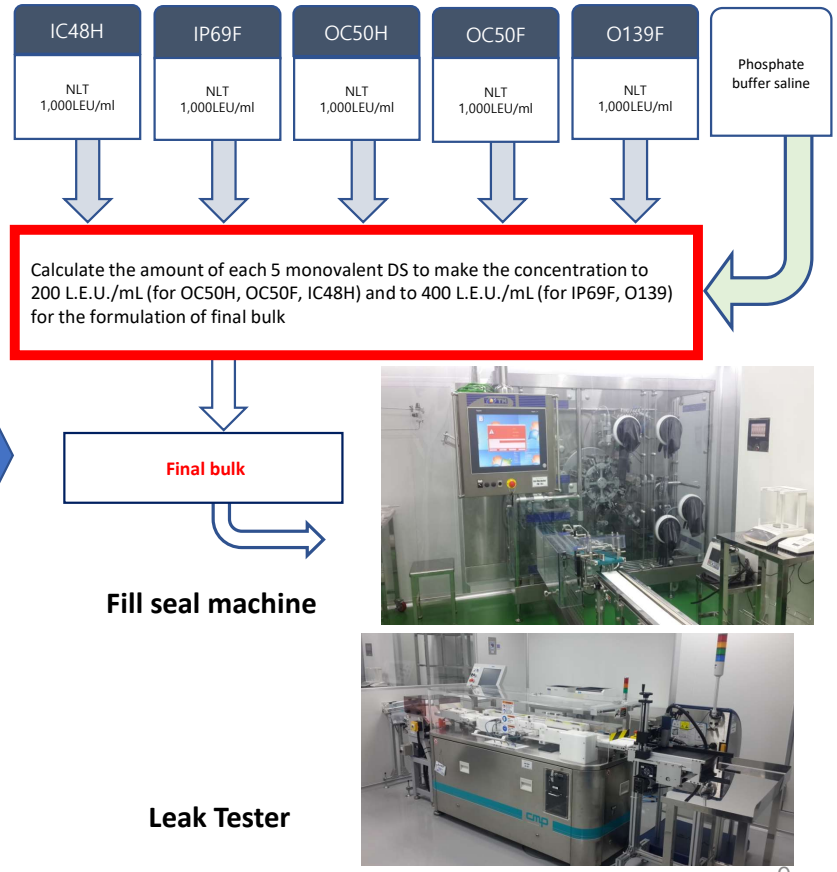
- Layout for Fill Seal Production Area



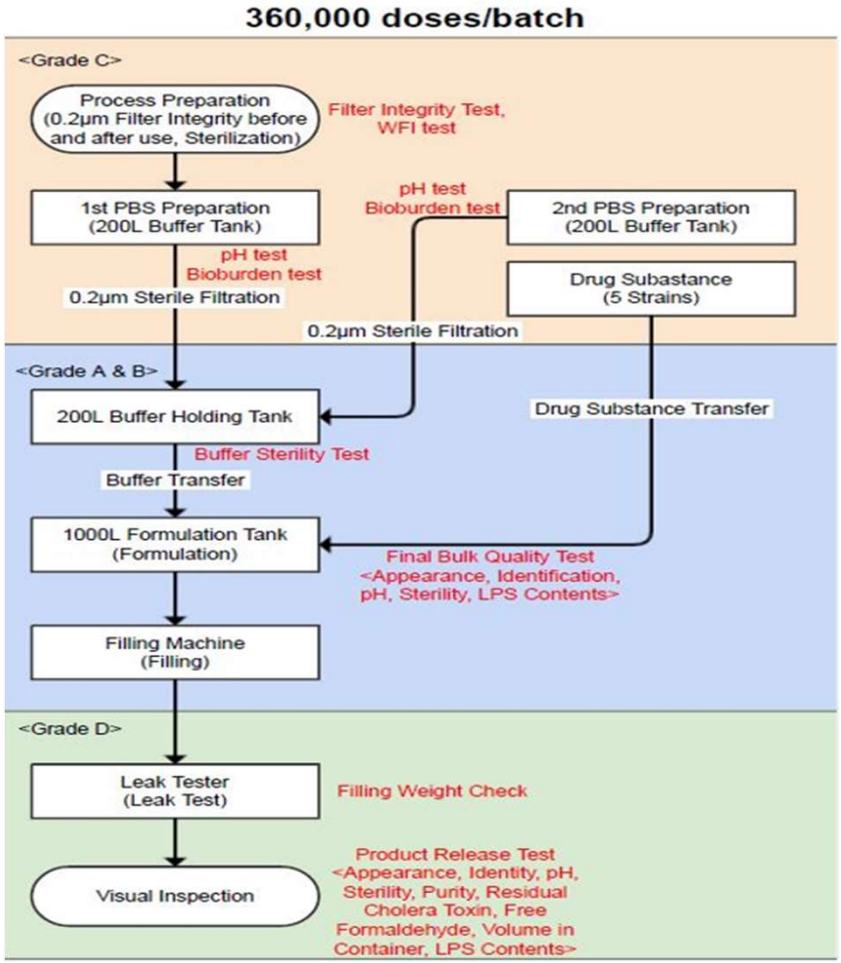
- Filling & Leak Test



Fill seal machine

Leak Tester

IV. Euvichol-Plus_Process



- **Tube Labeller**

- Capacity: Max 100 strips/min (500 doses/min)
- Application: Labels and VVM
- Additional roller to press the tube for labels & VVM

IV. Euvichol-Plus_Process

- Packaging

- Packaging in packaging room
  - EuB outsourced the packaging (manual)
  - 10 strips in one carton box with insert

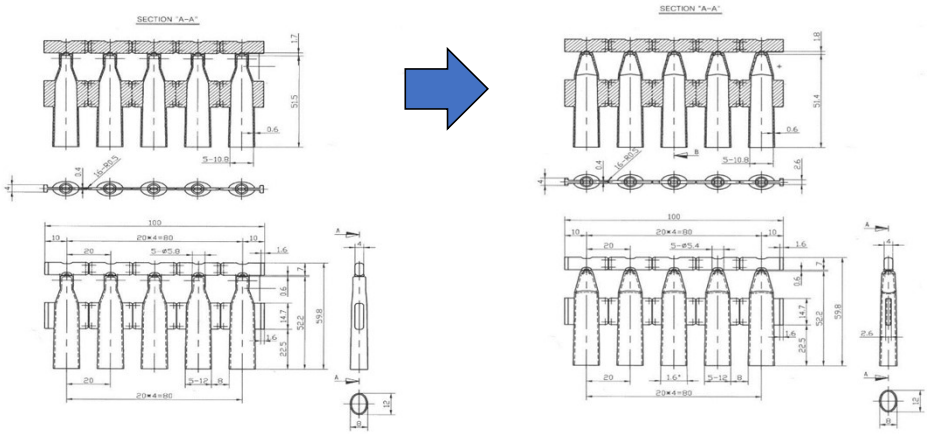
- After packaging, weight check is required
  - To confirm if all is included

