Agenda 3.1.3

Follow up Actions of 30th SEA-ACHR:

Promotion of Research and Development on Drugs and Vaccines

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Translational Health Science and Technology Institute
National Institute of Immunology
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Outline of Talk

- Existing facilities & strengths
- Challenges
- The way forward
R&D Facilities for Drugs & Vaccines in SEAR

Thailand

Indonesia

Korea

Bangladesh

India
Drugs & Vaccines : R&D Facilities

- Thailand
  - US Military HIV Research Program
  - Vaccine Trial Center
  - Mahidol University

- Indonesia
  - Bio Farma

- South Korea
  - The International Vaccine Institute
  - LG Life Sciences Ltd.
  - Crucell / Berna Biotech Korea Corp.

- India
  - Various organizations
**Major R&D Facilities : India**

- **Public Sector**
  - Indian Immunologicals Ltd.
  - Bharat Immunologicals & Biologicals Corp. Ltd.
  - Central Drug Research Institute
  - Haffkine Bio-Pharmaceutical Corp. Ltd.

- **Private Sector**
  - Serum Institute of India Ltd.
  - Panacea Biotech Ltd.
  - Bharat Biotech International Ltd.
  - Biological E. Ltd.
  - Shantha Biotechnics Ltd.
  - Zydus Cadila
  - Cipla
  - Ranbaxy
Drug Development: Indian Efforts

- Anti-tuberculosis drugs
- Anti-malarial drugs
- Anti-diabetic agents
- Anti-cancer drugs
- Anti-Dyslipidemic agents
- Cholesterol-lowering drugs
- Oseltamivir
- Anti-HIV drugs
<table>
<thead>
<tr>
<th>Organizations</th>
<th>IND molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDRI, Lucknow</td>
<td>Anti-hyperglycaemic agent</td>
</tr>
<tr>
<td>DRDO, New Delhi</td>
<td>Adjuvant in the radiotherapy of cerebral glioma patients</td>
</tr>
<tr>
<td>Ranbaxy, New Delhi</td>
<td>For treatment of overactive bladder and urinary incontinence</td>
</tr>
<tr>
<td>Ranbaxy, New Delhi</td>
<td>Anti-microbial agent</td>
</tr>
<tr>
<td>Ranbaxy, New Delhi</td>
<td>For treatment of benign prostatic hyperplasia</td>
</tr>
<tr>
<td>Wockhardt Ltd., Mumbai</td>
<td>Antibacterial agent</td>
</tr>
<tr>
<td>Dr.Reddy’s Lab., Hyderabad</td>
<td>Anticancer agent</td>
</tr>
<tr>
<td>Lupin Ltd, Mumbai</td>
<td>Nasal formulation for migraine</td>
</tr>
<tr>
<td>Lupin Ltd., Mumbai</td>
<td>Herbal preparation for psoriasis</td>
</tr>
<tr>
<td>Lupin Ltd., Mumbai</td>
<td>Anti-tuberculosis agent</td>
</tr>
<tr>
<td>Sun Pharma, Baroda</td>
<td>Anti-histaminic agent</td>
</tr>
<tr>
<td>Malladi, Chennai</td>
<td>Thrombolytic agent</td>
</tr>
<tr>
<td>Dr.Reddy’s Lab., Hyderabad</td>
<td>Dyslipidemic agent</td>
</tr>
<tr>
<td>Zydus Cadila, Ahmedabad</td>
<td>Dyslipidemic agent</td>
</tr>
</tbody>
</table>
India: Strengths in R&D

- Drugs Testing Laboratories
- Educational & Research Institutes
- Medical Colleges & Hospitals
- Bio-Safety Level 2, 3, 4 Facilities
- Transgenic Animal Facility
- CROs
- National Ethical / Regulatory Guidelines
- Clinical Trial Centres
- Indian Pharma Industry
- National Animal Resource Facility
- Toxicology Research Centres
### Top ten pharmaceutical companies in India: revenue growth rate in 2007

<table>
<thead>
<tr>
<th>Company</th>
<th>Revenue growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranbaxy</td>
<td>INR 42 billion</td>
</tr>
<tr>
<td>Dr. Reddy’s Laboratories</td>
<td>INR 42 billion</td>
</tr>
<tr>
<td>Cipla</td>
<td>INR 38 billion</td>
</tr>
<tr>
<td>Sun Pharma Industries</td>
<td>INR 25 billion</td>
</tr>
<tr>
<td>Lupin Labs</td>
<td>INR 22 billion</td>
</tr>
<tr>
<td>Aurobindo Pharma</td>
<td>INR 21 billion</td>
</tr>
<tr>
<td>Glaxo Smith Kline Pharma</td>
<td>INR 18 billion</td>
</tr>
<tr>
<td>Cadila Health Care</td>
<td>INR 17 billion</td>
</tr>
<tr>
<td>Aventis Pharma</td>
<td>INR 10 billion</td>
</tr>
<tr>
<td>Ipca Laboratories</td>
<td>INR 10 billion</td>
</tr>
</tbody>
</table>
WHO prequalified drugs from the SEAR

- 87% of drugs manufactured in the SEAR that attain WHO prequalification are manufactured in India.

