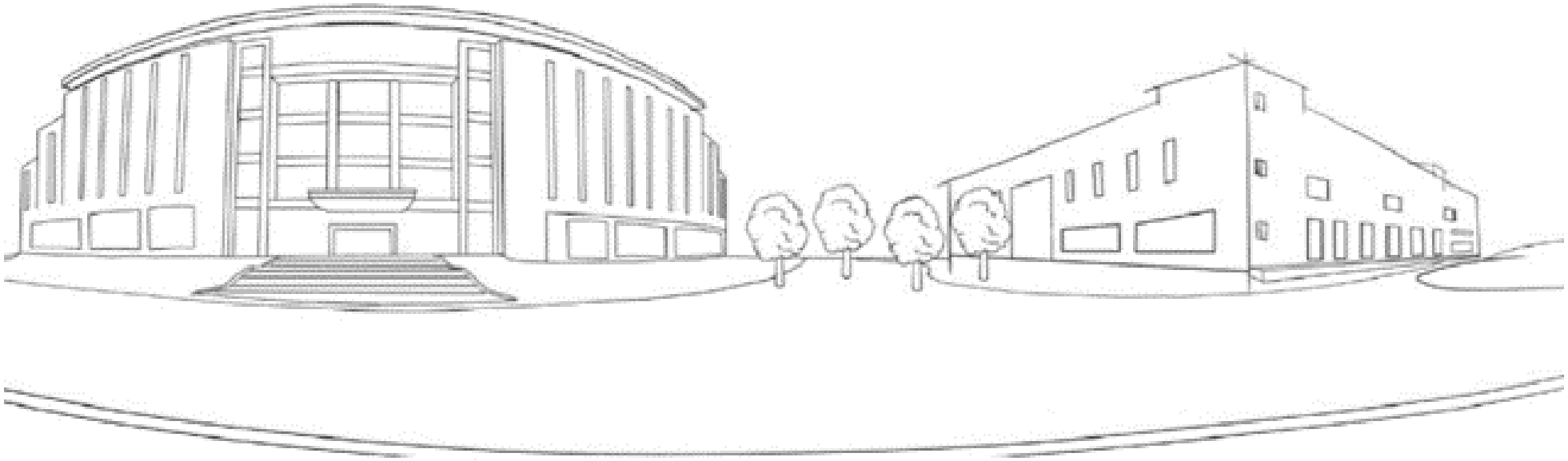
# Advancements in Novel Vaccines against Hepatitis E & Cervical Cancer at Innovax



*Xiamen Innovax Biotech Co. Ltd.*

*James Wai Kuo Shih*

*October 31, 2018*

*DCVMN 19th Annual General Meeting, Kunming, China*

Innovation For Life

# Content

INNOVAX 万泰疫苗

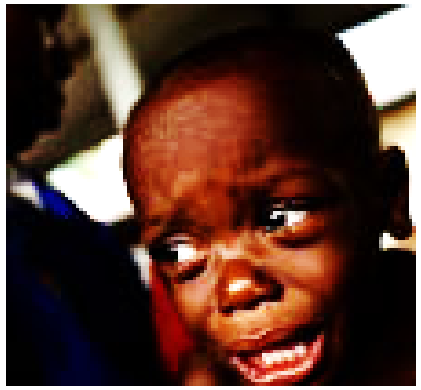
1 Hecolin® -- World's only Vaccine against Hepatitis E

2 Cecolin® -- World's Brand New HPV Vaccine

# 1 Hecolin® --

# World's only Vaccine against Hepatitis E

# 1 Hepatitis E — A Global Health Issue



2012.08-2013.09, South Sudan, 12,386 cases , 225 deaths.

2004 ,Darfur,Sudan, 2,621 cases, 45 deaths.

1955-1956 ,New Delhi, India, 97,000 cases.

1978-1982,Kashmir,India, 52000 cases, 1,700 deaths.