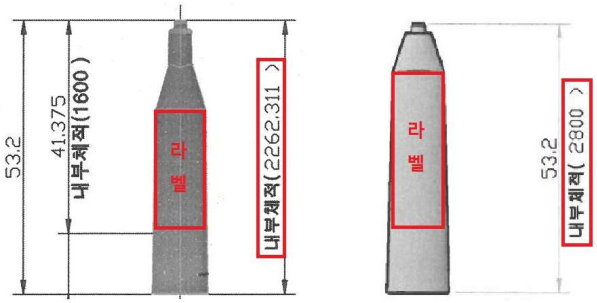
- Taping is the final step before NRA release submission

- 2D barcoding in secondary packaging adopted

V. Considerations_Plastic Container Design

- **Sufficient space on plastic tube for label including VVM and sufficient air space for thorough mixing is needed. It is also designed to avoid heating of vaccine during sealing.**





	Details
Thickness	0.6mm (±0.2mm)
Height	59.8mm (±0.5mm)
Total height	100mm (±0.5mm)
Weight	5.950g~6,250g

V. Considerations_FS System and Specification

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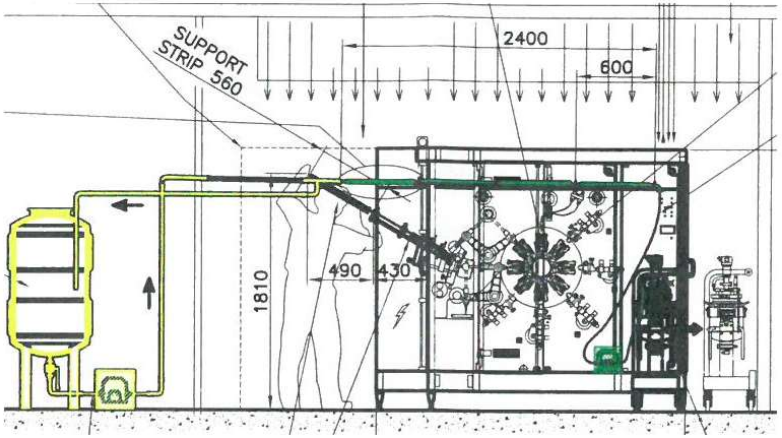
- **Configuration of FS System**