- HIV / AIDS Drugs (single & combo) : 93
- Tuberculosis Drugs (single & combo) : 17
- Anti-Malarial Drugs (single & combo) : 5
Challenges

- Slowdown in pharmaceutical innovation after 2000.
- Escalating costs and prolonged time taken to develop new drugs.
- Stringent regulatory focus on drug safety.
- A single drug development process takes over USD 1.2 billion investment.
- A single vaccine development process takes over USD 0.5 billion investment.
Drug development pathway

Phase I
20-50 healthy volunteers to gather preliminary data

Animal experiments for ADME-TOX studies, carcinogenicity, mutagenicity / teratogenicity

Phase II
150-350 subjects with disease – to determine safety and dosage recommendations

Phase III
250-4000 more varied patient groups – to determine short-term safety and efficacy

Phase IV
Post-approval studies to determine specific safety issues

Preclinical development → Phase I → Phase II → Phase III → Phase IV : Post marketing surveillance

Single drug : USD 1.2 billion investment !!!
Vaccine development pathway

Laboratory development → Technology transfer → GMP grade material → Preclinical toxicity → Phase I trial

- No Go

- Phase II trial

- No Go

- Phase III trial

- No Go

Production

USD 0.5 billion !!!

Post-marketing surveillance further adds to the cost!
CHALLENGES

Access

- Treatment costs
- Drug financing
- Public funding
- Antimicrobial resistance
- Global trade
The Way Forward
Neglected Diseases: A High Priority for the SEAR

- Drugs for Neglected Diseases Initiative (DNDi) set up in 2003 to tackle specifically the issue of neglected diseases.
- Scientific Advisory Group on Tropical Diseases was established by WHO.

- **Focus on drug development efforts for:**
  - Soil transmitted Helminthiasis
  - Leishmaniasis – Drawbacks of Miltefosine. Need for cheaper AmBisome
  - Need for more antimalarials
Promoting R&D in Drugs: Role of Collaborative Networks

- **DNDi**: Anti-leishmania combos (DNDi & ICMR collaboration)
  - Ambisome + Paramomycin
  - Ambisome + Miltefosin
  - Paramomycin + Miltefosin

- **Stop TB partnership**: Established in 2000 to realize the goal of eliminating TB – vision for a TB free world.

- **TB Alliance**: Development of new affordable TB drugs for short treatment time, activity against MDR-TB, compatibility with HIV anti-retrovirals. Mainly funded by B&M Gates Foundation, Govts of USA, UK and the Netherlands.

Complete report will be available in 2010.

Amphotericin B deoxycholate (the standard)
Application of genomics technologies to develop new antimicrobial compounds against essential proteins in bacteria.

Targeting **6 essential enzymes** involved in bacterial cell wall synthesis.

Novel way of tackling multi-drug resistant bacterial infections since it will be extremely difficult for bacteria to develop resistance to critical house-keeping proteins.
Promoting more clinical trials in the SEAR

The SEAR countries are conducive for clinical trials...

- Low cost for clinical trial implementation.
- Genetically diverse population.
- Faster regulatory approvals.
- Presence of pharmaceutical know-how and well trained technical personnel.
- High quality clinical trial set-up.
- More clinical trials translates into more opportunities for manufacture of generic drugs.
Promoting Manufacture and Uptake of Generic Drugs

An important way of reducing cost and increasing access to life-saving drugs.

- Generic versions of drugs are 30-80% cheaper than the branded product.
- Generic versions can be manufactured legally when the drug is off-patent.
- Generic versions can be produced as “approved generics” with license from the manufacturer of the parent drug.
- Generic versions can be legally manufactured in countries that take part in clinical trials of the original drug.
Promoting Biosimilars

- Over 60% of the top players in the global biosimilars market are based in the SEAR.
- Top companies working on Biosimilars – Biocon, Bioton, Emcure (Gennova), Hospira, Intas, Bio Farma, LG Life Sciences, Novartis (Sandoz), Ranbaxy, Teva, and Wockhardt.
- Elaxim (Tenecteplase) and erythropoietin, manufactured by Gennova, have been approved by the USFDA.

