Better vaccines and healthier life: PATH's innovative approach to developing rotavirus vaccines in China

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Rotavirus vaccine development project

Goal: To accelerate the development and introduction of new safe, affordable, and effective rotavirus vaccines into the developing world through technical and financial support to emerging-country manufacturers.

Outline

- PATH/Chinese National Biotec Group (CNBG) collaboration
- GMP assessment of the six CNBG institutes
- Case study: Remediation plan at Wuhan Institute of Biological Products (WIBP)
- Quality Management Systems
- GMP-grade pilot facilities
- Industrial production facilities
- Technology watch
- Conclusion



PATH/CNBG Collaboration

Collaboration with different institutes based on projects

- All projects managed under contracts
- Supported by Bill & Melinda Gates Foundation (BMGF)
 - Chengdu: Japanese encephalitis vaccine
 - WIBP: BRV rotavirus vaccine
 - Beijing Tiantan Bio: Oral polio vaccine
 - Langzhou, Shanghai, Changchung: GMP assessment only
 - All six institutes: Assessment of Chinese Vaccine Manufacturers project

Meetings

- Overall Steering Committee: Annual meeting with PATH, CNBG, Sinopharm, BMGF
- Technical review meetings/workshops by project (2-3 times a year according to progress)
- Overall supervision by PATH Beijing leader and CNBG

Periodic reports to BMGF



GMP assessment in all six CNBG institutes

Objective

• Identify gaps and develop a remediation plan in all the CNBG institutes in order to prepare vaccines that meet Chinese FDA GMP status and WHO prequalification

Methods

- Gathered the information to assess the readiness of the six Chinese CNBG institutes on GMP compliance with international standards
- Identified and classified gaps into "critical," "major," and "other"
- Developed a remediation plan for each of the CNBG institutes based on the criticalness of the gaps observed:
 - Quality management
 - Quality assurance
 - Validation and qualification
 - Change control

Case study: Work plan for Wuhan Institute of Biological Products (WIBP)

Objectives

- Establish Quality Management Systems (QMS).
- Rotavirus vaccine development project: Design, build, and validate new industrial facilities for the manufacturing of oral rotavirus vaccine with the ultimate goal of WHO prequalification

Major milestones

- Provide technical advice on the Master Validation Plan
 - Design qualification: conceptual design, basic design
 - Installation Qualification (IQ), Operational Qualification (OQ), Performance Qualification (PQ)
 - Mock inspection prior to manufacturing the consistency lots at full scale



Quality Management Systems QMS (1)

Goal

- Establish QMS at WIBP:
 - Steering Committee established in October 2012 composed of leaders from CNBG/WIBP and one PATH representative
 - QMS working groups in place including employees from all departments

Preliminary work

- PATH provided international regulatory documentation (December 2012)
- Gap analysis of existing documentation at WIBP in comparison with international standards (in progress)

Quality Management Systems QMS (2)

Major steps	Status required
Research	GLP
Development	GLP
Preparation of clinical material for Phase 1 and 2 at pilot facilities	GMP
Scale up> Process validation	GMP
Preparation of clinical material for Phase 3 and commercial lots in new industrial facilities	GMP

GMP pilot facilities (1)

History

- Created in 2006, with validation completed in 2008, GMP pilot facilities have been dedicated to the manufacturing (production and QC) of material for preclinical and Phase 1 and 2 clinical studies
- Pilot facilities were inspected in October 2012 and were found acceptable for the manufacturing of Phase 1 and 2 clinical material, although there are some areas for improvement

GMP pilot facilities (2)

Project framework:

- Design, build, and validate pilot facilities (2008)
- Develop production processes at pilot scale (in progress)
- Develop and validate analytical methods (completed 2012)
- Prepare master and working cell banks and master and working virus seeds banks (completed 2011)
- Prepare drug substance and final product at pilot scale under GMP conditions (in progress)
- Mock inspection prior to the manufacturing of clinical lots (October 2012); no critical issues identified

Preparation of material for preclinical and clinical studies

Further milestones:

- Consolidation of quality systems as recommended in the mock inspection
- Batches to be performed in GMP pilot facilities
- Animal source raw material imported from BSE-free countries (New Zealand) completed
- Vendor audit for critical material: culture media, trypsin, calf serum in progress
- Process validated at pilot scale in progress
- Analytical methods fully validated completed
- Final product: Full liquid formulation selected and validated based on stability data – in progress

GMP industrial facilities (1)

Goal

• Design, build, and validate pilot facilities for the manufacturing of Phase 3 clinical material and for commercial lots

Major Milestones

- Design of facilities: Technical advice for conceptual design meeting both Chinese requirements and WHO recommendations oriented towards prequalification
- Assessment and technical advice on further steps
- Technical advice on master validation plan
- Technical advice



GMP industrial facilities (2)

Milestones

- Design, build, and validate industrial facilities for the production of clinical material for Phase 3 and commercial lots
- Develop a project management plan (example below)

Activity	/	months	- 1	2	36	-	- 20	6	.	8	-90	10	11	12	105	144	185	165	177	186	150	320	21	22	3256
Conceptual de	sign																								
Basic design																									
Basic design n	eview																								
Tendering																									
Detailed design	1																								
Purchase equip	pment		Purchase, shipping, FAI and SAI																						
Exterior constr	uction																								
Interior works																									
Installation ma	chines																								
Qualification e	quipment																								
Qualification u	tilities and	d systems																							
Process validat	tion																								

GMP industrial facilities (3)

Milestones in progress involving PATH experts

- Develop a state-of-the-art conceptual design (completed)
- Review basic design of new facilities and provide recommendations



Global overview



Detailed overview

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GMP industrial facilities (4)

Further steps

- Provide technical advice for the Master Validation Plan
- Provide technical advice during scale up and Process Validation (PV)
- Conduct mock inspection prior to the "Go/no-go decision" for the manufacturing of the consistency lots for the clinical Phase 3.
- Manufacture consistency lots in new industrial facilities
- In-house control and release
- Laboratory control and release by National Institute for food and drug (NIFDC)
- Submission to Chinese National Authorities (CFDA)
- Submission of dossier to WHO for prequalification



Technology watch

Maintain technology watch on innovative technologies, including formulation, analytical methods, delivery devices, cold chain technologies, vaccine vial monitor, controlled temperature chain, etc.















Conclusion

- The rotavirus vaccine development team, which is currently implementing several grants from BMGF, is part of PATH's Vaccine Development Global Program (VAC). VAC has extensive experience and close working partnerships with several CNBG institutes (Chengdu, Wuhan, Tiantan Bio) and with CNBG itself through the PATH-CNBG steering committee.
- The case study developed with WIBP is a demonstrative example of how PATH is involved in a strategic and innovative effort to advance the development and introduction of safe, efficacious, and affordable new vaccines to the developing world.
- Better vaccines and healthier life: a leitmotiv at PATH!



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