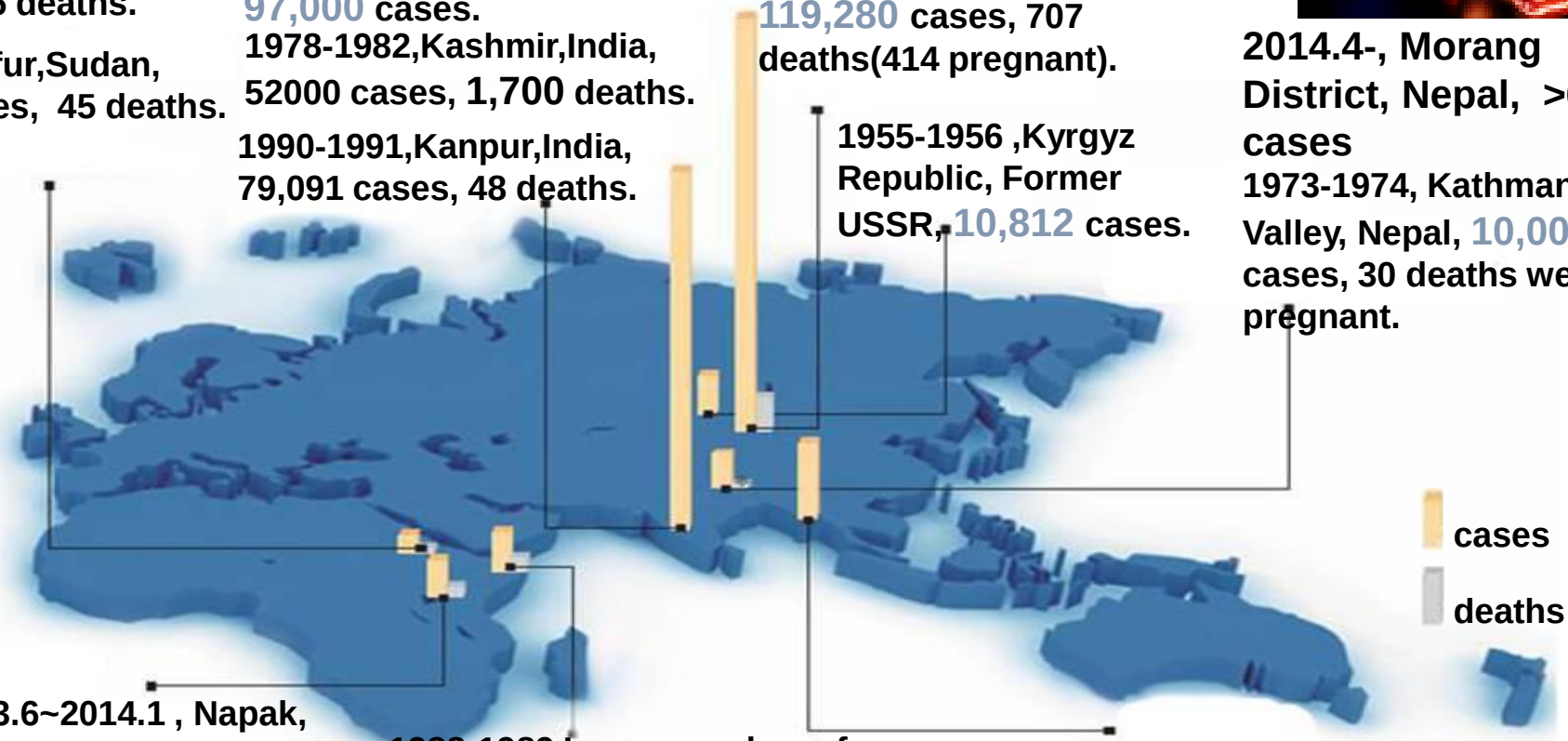
1990-1991,Kanpur,India, 79,091 cases, 48 deaths.

1986-1988 Xinjiang,China, 119,280 cases, 707 deaths(414 pregnant).

1955-1956 ,Kyrgyz Republic, Former USSR, 10,812 cases.

2014.4-, Morang District, Nepal, >6000 cases

1973-1974, Kathmandu Valley, Nepal, 10,000 cases, 30 deaths were pregnant.




2013.6~2014.1 , Napak, Uganda, 656 cases, 19 deaths

2007-2009, Kitgum , Uganda,

10,196 cases ,160 deaths.