Source: Business Insights, May 2009
# Recombinant Therapeutic Drugs Approved for Marketing in India

<table>
<thead>
<tr>
<th>Molecules</th>
<th>Therapeutic Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B vaccine (r-HBsAg based)</td>
<td>Immunization against Hepatitis B virus</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>Treatment of anemia</td>
</tr>
<tr>
<td>Interferon alpha 2B</td>
<td>Treatment of leukemia, Hepatitis B and Hepatitis C</td>
</tr>
<tr>
<td>Epidermal Growth factor (EGF)</td>
<td>Organ morphogenesis and mitogenesis</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>Dissolution of clot in acute myocardial infarction</td>
</tr>
<tr>
<td>Human insulin</td>
<td>Treatment of diabetes</td>
</tr>
<tr>
<td>GM-CSF; G-CSF</td>
<td>Treatment of chemotherapy induced neutropenia; treatment of neutropenia</td>
</tr>
<tr>
<td>Interferon alpha 2A</td>
<td>Chronic myeloid leukemia</td>
</tr>
<tr>
<td>Human growth hormone</td>
<td>Treatment of dwarfism in children</td>
</tr>
<tr>
<td>Nimotuzumab</td>
<td>Treatment of breast cancer</td>
</tr>
<tr>
<td>Tissue Plasminogen Activator</td>
<td>Dissolution of clot in acute myocardial infarction</td>
</tr>
<tr>
<td>Blood factor VIII</td>
<td>Treatment of hemophilia type A</td>
</tr>
<tr>
<td>Follicle stimulating hormone</td>
<td>Treatment of reproductive disorders</td>
</tr>
<tr>
<td>Teriparatide (Forteo)</td>
<td>Parathyroid hormone for treating osteoporosis</td>
</tr>
<tr>
<td>Drerecogin alpha (Xigris)</td>
<td>Burns and severe sepsis</td>
</tr>
<tr>
<td>Platelet Derived Growth Factor (PDGF)</td>
<td>Receptor antagonist in certain types of cancer</td>
</tr>
<tr>
<td>Interleukin 2; interleukin 11</td>
<td>Treatment of renal cell carcinoma; treatment of thrombocytopenia</td>
</tr>
<tr>
<td>Blood factor VII (Eptacogalpha)</td>
<td>To control bleeding in hemophilia patients</td>
</tr>
<tr>
<td>Interferon gamma</td>
<td>To treat chronic granulomatous disease &amp; osteoporosis</td>
</tr>
</tbody>
</table>
### Biotechnology based drugs in development in India

<table>
<thead>
<tr>
<th>Therapeutic category</th>
<th>No. of drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS / HIV / infection / Related Conditions</td>
<td>22</td>
</tr>
<tr>
<td>Autoimmune disorders</td>
<td>44</td>
</tr>
<tr>
<td>Blood Disorders</td>
<td>10</td>
</tr>
<tr>
<td>Cancer / Related conditions</td>
<td>210</td>
</tr>
<tr>
<td>Cardiovascular Diseases</td>
<td>22</td>
</tr>
<tr>
<td>Diabetes / Related Conditions</td>
<td>15</td>
</tr>
<tr>
<td>Digestive Disorders</td>
<td>14</td>
</tr>
<tr>
<td>Eye conditions</td>
<td>6</td>
</tr>
<tr>
<td>Genetic Disorders</td>
<td>9</td>
</tr>
<tr>
<td>Growth Disorders</td>
<td>4</td>
</tr>
<tr>
<td>Infectious Diseases</td>
<td>50</td>
</tr>
<tr>
<td>Neurological Disorders</td>
<td>17</td>
</tr>
<tr>
<td>Respiratory Disorders</td>
<td>13</td>
</tr>
<tr>
<td>Skin Disorders</td>
<td>7</td>
</tr>
<tr>
<td>Transplantation</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>18</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>465</strong></td>
</tr>
</tbody>
</table>
Promoting R&D in Vaccines

- **Gaining strength by acquisitions and joint ventures in SEAR**: Cadila Pharmaceuticals (India) and Novavax (USA) to conduct R&D of VLP-based vaccines for seasonal flu and HPV.

- **WHO prequalified pentavalent vaccine suppliers from SEAR**: Serum Institute of India (India), Panacea Biotech (India), Shantha Biotechnics (India), and Berna Biotech/Crucell/Novartis (Korea).