- **Photo of FS Machine: Time/Pressure Type Filling System**

- **Specification of FS Machine (customized)**

Items	Specification
Manufacturer	TM Srl (Italy)
Type	Filling & Sealing
Size	L2460 X W1220 X H2000 mm
Tube Material	Low Density Polyethylene (LDPE)
Working Pressure	5 ~ 6 bar
Machine Operation	Electro mechanical pneumatic
Mechanical speed	15 ~ 35 cycles / min (Max. 20,000 dose/min)
Power supply	380V , 50 ~ 60 Hz , 3-ph

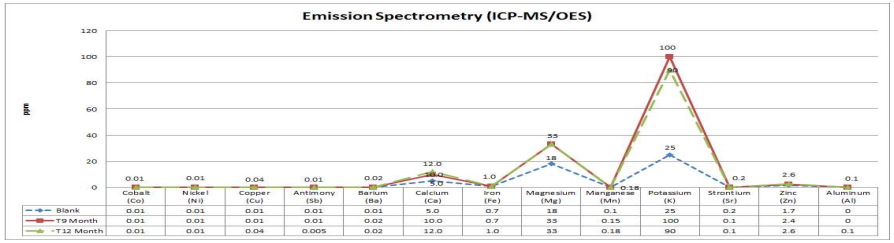
- **Executed Qualification test lists**

Qualification	Test Items
Installation Qualification	- Documentation availability - Check instrument calibration - Check connection to utilities and system predisposition - Check installation and components identification - Audit wiring diagram and I/O - Check graphic pages : control panel - Materials in contact with the product - Check configuration
Operation Qualification	- Check I/O control panel - Check operating sequences - Check logical access - Operator safety check - Check critical alarms - Check audit trail : Audit trail - Check blackout - Check dosage accuracy and repeatability - Check blister welding accuracy - Operation speed check : - Report check
Performance Qualification	- Operator qualification, Education and training for SOPs - Welding accuracy check - Filling accuracy (filling amount ±3%) - Cell sedimentation, simulation study etc.

V. Considerations_Comparability, L&E Study

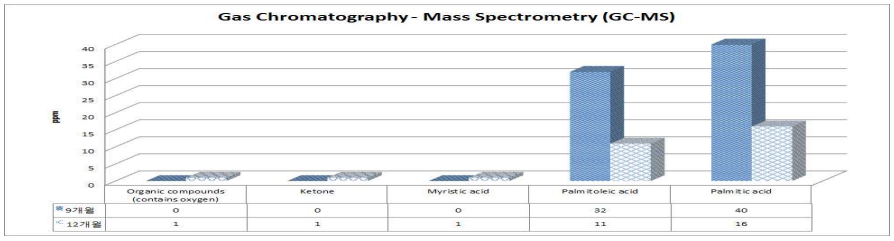
- **Assurance of quality comparability through the analysis between two presentations**
- **Comparison of stability test (2 to 8 degrees of Euvichol and Euvichol-Plus has been reviewed with updated stability data for the period of 18 months of Euvichol and 15 months of Euvichol-Plus. All test results satisfied the acceptance criteria.**
- **Leachable study by Satorius Korea (funded by DCVMN)**
  - Study of test LDPE tubes in contact with cholera vaccine

(1) Leachable (inorganic)



	EMEA CHMP Limits for residue of metals (PDE in µg/day)	USP <232> Limits for parenteral 10-100 mL/day (PDE in µg/day)	ICH Q3D current step 4 version for Parenteral (PDE in µg/day)
Ca	Not listed	No toxicological concern	No toxicological concern
Mg	Not listed	No toxicological concern	No toxicological concern
K	Not listed	No toxicological concern	No toxicological concern

(2) Leachable (inorganic)



Organic compounds (contains oxygen), Ketone and Palmitoleic acid are assumed to be a typical extractables of inactivated cholera vaccines. Palmitoleic acid and Myristic acid are remarkably lower than 50.000 g/human of PDE and seems to be no risk. In case of Organic compounds (contains oxygen), Ketone and Palmitoleic acid, trend analysis of 18 months and assessment according to increased amount would be conducted and evaluated.

