The Role of NIFDC in the Regulation of Biologics in China

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National Institutes for Food and Drug Control (NIFDC)
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National Institutes for Food and Drug Control (NIFDC)

- Founded in 1950
- National Control Laboratory (NCL)
- Quality control of Food, Functional Food, Pharmaceutical Products, Cosmetics and Medical Devices
- Pharmaceutical Products including Biological Products, Traditional Chinese Medicine, Chemical Drugs, and others
Accreditation

- Chinese Metrology Organization (mandatory)
- Chinese National Accreditation Board for Laboratories (CNAL, volunteer)
- GLP approved by CFDA
- WHO Collaboration Center for Pharmaceutical Products (since 1980)
- WHO Collaboration Center for Biologicals (since 2013)
Institute for Biological Products Control (IBPC)

- Division of General Affairs
- Division of Arboviral Vaccines
- Division of Hepatitis Virus Vaccines
- Division of Respiratory Virus Vaccines
- Division of Enterovirus Vaccines
- Division of HIV/AIDS and sex-transmitted virus vaccines
- Center of Cell Collection and Research
- Center of Medical Bacterial Collection and Research
- Division of Respiratory Bacterial Vaccines
- Division of Enteric Bacterial Vaccines
- Division of Tuberculosis Vaccines
- Division of DTP Vaccine and Antitoxin
- Division of Recombinant biological Products
- Division of Monoclonal Antibodies
- Division of Blood Products

Staff: 177

1 office, 13 technical divisions, 2 research centers
- **10,239** strains, more than **270,000** copies of reference bacteria (viruses)

- Provides **>12,000** copies of strains for **>900** organizations in China in 2016

- Genome database for quality control of vaccine seed strains

The National Genome and Protein Databases of Vaccines Strains
Biological Products

Be responsible for the quality control of Biological Products

- Vaccines
- Blood products
- Biotherapeutics
  - Antibodies
  - Cytokines
  - Hormones
  - Enzymes, etc
- IVD for blood screening etc.
- Cell Therapy Products
Main responsibility of IBPC

IBPC plays a major role in assuring the quality of biological products through:

- Quality Control
  - Lot release
  - Post-market surveillance and incident investigation
  - National standards/references
  - Research Work
  - Registration test
  - International cooperation
Research Works

- Establishing new QC methods based on our research
- Transferring new technologies into QC methods
- Validating and verifying QC methods
- Establishing specifications for different products
- Generating reference materials and standards
- Establishing methods to identify counterfeit biological products
Scientific research is the foundation of control activity in NIFDC. NIFDC undertakes many cross-cutting research projects besides control testing, obtaining massive fundings from multiple sources.

- National Science and Technology Major Projects
- National High-tech R&D Program (863 Program)
- Key Technologies R&D Program
- NSFC (Natural Science Foundation of China)
- CFDA
- Local foundation of Beijing
- International organizations
- Other organizations
Research Works

Funds acquired by NIFDC during 2011-2016
million Yuan (RMB)

Note: 100 RMB is about 15~17 USD in 2011~2016
Research Works on Vaccines

- **New methods to analyze chemical property**
  eg. NMR, MS, next generation sequencing, qPCR

- **New methods to detect activity of biological products**
  eg. reporter-gene assay, pseudovirus model

- **New methods to detect efficacy of biological products**
  eg. Constructing transgenic animal, animal imaging model

- **Improving the quality specifications**

- **Generating reference materials for physical-chemical and efficacy testing**

- **Understanding the mechanism of immunity and infection**
### Research Works on mAb

#### High order structure
- Secondary & tertiary structure
- Correct disulfide bond paring
- Free thio group
- Thermodynamics stability

#### Charge heterogeneity
- Acidic forms: deamidation, sialylation, and etc..
- Basic forms: Oxidation, incomplete C-terminal lysine truncation

#### Sequence confirmation
- Amino acid sequence

#### Stability
- Shelf-life time
- Degradation prosperity

#### Impurity content
- Product related impurity
- Host cell protein (HCP)
- Protein A leakage
- Cell culture ingredients
- DNA
- Endotoxin
- Particulate matters