- **Developing Country Vaccine Manufacturers Network (DCVMN) members from SEAR**: Bharat Immunologicals & Biologicals Corp. (India), Bharat Biotech Intl. Ltd. (India), Bio Farma* (Indonesia), Haffkine Bio-Pharmaceutical Corp. Ltd. (India), Indian Immunologicals Ltd. (India), Queen Saovabha Memorial Institute (Thailand), LG Life Sciences* (Korea), Panacea Biotech* (India), Biological E (India), Serum Institute of India* (India), and Zydus Cadila (India).

* WHO prequalified vaccine manufacturers
Surveillance Networks

Hib Initiative

- India
- Indonesia
- Nepal
- Sri Lanka
- Bangladesh

Pneumococcal Vaccines Accelerated Development and Introduction Plan (PneumoADIP)

- ICDDR,B
- IVI

International Emerging Infections Program (IEIP)

Invasive Bacterial Infection Surveillance/South Asian Pneumococcal Alliance (IBIS/SAPNA)
Major Vaccine Initiatives

- Pediatric Dengue Vaccine Initiative (PDVI)
- Malaria Vaccine Initiative (MVI)
- Cholera Vaccine Initiative (CHOVI)
- Vi based Vaccines for Asia (VIVA)
- Rotavirus Vaccine Programme (RVP)
- Diseases for the Most Impoverished (DOMI)
## DOMI Cholera Program Field Studies in the SEAR

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Bangladesh</th>
<th>Indonesia</th>
<th>India</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective disease surveillance</td>
<td></td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Cost-of-illness studies</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Socio-behavioural surveys</td>
<td></td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Vaccine trials</td>
<td>√</td>
<td>(Phase I and II Peru-15 trials)</td>
<td>(Phase II and III killed WC trials)</td>
</tr>
<tr>
<td>Vaccine private demand surveys</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Vaccine delivery cost analyses</td>
<td></td>
<td></td>
<td>√</td>
</tr>
</tbody>
</table>
DOMI Typhoid Program: Vi Vaccine Demonstration Projects in the SEAR

<table>
<thead>
<tr>
<th>Criteria</th>
<th>N. Jakarta, Indonesia</th>
<th>Kolkata, India</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting</td>
<td>Urban slum</td>
<td>Urban slum</td>
</tr>
<tr>
<td>Design</td>
<td>Mass immunization</td>
<td>Randomized control trial</td>
</tr>
<tr>
<td>Vaccine delivery</td>
<td>School-based</td>
<td>Community-based</td>
</tr>
<tr>
<td>Target population</td>
<td>Grades 1 – 5</td>
<td>2 years and above</td>
</tr>
<tr>
<td>Number of vaccinees</td>
<td>4,828</td>
<td>37,686</td>
</tr>
<tr>
<td>Vaccination coverage</td>
<td>91%</td>
<td>69%</td>
</tr>
</tbody>
</table>
The AERAS Global TB Vaccine Foundation is working with the Oxford-Emergent Tuberculosis Consortium to develop the vaccine, called MVA85A/AERAS-485, with additional funding from the Wellcome Trust.

AERAS Global TB Vaccine Foundation is conducting epidemiological studies to find out the burden of TB in India.

Funding is being provided by CDC to develop TB vaccine trial sites in India.

AERAS is also planning to conduct a Phase I clinical trial at St Johns' Research Institute, India, during the course of 2009.
### PATH MVI : Malaria Vaccine Candidates

<table>
<thead>
<tr>
<th>Platform</th>
<th>GSK RTS,S ASO1/ASO2</th>
<th>ICGEB PvRlI</th>
<th>Sanaria PfSPZ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antigen</strong></td>
<td>RTS,S (consists of sequences of the circumsporozoite (CS) protein and the hepatitis B surface antigen (HBsAg).)</td>
<td>Region II of blood-stage Duffy Binding Protein of <em>P. vivax</em></td>
<td>Live attenuated sporozoites</td>
</tr>
<tr>
<td><strong>Adjuvant</strong></td>
<td>AS02: proprietary oil-in-water emulsion formulated with MPL® and Stimulon® QS21 immunostimulants. AS01: liposome formulation with MPL® and QS21 immunostimulants.</td>
<td>Formulation with AS02 selected for clinical development.</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Development stage</strong></td>
<td>Phase II trials; preparation for Phase III.</td>
<td>Scale up (50L) and cGMP production – Bharat Biotech, Hyderabad.</td>
<td>Biodistribution study and preparation for Investigational New Drug (IND) ongoing.</td>
</tr>
</tbody>
</table>
HIV Vaccine Clinical Trials in India: Previous Phase I Trials

- **tgAAC09 HIV-1 Vaccine trial started in Feb 05 at NARI, Pune**
  - Adeno-associated virus based vaccine.
  - Vaccine is well tolerated and safe in the 3 dosages used.
  - Weakly immunogenic in the doses used in the trial.
  - Evidence of high baseline titer of AAV2 neutralizing antibody in Indian population as compared to European participants.