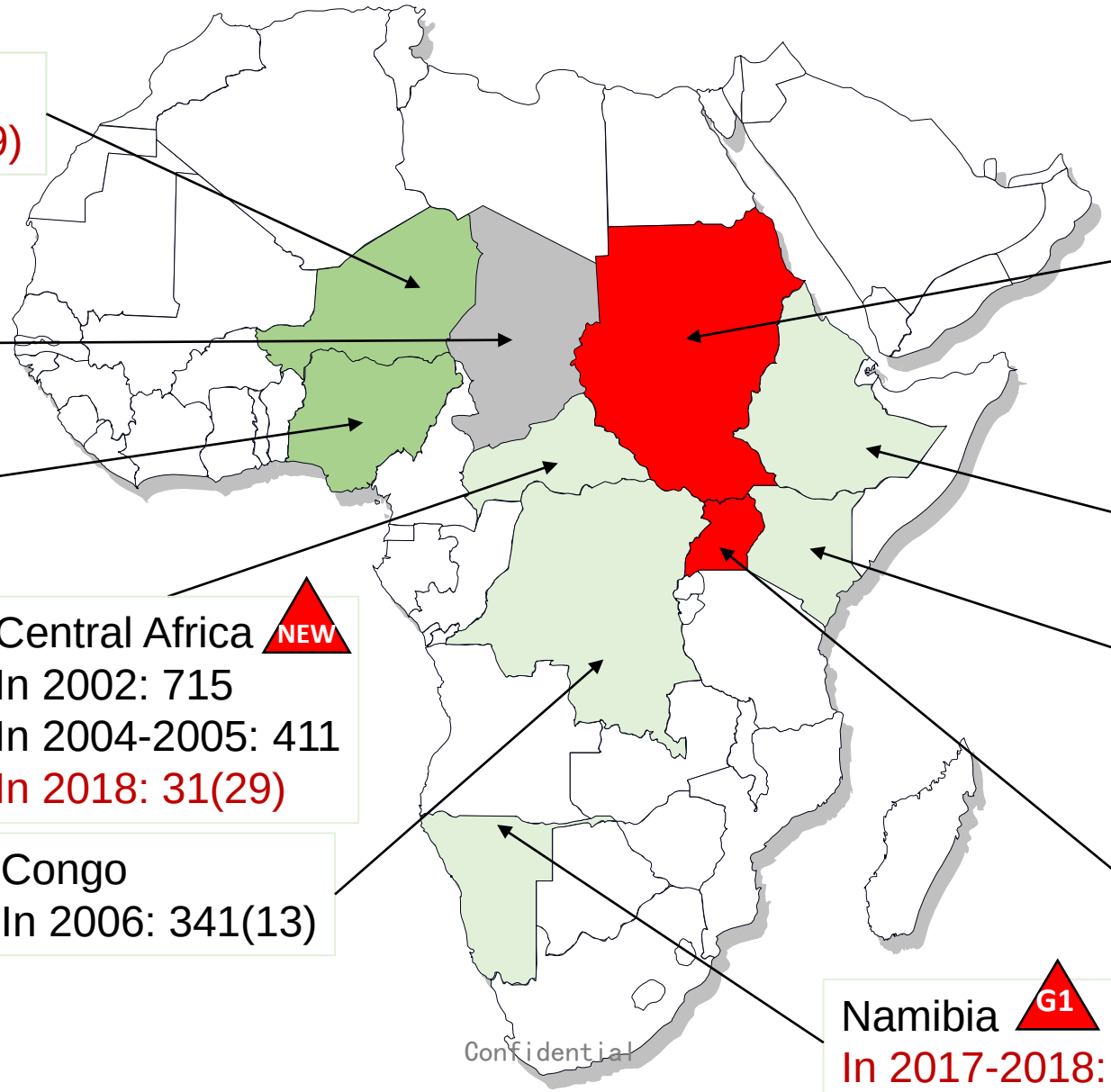
1988-1989 Lower reaches of Shebelle River, Somalia , 11,413 cases, 346 deaths.

1976-1977, Mandalay City, Burma, 20,000 cases.

**In highly endemic area, big outbreak with thousands cases appears periodically.**

# 2 Hepatitis E — Recent Outbreaks in Africa

（Oct. 5th, 2018）



Niger
In 2017-2018: 2078(439)

Chad G1
In 2004: 1442(46)
In 2016-2018: 1874(98)

Nigeria
In 2017-2018:1651 (182)

Central Africa NEW
In 2002: 715
In 2004-2005: 411
In 2018: 31(29)

Congo
In 2006: 341(13)

Sudan
In 2004: 2621(45)
In 2010-2011: 39(11)
In 2014: 712(3)
in 2018: 129(16)
South Sudan
In 2012-2013: 12386(225)
In 2018: 147(19)

Ethiopia
In 2014: 367(13)

Kenya
In 2012: 349(10)

Uganda
In 2007-2009: 10356(30)
In 2013-2014: 656(19)