VI. Training

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- **EuBiologics made 83 new SOPs for fill/finish (sterile) and trained operators on a regular basis**

< A list of SOPs>

No.	제목	문서번호
1	제조(포장)지시 및 기록서 작성 및 관리 방법	QS-SOP-2006
2	기관생물안전위원회 운영규정	QS-SOP-4005
3	재가공 및 재작업	QS-SOP-6003
4	유틸리티 라벨관리	FE-SOP-1003
5	HEPA 필터 관리	FE-SOP-1007
6	완제작업장 필터 관리	FE-SOP-1010
7	공정용 호스의 관리	FE-SOP-2203
8	패스박스(PB-201 외) 관리	FE-SOP-2206
9	Filter Integrity Tester(FI-601 외) 작동 및 관리방법	FE-SOP-2211
10	폐기물 멸균기(AC-603, AC-103) 작동 및 관리방법	FE-SOP-2242
11	고압증기 멸균기(AC-101) 작동 및 관리방법	FE-SOP-2217
12	동결건조기(LY-701) 작동 및 관리	FE-SOP-2243
13	바이알충전기(FM-702) 작동 및 관리방법	FE-SOP-2244
14	고압증기 멸균기(AC-155) 작동 및 관리	FE-SOP-2255
15	500L CIP Skid(CI-154) 작동 및 관리방법	FE-SOP-2253
16	전자저울(SC-777 외) 작동 및 관리	FE-SOP-2273
17	마이크로파이펫(생산용) 사용 및 점검	FE-SOP-2275
18	바이알실링기(CA-704) 작동 및 관리	FE-SOP-2277
19	교반기(SH-281, SH-282) 작동 및 관리	FE-SOP-2282
20	리크테스터(IS-767) 작동 및 관리	FE-SOP-2287
21	완제 작업소 훈증기(FG-782) 관리 및 훈증방법	FE-SOP-2288
22	Tube Welder(WE-753) 작동 및 관리	FE-SOP-2289
23	잉크젯 프린터기(PM-768) 작동 및 관리	FE-SOP-2291
24	필터 완전성 테스트기(FI-707) 작동 및 관리	FE-SOP-2292
25	Buffer Tank(TK-758) 작동 및 관리	FE-SOP-2293
26	Formulation Tank(TK-754) 작동 및 관리	FE-SOP-2294
27	Buffer Holding Tank(TK-776) 작동 및 관리	FE-SOP-2295
28	고압증기 멸균기(AC-755) 작동 및 관리	FE-SOP-2296
29	Glove Leak Tester(LT-760) 작동 및 관리	FE-SOP-2297
30	pH meter(PH-759) 작동 및 관리	FE-SOP-2298
31	완제작업장 패스워드 및 마스터키 관리	FE-SOP-2299
32	Tube Sealer(WE-790, WE-791) 작동 및 관리	FE-SOP-2300
33	이동용 수레 사용 및 관리방법	FE-SOP-2423
34	플라스틱 튜브 충전기(FM-751) 작동 및 관리	FE-SOP-2430
35	완제작업장 Disposable bag 액송방법	FE-SOP-2432
36	무선 밸리데이터(SE-060) 작동 및 관리방법	FE-SOP-2601
37	유선 밸리데이터 작동 및 관리방법	FE-SOP-2602
38	부유입자측정기(PA-051 외) 작동 및 관리	FE-SOP-2605
39	부유균포집기(AP-053 외) 작동 및 관리방법	FE-SOP-2606
40	압축공기 부유균(SE-068) 포집기 작동 및 관리방법	FE-SOP-2607
41	이슬점 측정기(SE-072) 작동 및 관리방법	FE-SOP-2610
42	온습도 Data Logger(DL-062 외) 작동 및 관리방법	FE-SOP-2612
43	부유입자측정기(PA-069 외) 작동 및 관리	FE-SOP-2613
44	부유입자측정기(PA-038 외) 작동 및 관리	FE-SOP-2614
45	PMS(PM-756) 작동 및 관리	FE-SOP-2615
46	온습도 Data Logger(DL-611 외) 작동 및 관리방법	FE-SOP-2617
47	멸균백 실링기(WE-793 외) 사용 및 관리	FE-SOP-2703
48	튜브 자동정렬장치(TI-795) 작동 및 관리방법	FE-SOP-2705
49	완제작업장 밸브 관리	FE-SOP-2710
50	pH meter(PH-748, PH-749) 작동 및 관리	FE-SOP-2712
51	API작업소 훈증기(FG-613)관리 및 훈증방법	FE-SOP-3003
52	작업복장 세탁 및 멸균	FE-SOP-3006
53	배수구 관리	FE-SOP-3007
54	소독액 관리	FE-SOP-3008
55	완제 작업장 출입복장 규정	FE-SOP-3009
56	작업장 청소기(VC-610 외) 관리	FE-SOP-3010
57	COP 세척방법	FE-SOP-3011
58	RABS(CB-912)내 반출입 및 관리방법	FE-SOP-3012
59	완제 작업장 호스관리	FE-SOP-3013
60	완제 작업소 소독액 관리	FE-SOP-3014
61	튜브연동식 펌프(PU-237 외) 작동 및 관리	FE-SOP-4001
62	작업실 작업현황 표시	PS-SOP-1004
63	작업중인 시설 및 기기상태 표시방법	PS-SOP-1005
64	제품, 작업원, 원료, 폐기물 이동경로	PS-SOP-1006
65	원액 및 완제품 이관방법	PS-SOP-1008
66	제품전환공정	PS-SOP-1012
67	완제 작업장 원자재 및 제품의 반출입	PS-SOP-1015
68	냉장보관실 관리 및 반제품의 반출입	PS-SOP-1018
69	물품 이동방법	PS-SOP-1028
68	냉장보관실 관리 및 반제품의 반출입	PS-SOP-1018
69	물품 이동방법	PS-SOP-1028
70	유비콜-플러스 제조 공정용 호스 Assembly	PS-SOP-1038
71	제조공정 이전	PS-SOP-1041
72	보툴리눔 독소 관리	PS-SOP-1043
73	포장 작업장 관리	PL-SOP-1003
74	표면균 측정법	LC-SOP-4502
75	낙하균 측정법	LC-SOP-4503
76	부유균 측정법	LC-SOP-4504
77	부유입자 측정법	LC-SOP-4505
78	제조용수 모니터링	LC-SOP-4507
79	Gas류 모니터링	LC-SOP-4509
80	검체채취 및 이송방법	LC-SOP-5001
81	제조용수 검체채취 방법	LC-SOP-5004
82	클린스팀 검체채취 방법	LC-SOP-5005
83	Grade B 무균갱의검증 절차	FE-SOP-3015