- **MVA Vaccine trial started in Jan 06 at TRC, Chennai**
  - TBC-M4 – Modified Vaccinia Ankara HIV-1, clade C, multigenic; developed in collaboration with NICED (Kolkata).
  - Dose-dependant response seen.
  - TBC-M4 immunogenic at both low and high dose with 75% and 100% of low and high dose vaccinees responding after 3 injections.
  - Most of responses are balanced, directed to both env and gag, then against pol, nef or tat-rev.
  - Lack of impact of previous small pox vaccination on response rate.

Indian Council of Medical Research
Current HIV Vaccine Phase I Clinical Trial in India: Prime - Boost Strategy

- TBC-M4 was found to be safe, well tolerated.
- Modest immune response in 100% volunteers.
- To enhance the breadth and magnitude of immune response a prime-boost approach has been initiated in Feb 09.
- ADVAX, a DNA vaccine with synthetic copies of HIV-1 clade C genes env, gag, pol, nef and tat will be used to prime and TBC-M4 will be used to boost.
- ADVAX was designed by the Aaron Diamond AIDS Research Centre in New York, in collaboration with the Rockefeller University in New York and IAVI.
- NARI and TRC to conduct Phase I trial with YRG Care, an NGO to support TRC for advocacy and community mobilization for the trial.
H5N1 / H1N1 Vaccine: Urgent need for production in the SEAR

- Organizations from SEAR having capacity to produce seasonal influenza vaccines (LAIV and IIV):
  - Serum Institute of India Ltd. (India)
  - Cadila (India)
  - Bio Farma (Indonesia)
  - Government Pharmaceutical Organization (Thailand)

- Need for increasing production capacity for manufacturing H5N1 / H1N1 vaccines to cope with increasing demands.
- Need to attain self-sufficiency in pandemic influenza vaccine stocks in the SEAR.
Cadila’s Vaccine Initiative

• Platform Technology Identification for affordable scalable technology
  • Virus Like Particles (VLP)

• Became major stake holder and Board Member in a key company (NOVAVAX)

• Formed a special JV – CPL BIOLOGICALS

Single Protein
Crystalline VLP

e.g. Gardasil®
(HPV vaccine)

multi-component influenza VLP vaccine

Exclusive composition of matter on Target Surface Proteins

Patent protection for VLP matrix platforms

Lipid Envelope
**Preparedness for Pandemic H1N1 Influenza**

| TASK NAME               | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
|-------------------------|----|----|----|----|----|----|----|---|---|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|
| 1 H1N1 vaccine starts   |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |
| 2 Genes from CDC       |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |
| 3 Genes cloned         |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |
| 4 Recombinant clone    |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |
| VLP - Pre-clinical     |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |
| 5 HA- Reagent          |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |
| 6 H1N1 bulk            |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |

- Ferret studies successfully completed
- GLP batch shipped on June 2, 2009
- Contract signed with NIAID for clinical testing of H1N1 VLPs
The road ahead...

- Prioritization of regional needs by thorough mapping of prevalent diseases.
- Develop a better infrastructure for identifying disease pathways.
- Need for better tools for choosing and validating successful targets.
- Improvement of industry-academic interface.
- Improve accessibility and affordability of essential medicines.
- Need to improve infrastructure of healthcare system.
The road ahead...

- Promote health insurance schemes.
- Promote knowledge sharing between basic scientists and clinicians at national and international level.
- Exposure of teaching faculties and students to translational research.
- Harness the IT strength in the region.
- Capacity building of all stakeholders.
- More dedicated HRD for drugs and vaccine research.
- Strengthening of the regulatory and testing facilities.
The road ahead...

- Develop safe and efficacious biosimilars.
- Promote manufacture of off-patent drugs.
- Promote contract research / manufacturing.
- More focused clinical research.
- More rigorous clinical trials.
- Increase investment in biomedical field.
- Promote research in chemoprophylaxis.
- Promote traditional medicine and herbal / herbal-mineral drug development.
Thank You