Namibia G1
In 2017-2018: 2554(395)

<1000
1000-5000
5000-10000
10000-15000

# 3 Hecolin® -- World's only Vaccine against Hepatitis E

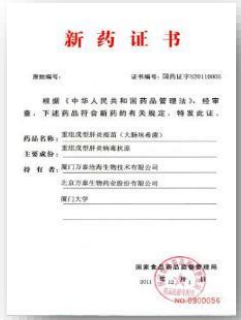
INNOVAX 万泰疫苗

**~2019** WHO Prequalification

**2012** • Launched in China


GMP Certificate

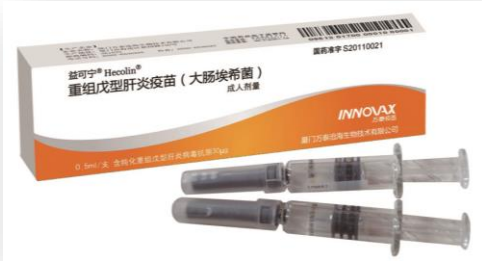
**2007-2009** • Ph3 CT completed and NDA application submitted




New Drug Certificate

**2004-2006** • Ph1 & Ph2 CT

**2003** • Pre-clinical study finished and IND submitted




**1998** • HEV vaccine program initiated by NIDVD

# 4 Target Product Profile of Hecolin®

| | |
|---|---|
| **Serotype** | • 30μg HEV239 VLPs, arising from genotype 1 |
| **Expression system** | • *Escherichia coli* expressed VLP vaccine |
| **Target population** | • ages ≥ 16yr |
| **Presentation** | • 0.5ml of suspension per dose in pre-filled syringe |
| **Shelf-life** | • 2-8℃ for 36 months |
| **Schedule** | • 0, 1, 6 m |
| **Formulation** | • Adjuvanted with Alum;  Thiomersal as preservative. |

# 5 Registration of Hecolin®


## Designed capacity

5 million doses/year

## Regular stock

≥ 100,000 doses

## Registration Status

| Country | Registration status |
|---|---|
| China | Approved in 2012 |
| Pakistan | Technical review completed<br>GMP inspection finished smoothly in September 2018 |
| Thailand | GMP approved<br>Sample testing completed in May 2018<br>Under technical evaluation |
| India | Under technical evaluation |
| USA | Pre-IND dossier finished;<br>IND dossier under preparation, to be submitted in 2018 |
| Indonesia | Dossier under preparation, to be submitted in 2018 |
| Bangladesh | Dossier under preparation, to be submitted in 2018 |
| WHO PQ | Dossier under preparation, to be submitted in 2019 |

# 6 Major Phase IV Clinical Studies of Hecolin®

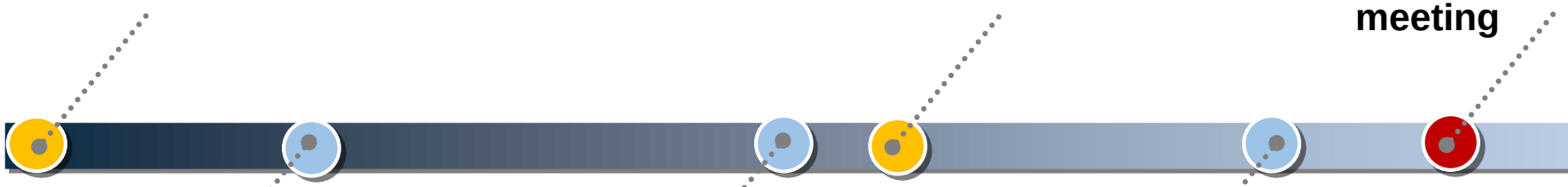
| Subject | Conclusion |
|---|---|
| To evaluate the safety and immunogenicity in elderly | ▪ The vaccine is safe and immunogenic in test group (age >65yr) to control group (age 18-65)<br>▪ The vaccine is well-tolerated :<br>▪ no vaccine associated SAE was observed;<br>▪ The rate of solicited AE in test group (age >65yr) has no statistical significant difference with control group (age 18-65);<br>▪ The rate of unsolicited AE in test group (age >65yr) has no statistical significant difference with control group (age 18-65). |
| To co-administrate Hecolin® with Hepatitis B vaccine. | ▪ Co-administration was immunogenic and generally well tolerated.<br>▪ The study results support the co-administration of Hepatitis E vaccine with Hepatitis B vaccine in healthy adults aged above 18 years old |
| To evaluate the immunogenicity and safety in the chronic Hepatitis B patients | ▪ The hepatitis E vaccine is well tolerated and immunogenic in the CHB patients aged 30 and older. |
| To evaluate the immunogenicity and safety with accelerated vaccination schedule | ▪ An accelerated schedule is safe and provides protective antibody in a shorter time compared to the routine schedule.<br>▪ The accelerated schedule should be recommended to adults who are hurried travelers to a Hepatitis E endemic area or during a Hepatitis E outbreak setting. |