VI. Training

- **EuBiologics introduced the certification system issued by QA for operators in FF**

GMP training	GMP and quality system training by QA
FF process training (formulation, filling, capping)	FF process including the understanding of sterile product,
Microbiology training	Performed once a year by external trainer
Gowning Process	Qualification of aseptic gowning process is performed consecutively for three times and once a year for those qualified
On-site Training (at least 3 times)	On-site training under supervision
Media Fill Simulation Participation	Media fill simulation is performed twice a year for sterile process validation, and operators participate at least once a year
Certification	Certification is issued to those who satisfy the above criteria

VII. Challenges encountered

- **Airtightness of plastic tube**
  - *KMFDS, WHO PQ and external consultants were interested in airtightness of plastic tube, in particular, how plastic tube can absorb the external shock. EuB tested many times in our lab and even trampling on it*

- **Foreign particle identification by visual inspection due to opaque container**
  - *EuB intently included foreign particle likely to be mixed in the tube to make a standardized sample for training operators*

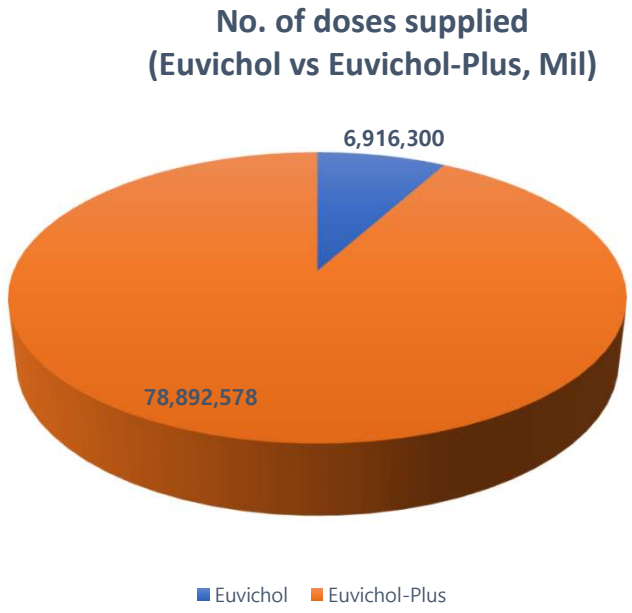
- **Labelling was challenging due to the curved tube**
  - *Labels and VVM are smaller and attached on the carved LDPE. We set up a roller to press the labels one more time.*