#### N-glycan profile
- Galactosylation
- Sialylation
- Manosylation
- Fucosylation

#### Molecular size
- Aggregates
- Fragments
- HMW & LMW

#### Bioactivity
- Target
- CDC
- ADCC
- Apoptosis...

#### Physicochemical activity
- Total concentration
- Concentration with bioactivity
- Binding activity
- FcR binding activity

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*Aspirin vs Antibody*

*Developing the Nation's Biosimilars Program*

Steven Kozlowski, M.D., Janet Woodcock, M.D., Karen Midthun, M.D., and Rachel Behrman Sherman, M.D., M.P.H.

Equipment of quality study of mAbs

- LC-MS, CE-MS, BIACORE, Fortebio, TOP Count, Envision, Flow CAM, Freeze drying microscope, DSC, Solo VP, iCE3/iCE280, UPLC, MSD
Registration Tests

- When applying for: clinical trial and production
- Test products based methods and specification manufactures provided
- Give comments about methods and specifications based reviewing and testing
- Send Testing reports and comments to CDE, provincial FDA, and applicants respectively
Post-market surveillance

- CFDA sets up plans for post-market surveillance based on risk assessment of lot release, AEFI, product properties and production process

- Samples were randomly drawn from manufacturers, distributors and users nationwide

- The samples were tested in our labs based on official method and exploratory research method

- Assessment reports
  - Unqualified products reported to CFDA and provincial FDA for further investigation
  - Provide suggestion on improving drug specification
  - Provide technical advice for drug regulation
<table>
<thead>
<tr>
<th>Year</th>
<th>Planned products for post-market surveillance</th>
<th>number of manufacturers</th>
<th>Result(qualified/total lots)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>1. HIV antibody diagnostic reagents</td>
<td>18</td>
<td>53/53</td>
</tr>
<tr>
<td></td>
<td>2. rhEPO</td>
<td>9</td>
<td>47/47</td>
</tr>
<tr>
<td></td>
<td>3. TB-PPD and BCG-PPD</td>
<td>2</td>
<td>13/13</td>
</tr>
<tr>
<td></td>
<td>4. Varicella vaccine</td>
<td>4</td>
<td>26/26</td>
</tr>
<tr>
<td>2015</td>
<td>1. Interferon α1b</td>
<td>2</td>
<td>42/42</td>
</tr>
<tr>
<td></td>
<td>2. Inactivated hepatitis A vaccine</td>
<td>2</td>
<td>15/15</td>
</tr>
<tr>
<td></td>
<td>3. Group A and C meningococcal polysaccharide vaccine</td>
<td>3</td>
<td>30/30</td>
</tr>
<tr>
<td></td>
<td>4. BCG Vaccine</td>
<td>1</td>
<td>26/26</td>
</tr>
<tr>
<td>2016</td>
<td>1. HIV antibody diagnostic reagents</td>
<td>9</td>
<td>55/55</td>
</tr>
<tr>
<td></td>
<td>2. rhEGF eye drops</td>
<td>2</td>
<td>55/55</td>
</tr>
<tr>
<td></td>
<td>3. BCG Vaccine</td>
<td>1</td>
<td>16/16</td>
</tr>
<tr>
<td></td>
<td>4. Recombinant Hepatitis B Vaccine</td>
<td>5</td>
<td>44/44</td>
</tr>
</tbody>
</table>
NIFDC is responsible for developing and distributing national biological standards

- About 190 national biological standards
  - 1/3 traced to WHO IS
  - 80 belong to Chinese Pharmacopoeia Standards
- EV71 NTAb WHO IS (adopted by ECBS in October 2015)
  - First collaborative achievement of IS by NIFDC and NIBSC
  - More collaborative projects of IS are undergoing with NIBSC
Since 2001, lot release for the 5 EPI vaccines and Human Serum Albumin has being implemented.