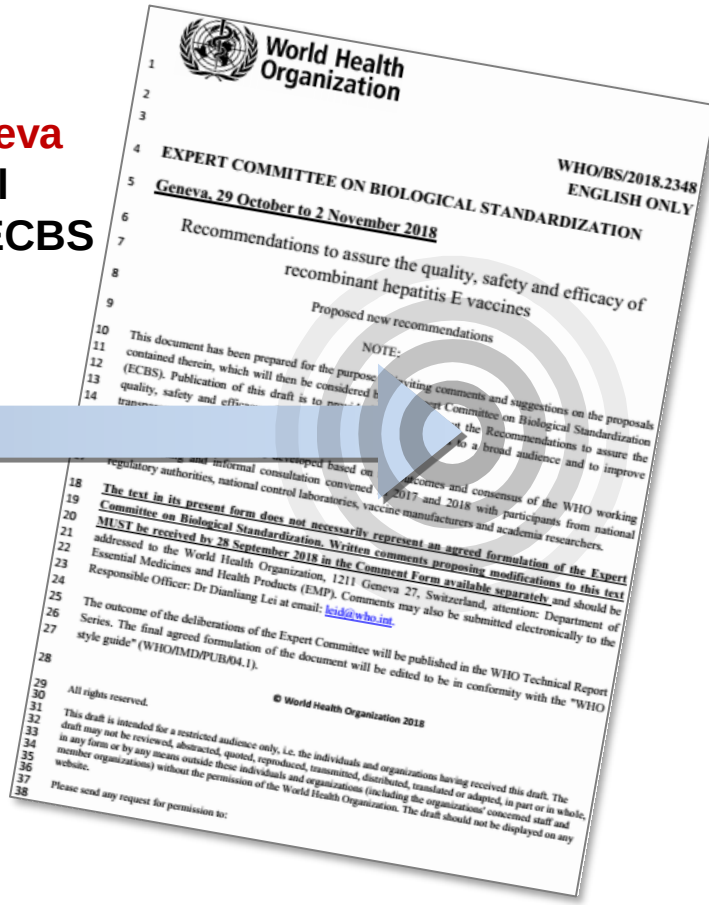
# 7 WHO Recommendation (TRS) and Standard

**May 2017, Geneva**
**First working group meeting**

**April 2018, Beijing, China**
**Informal consultation**

**Oct. 2018, Geneva**
**Submit for final adoption in ECBS meeting**




World Health Organization

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

WHO/BS/2018.2348
ENGLISH ONLY

Geneva, 29 October to 2 November 2018

Recommendations to assure the quality, safety and efficacy of recombinant hepatitis E vaccines

Proposed new recommendations

NOTE:

The text in its present form does not necessarily represent an agreed formulation of the Expert Committee on Biological Standardization. Written comments proposing modifications to this text MUST be received by 28 September 2018 in the Comment Form available separately and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention: Department of Essential Medicines and Health Products (EMP). Comments may also be submitted electronically to the Responsible Officer: Dr Dianliang Lei at email: leid@who.int.

The outcome of the deliberations of the Expert Committee will be published in the WHO Technical Report Series. The final agreed formulation of the document will be edited to be in conformity with the "WHO style guide" (WHO/IMD/PUB/04.1).