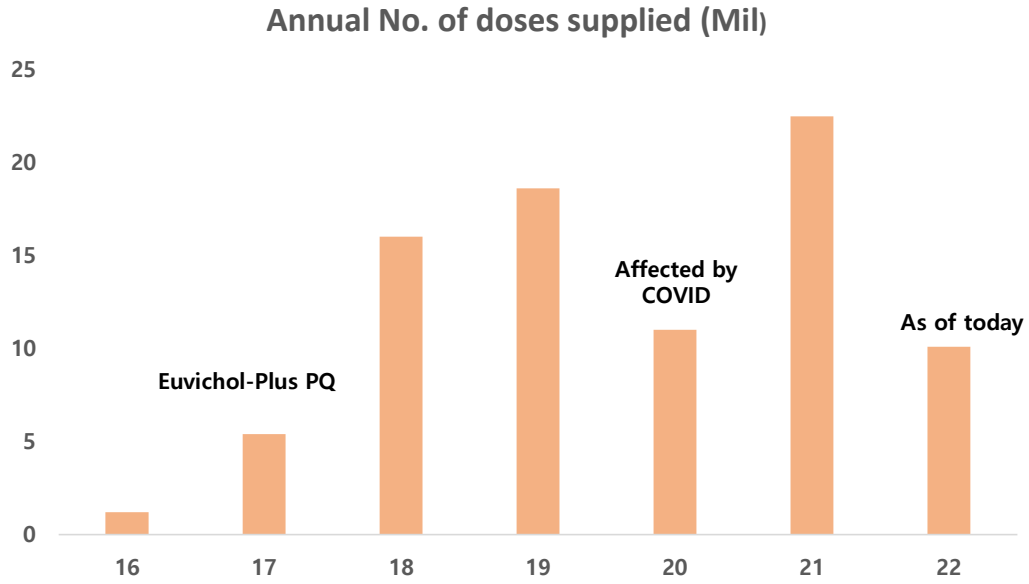
- **Errors in compression molding of plastic tube**
  - *Appropriate temperature was found through trial and error*

- **Additional study (Leachable & Extractable study needed)**

VIII. Conclusion

- **EuBiologics is currently the largest supplier of OCV to LMICs through UNICEF**
  - *Attributed to in-house FF facility and plastic tube presentation in addition to demand*





VIII. Conclusion

eubiologics

- **Advantages of Euvichol-Plus (Wastage, transportation, storage management)**

External Box for export	Width (mm)	Length (mm)	Height (mm)	Quantity per carton	Volume /dose (㎤)	Weight/dose (g)
Euvichol	570	530	425	2,400	53.5	14.6
Euvichol-Plus	700	700	505	6,400	38.7	6.7

☞ **Almost 30 % reduction in volume,** ☞ **More than 50% reduction in weight**

☞ **23% reduction in pricing offered to UNICEF**

- **Easier Administration**

	Euvichol	Euvichol-Plus	Note
Opening	Challenging	Simple	For Euvichol, field workers often complain about difficulty to remove caps & need tweezers/forceps
Administration	Upside down & hit the bottom	Squeeze	Exact AMT can be administered using plastic tube

VIII. Conclusion

- **Development plan for Capacity Increase**
  - Current DS capacity is capped at 33M, however, EuB has been working on expansion to double DS capacity in support of BMGF
  - *If the 2nd site is prequalified, FF capacity is not sufficient to meet the DS capacity*
  - *Additional FF facility up to 50M doses will be ready from 2025 onwards*

(Unit: Mil)		2022	2023	2024	2025	Notes
Euvichol-Plus	DS	33	33	58	65	Currently 33md, increasing to 65md by April 2024 when 2nd site online
	FF	33	33	41	91	Currently 41md capacity, increasing to 91md by end-2024 when 2nd site is online

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eubiologics

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PATH

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