Overview of BCHT and Update to LAIV Project

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Changchun BCHT
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Established in March 2004 at Changchun High-tech Zone, Jilin Province, Northeast China

- Research, development, production and marketing of vaccines, biologics and peptide & chemical drugs
- More than 600 scientists, technicians and supporting staffs
- Three manufacturing plants and advanced R&D facilities
- Two vaccines on the market
- One peptide drug in clinical trial and with strong product pipeline
- Full domestic marketing organization and international cooperation
- Foundation of BCHT
- Built up pilot plants for vaccine development
- Extended research in biologics and chemical drug

2005
- Started to manufacture Varicella vaccine
- Start clinical trial I for AIDS vaccine

2006
- Started clinical trial II for AIDS Vaccine
- Started manufacture Rabies vaccine

2007
- Established subsidiary Beyel Pharmaceuticals for peptide drugs

2008
- LAIV with WHO
- Varicella Vaccine, Live on market
- Approval for clinical trial of a peptide drug

2010
- Started manufacture of Rabies vaccine

2012
Joint Research Programs with University & Institutes

State Engineering Laboratory for AIDS Vaccine
BCHT and Jilin University
Product Quality Assurance and Control

Audit all suppliers and verified and certificated by QC all materials before use.

Bacterium and virus seeds are strictly carried out by three tiers seeds batch administration and the same as for cell bank.

Monitor environment and water for production at regular intervals.

Verify the equipments, factory facilities and production process at regular intervals.

Manufacture products strictly under GMP compliance and control the whole production process on three levels.

Equip the most advanced analytical, test product quality by verified methods to guarantee accurate data from the test, follow SFDA regular for batch certificate.

Follow strictly state’s regular to provide all the detailed data in the cold chain in transport from factory to the delivery terminal, ensuring quality control of the product in logistic.

Establish the completed and efficient system for warning and handling adverse reaction events. An emergency committee headed by President and consist of assigned staffs has been set.
Approvals of Clinical Trail and Production

Certificate of state and province projects

Patents
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<td>Rabies vaccine, freeze-dried</td>
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<td>HAV inactivated vaccine (MRC-5)</td>
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<td>Zoster virus attenuated vaccine</td>
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<td>Varicella vaccine (two dose)</td>
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<td>Rotavirus vaccine</td>
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<td>Influenza vaccine (MDCK)</td>
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<td>Influenza vaccine (attenuated) (cooperated with WHO)</td>
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<td>New rabies vaccine</td>
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<td>Cancer therapeutic vaccine</td>
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<td>New tuberculosis vaccine</td>
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<td>Rabies scFv antibody</td>
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**Legend:**
- Pre-clinical
- Apply for production
- Approve to produce
- Market
Why Influenza Vaccine LAIV

- Social benefits
  In China, only a very small portion of population vaccinated (<5%)
- Market potentiality
- LAIV features with lower production cost and shorter time for mass production in pandemic outbreak
- Unique inoculation via Intranasal procedure
- BCHT is in a fast-growing phase
Accomplished Tasks

- Tech-transfer from IEM, Russia
- Master and Working Seed virus built up
- Production process optimized
- Analytical methods established
- IND samples prepared
- IND application documents in finalizing
- Facility design (CD and BoD completed and DD under review)
- Facility construction
Production Process

H1N1 / H3N2 / B strain

- Innoculation
- Harvest
- AF
- UF/DF
- Monovalent
- Pooling
- Trivalent
- Lyophilization
- Final product

Key development:

- Egg disinfection
- Sterile operation
- Phenotypical study
- ID test
- Infection titer testing
- Exogenous factor detection
- Liquid formulation development
## Infection Titer Testing of Monovalent and Trivalent

<table>
<thead>
<tr>
<th>Samples</th>
<th>Antiserum</th>
<th>Infection titer LogEID$_{50}$/0.5ml</th>
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<tr>
<td>H1N1</td>
<td>-</td>
<td>7.1</td>
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<tr>
<td>H1N1</td>
<td>Anti H3+B</td>
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<tr>
<td>Trivalent</td>
<td>Anti H3+B</td>
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<tr>
<td>H3N2</td>
<td>-</td>
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<td>H3N2</td>
<td>Anti H1+B</td>
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<tr>
<td>Trivalent</td>
<td>Anti H1+B</td>
<td>6.3</td>
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<td>B</td>
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<tr>
<td>B</td>
<td>Anti H1+H3</td>
<td>7</td>
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<tr>
<td>Trivalent</td>
<td>Anti H1+H3</td>
<td>7</td>
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</tbody>
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Short Term and Long Term Development Plan

- IND filing (April, 2013)
- Site inspection by local SFDA (June, 2013)
- Production process optimization (end 2013)
- Finish pre-clinical (Ferret) studies (mid 2013)
- Complete facility construction (end 2013)
- Purchase and install of production equipments (end 2013)
- Market the vaccine by the end of 2016
Lessons and Challenges

- Import of strains
- Titer of virus test
- Egg supply
- Stabilizer and freeze drying cycle
- Spray device
- Preclinical study (efficacy and toxicity studies)
- Clinical trial (HAI, MN, IgG, IgA, CD4+ and CD8+)
- SFDA approval with non-correlated data of immunological markers for efficacy and limited subjects in the trial
- GMP compliance by SFDA and pre-qualification by WHO
Thank you!
谢谢！

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