**May~Nov. 2017**
**First version of TRS**
**Nov. 2017**
**Posted on WHO biological website for public comment**

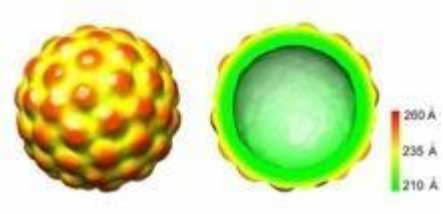
**Jan.~Feb. 2018**
**Comments provided by XMU and INNOVAX**

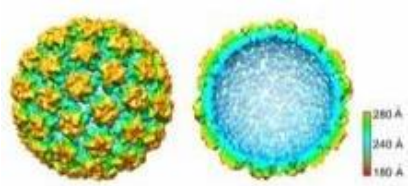
**Jun. 2018**
**The second draft of HEV TRS posted on WHO website**

# 2 Cecolin® -- World's Brand-New HPV 16&18 Vaccine: VLP Produced in *E. coli* by a Member of DCVMN

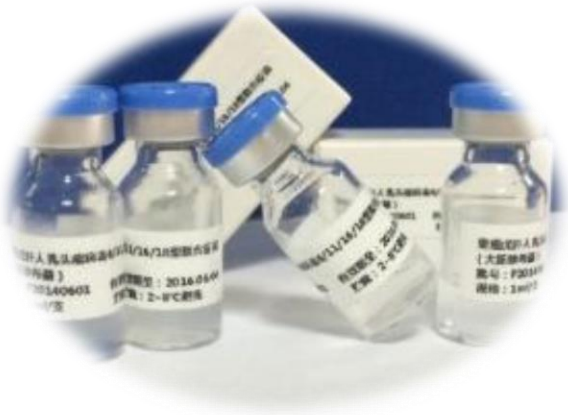
# HPV 16 &18 Bivalent Vaccine Development

## First HPV vaccine based on *E. coli* expression system




| 2002 | 2007 | Mar. 2010 | Aug. 2011 | Jan.2012 | Dec. 2012 | Dec. 2015 | Nov. 2017 | Sept. 2018 | ~Jan. 2019 | ~May 2019 | 2020/2021 ? |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Project initiated | IND submitted in China | Clinical trial approved | Phase I finished | Phase II finished | Phase III initiated | Bridging study for young girl, as well as for 2-dose regimen | BLA submitted in China | Clinical study inspection finished | Launch in China | PQ submission | PQ approval? |



# Target Product Profile of Cecolin®

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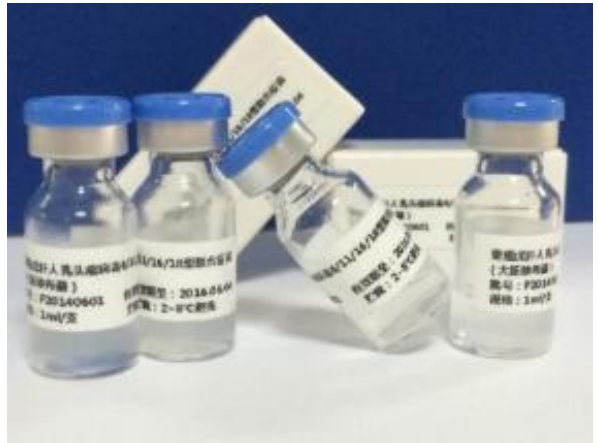
| | |
|---|---|
| **Serotype** | • 16 &18 bivalent vaccine<br>• 40μg HPV16 VLPs & 20μg HPV18 VLPs |
| **Expression system** | • *Escherichia coli* expressed L1-based vaccine |
| **Target population** | • women ages 9 - 45yr |
| **Presentation** | • 0.5 ml of suspension per dose in 2ml vial<br>• 0.5ml of suspension per dose in pre-filled syringe<br>• 1ml of suspension, 2 doses in 2ml vial (Gavi market) |
| **Shelf-life** | • 2 - 8℃ 48 months in application, with 60 months data |
| **Schedule** | • 0, 1, 6 m (0, 6m for 9 -14 yrs) |
| **Formulation** | • With Alum adjuvant. No preservative. |



# State of the Art Facility

INNOVAX 万泰疫苗

## Fermentation

Sterile Isolator
Wenzhou Weike, China

50-500L Fermentation Sysytem
Shanghai Sensong, China

## Primary Purification

Centrifuge
GEA, Germany

Homogenizer
ATS, Germany

Ultra-filtration system
PALL, US

## Purification & VLP assembly

Ultra-filtration system
PALL, US

Chromatography
GE, US

## Aseptic Filling

Vial Filling line
Marchesini, Italy

Syringe Filling line
Bosch, Germany

# Cecolin® - A New, Safe and Cost Effective HPV 16&18 Vaccine

INNOVAX 万泰疫苗

The randomized controlled phase III clinical trial (7,372 participants) showed **Innovax HPV bivalent has compatible efficacy profile with published results by other manufacturers.**