Since 2006, all vaccines licensed in China have been subjected to lot release system.

So far, 3 types of biological products are subjected to lot release, including Vaccines, Blood products, IVD for blood screening.

Lot release based on three modes:

- Reviewing summary lot protocol
- Reviewing summary lot protocol and testing partial QC items
- Reviewing summary lot protocol and testing whole QC items
8 Organizations Authorized by CFDA

NIFDC as national control lab

- Beijing
- Hubei
- Jilin
- Sichuan
- Gansu
- Guangdong
- Shanghai

8 Organizations: NIFDC + 7 authorized provincial institutes

- NIFDC, which is responsible for all lot released products, provides technical guidance to other lot release institutes

- The seven provincial control labs: blood products, and the specified testing items of vaccines

- Shanghai, as a Provincial control lab: blood products, flu vaccines and the specified testing items of other vaccines
证书名称：生物制品批签发合格证

Certificate for the Release of Biological Products

审批编号：SBN200702813

Lot No.：2007080666 (1 3 4)

规格：0.5ml（复溶后）/人份/瓶

流通形式：注射剂

有效期至：2008年5月12日

批量/进口量：7694瓶

数量：Quantity

经审查，上述制品符合生物制品批签发的有关規定，判定合格。

The product mentioned above complies with the provisions for the release of Biological products and has been approved for release.

本证明书系基于对上述制品的审查及检验结果的判定审查和实验室检测（检验试剂、生物制品效价、残留量、病毒检查、免疫性检查、毒性检测，结果判定）而签发。

This certificate is based on examination of summary manufacturing protocol and laboratory test (identity, content of residual host serum albumin, sterility, abnormal toxicity, virus titration, non-relevance in mice).

签发日期：2008年2月20日

2008 FEBRUARY 2008

证书名称：生物制品批签发不合格通知书

Notice of Not Release of Biological Products

审批编号：SBN200704771

Lot No.：200708003

规格：0.25ml/支（预充式注射器）

流通形式：注射剂

有效期至：2008年6月14日

批量/进口量：15526支

数量：Quantity

经审查，上述制品不符合生物制品批签发的有关規定，判定不合格。

The product mentioned above does not comply with the concerned provisions for the release of biological products and is not approved for release.

不符合项目为：血凝素含量

The item(s) out of specification is (are)：Hemagglutinin content

签发日期：2007年8月8日

8 AUGUST 2007
vaccines released in China 2011-2015

Million doses
0 300 600 900

Lots
0 1000 2000 3000 4000 5000 6000

2011 2012 2013 2014 2015

4788 4898 740 5154 667 4125

775 762 4229 564

National Institutes for Food and Drug Control
blood products released in China 2011-2015

Lots

2011 2012 2013 2014 2015

Million doses

2011 2012 2013 2014 2015

National Institutes for Food and Drug Control
WHO Collaborating Centers for Standardization of Biological Products

- NIBSC (biologicals)
- NIID (vaccines)
- TGA (vaccines)
- CBER (biologicals)
- CVE (blood products & IVD)
- KFDA (biologicals)
- NIFDC (biologicals, Jan. 2013)
- PEI (vaccines, Aug. 2013)

Collaboration with other institutions

- NIBSC, UK
- CVE, BGTD, Health Canada
- NIFDC
- PEI, German
- Institute of Biological Products, Thailand
- NIID, Japan

Academic Exchange

MOU

National Institutes for Food and Drug Control
Example of cooperation between NIFDC&NIBSC 2005 ~ 2016

- Had **13** High Level delegation exchange visits
- Held **14** training courses at NIFDC
- Had **10** scholars to study at NIBSC
- Initiated many joint scientific research projects
- Jointly developed International and National Standards, including EV71 IS
International Collaboration

- MOU in place with more than 10 international institutes and universities
- Every year, more than 80 international experts visit NIFDC making presentations and attending meetings
- Every year, NIFDC system sent more than 50 scientists outside of China and organized more than 30 workshops and seminars
Thanks you for your attention