| Endpoint | | Vaccine group | | Control group | | Efficacy% |
|---|---|---|---|---|---|---|
| | | N | No. of Case | N | No. of Case | （95%CI） |
| **HPV 16 and/or 18 related CIN2+/VIN2+/VaIN2+** | | | | | | |
| INNOVAX | **INNOVAX bivalent vaccine** | **3306** | **0** | **3296** | **10** | **100(55.6 ,100)** |
| **Manufacturer 1** | **Bivalent vaccine** | **2524** | **1** | **2535** | **8** | **87.3(5.3 ,99.7)** |
| **Manufacturer 2** | **Quadirvalent vaccine** | **1265** | **0** | **1237** | **7** | **100(32.3 ,100)** |
| **HPV 16 and/or 18 related 6-month persistent infection** | | | | | | |
| INNOVAX | **INNOVAX bivalent vaccine** | **3240** | **1** | **3246** | **45** | **97.8(87.1 ,99.9)** |
| **Manufacturer 1** | **Bivalent vaccine** | **2480** | **2** | **2488** | **54** | **96.3(85.9 ,99.6)** |
| **Manufacturer 2** | **Quadirvalent vaccine** | **1275** | **7** | **1245** | **28** | **75.9(43.5 ,91.1)** |

**References:**
1. Zhu FC, Hu SY, Hong Y, et al. Cancer Med 2017; 6:12-25;
2. Gardasil® package insert in China;
3. Cervarix® package insert in China.

# Cecolin® - Non-inferiority of immunogenicity in Adolescent Girls with 2-dose Schedule

| Study | Design | Objective | Dosage | No. of participants | Conclusion/Status |
|---|---|---|---|---|---|
| Immunobridging Study | Randomized, controlled | • Safety and immunogenicity in female ages 9 to 17 in 3-dose schedule<br>• Safety and immunogenicity in adolescent girls age 9 to 14 in 2-dose schedule | 60μg (HPV16:HPV18=2:1 ) at 0,6 month or 0,1,6 month | 975 women ages 9-26 yr | 1. Non-inferiority of immunogenicity has been demonstrated in 2-dose group (9-14y) and 3-dose younger age group (9-17y) compared with 3-dose adult group (18-26y).<br>2. The candidate vaccine is well tolerated. |

# Cecolin® - AE in Clinical Studies (in China) with Compatible Results

| Vaccine | Most common ≥10% | | Common 1-10% | | Rare 0.1-1% | |
|---|---|---|---|---|---|---|
| | Local | Systemic | Local | Systemic | Local | Systemic |
| INNOVAX bivalent vaccine | Pain | Fever | Hard knot, red, Swelling and itching | Fatigue, headache, cough, myalgia, diarrhea, nausea, hypersensitivity | Rash | Vomit |
| Manufacturer 1 | Pain, erythema, swelling | Fever, fatigue, Myalgia, headache | Hard knot, itching | Diarrhea, hypersensitivity, cough, nausea, vomit | Rash | |
| Manufacturer 2 | Pain, redness, swelling | Fatigue, myalgia, headache, fever (≥37°C) | | Joint pain, gastrointestinal symptoms (including nausea, vomit, diarrhea, and abdominal pain), urticaria and rashes | | |

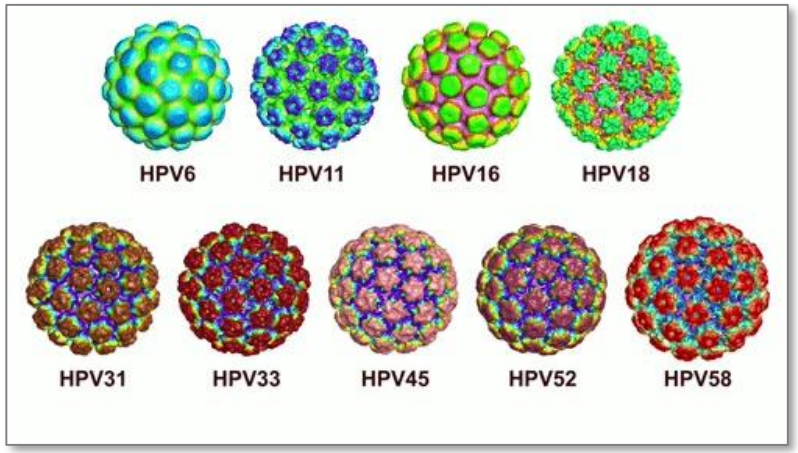
None of Serious Adverse Events (SAE) were related to vaccination

None adverse influence occured in pregnant women and newborns

# Our HPV Vaccine Products for Global Market

Preclinical | Clinical Study

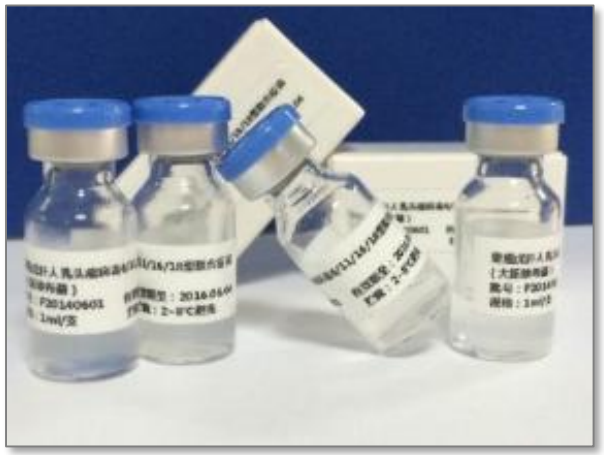
IND → NDA → Approved




**Cecolin™ 9**
**HPV 9-valent vaccine**

Clinical trial approved on Nov. 2017

- Draft protocol of clinical study phase I & II has been completed;
- Phase I to be initiated in Feb.~Mar. 2019



**Cecolin®**
**HPV 16/18 bivalent vaccine**

BLA submitted in Nov. 2017

Clinical Inspection in Sept. 2018

# Our Commitment: Providing Safe, Effective and Cost-Conscious Vaccines Globally

INNOVAX 万泰疫苗

## Two vaccines available for the global market

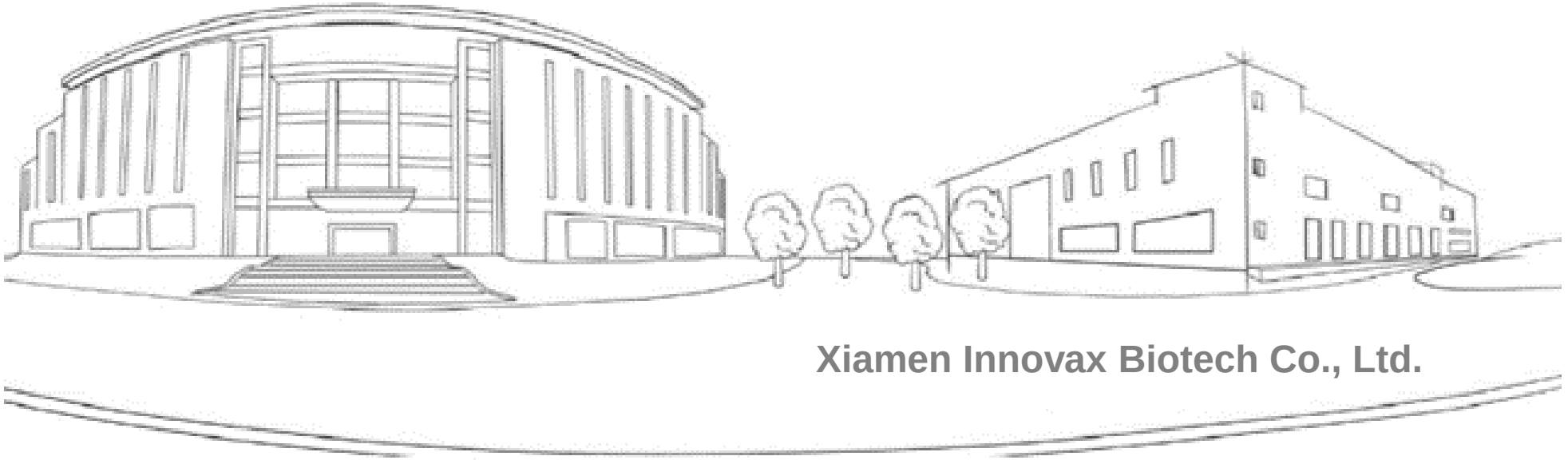
**Develop HPV 9-valent vaccine**

- **Single-dose study for matching different market need**

**To develop more high quality innovative vaccines with cost-effective *E.coli* expression system**

INNOVAX
万泰疫苗

# Thank you!



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