Critical Path 연구의 현황과 전망

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신약 출시의 정체현상(pipeline problem)을 타개하기 위해 신약 개발의 방법론 자체를 진지하게 연구하고 개선해야 한다는 취지를 담은 Critical Path Report가 미국 FDA에 의해 발표된 지 약 2년이 흘렀다. FDA는 이후 자국 내의 기업, 학계, 소비자단체 등으로부터 광범위한 의견 수렴을 거쳐 2006년 3월에 Critical Path Opportunity Report를 발표하였다. 2년 전의 Critical Path Report가 지난 20여년 간 실험실적 연구의 업적을 신약개발로 적절히 연결시키지 못한, 방법론의 부재를 반성하고 앞으로 나아갈 방향을 제시하는 선언적 의미를 지녔다면, 이번에 발표된 자료는 각계의 의견을 수렴하여 신약개발에 있어 어떤 분야의 어떤 기법을 발전시켜나가야 할 지에 관한 구체적인 설계도를 제공한 것이라 볼 수 있어 이를 소개하고자 한다.

Critical Path Opportunity Report에서 지목한 향후 연구 분야

Topic 1: Biomarker development

-omics 기술과 영상 기술을 적극 적용하여, 약효와 안전성의 새로운 표지자를 찾아낸다.

Topic 2: Streamlining clinical trials

단순히 신약이 효과, 안전성 여부의 한두 가지 질문에 대한 답을 얻기 위한 임상시험(confirmatory trial)만을 행하던 과거의 방식에서 벗어나, 신약의 약효나 안전성의 기전에 대한 지식을 임상시험 설계에 적용하여 다양한 정보를 추출해 낼 수 있는 learning trial을 시도하고자 함이다.

Topic 3: Harnessing bioinformatics

생물학적 데이터에 대한 수학, 통계, 전산학적 응용을 통해 정상적인 인체 생리, 질병의 자연경과, 치료에 따른 장기적 변화 등을 모델링하여 신약개발에 적용하는 model-based development를 추구한다.

Topic 4: Moving manufacturing into the 21st century

실험실적 연구를 벗어나 높은 품질의 의약품을 대량으로 생산하는 기술력의 부재는 Critical Path에 있어 흔한 애로사항 중의 하나이며, 오늘날에는 두 가지 이상의 활성성분을 섞은 combination product의 안정적인 생산 기술이 중요한 문제로 대두되고 있다.

Topic 5: Developing products to address urgent health needs

배양검사로만 진단이 되는 병원균의 조기 진단법의 개발, 바이오 테러에 쓰일 수 있는 미생물 감염에 대한 적절한 동물 모델의 개발 등이 이에 해당한다.

Topic 6: At-Risk Populations - Pediatrics

의약품뿐 아니라 체내에 삽입되는 각종의 의료용구들을 영유아, 소아, 청소년 등에서 그 기능을 떨어뜨리지 않고, 크기나 형태를 바꾸어 제조하는 문제, 성장하는 어린이들의 몸 속에서 장기간 적절한 유지할 수 있는 의료용구의 개발 등의 이들에서의 임상시험 윤리에 관한 이슈와 함께 논의되고 있다.

맺는 말

어느 나라건 이와 같은 Critical Path 연구를 제대로 수행하기 위해서는 산, 학, 관의 원활한 의사소통과 긴밀한 협력이 필수적이다. 관련 연구자들이 공통적으로 지적하는 선결과제는 무엇보다도 가장 큰 이전에 행해진 적이 없는 연구 분야들이므로 기존의 임상 연구자, 약학자, 약동학자, 통계학자 등을 적절히 재훈련 시킬만한 기관이나 인력이 절대 부족하다는 것이다. 그럼에도 불구하고 미국 내에서는 Critcal Path Institute의 설립이라든지 질병 종류별로 biomarker 개발을 위한 컨소시엄의 설립 등이 시작되고 있다. 유럽의 경우, 유사한 개념으로 4억 4천만 유로를 투입하여 2007년부터 2013년까지 신약개발의 효율화를 위한 연구를 EU와 제약산업계의 협력으로 추진하고 있다. 한 예로 독일의 다발성 경화증 연구소는 전 세계 최대의 다발성 경화증 데이터 베이스 구축을 시도하고 있으며 이 희귀 질환의 자연경과와 치료 시의 경과에 관한 자료를 집대성하여 신약개발의 기초자료로 사용하려 하고 있다.

지역임상시험센터의 발족과 더불어 막 임상시험의 중요성에 대한 공감이 확산되어 가는 우리나라에서도, 이들 Critical Path 이슈들 중 국내에서 경쟁력이 있는 분야를 선택하여 지역임상시험센터라는 인프라를 최대한 활용한 연구를 진행하는 것은 한국 제약산업의 생존 가능성을 높이기 위한 필수적인 전략임에 분명하다.

Central "Critical Path" Thesis

- Societal investment in R&D to improve the medical product development process – that is inextricably intertwined with FDA standards – has been lacking
- Huge private & public basic research & specific product development investment
- Minor investment in development tools & public standards
  - Academia not funded
  - Not conceptualized as FDA's role
  - Efforts in private sector not generalizable or are proprietary

Janet Woodcock, M.D.Acting Deputy Commissioner for Operations FDA May 5, 2005

지난 2년 동안

- Industry
  - Eager to collaborate by sharing data
    - Some are skeptical
- Academia
  - Few aware of problems
  - Many focused on discovery and preclinical development
- Regulatory
  - Many quite knowledgeable and enthusiastic

Janet Woodcock, M.D.Acting Deputy Commissioner for Operations FDA May 5, 2005

The FDA requested $6 million for the critical path program for fiscal 2007.

Critical Path Opportunity List

- The roadmap of Critical Path
  - Task List or Problem List
  - Six categories
    - Topic 1: Better evaluation tools (Biomarker)
    - Topic 2: Streamlining clinical trials
    - Topic 3: Harnessing bioinformatics
    - Topic 4: Moving manufacturing into the 21st C.
    - Topic 5: Developing products to address urgent health needs
    - Topic 6: At-Risk Populations — Pediatrics

U.S. Department of Health and Human Services Food and Drug Administration March 2004

Topic 1: BETTER EVALUATION TOOLS

Developing New Biomarkers and Disease Models

- Biomarker Qualification and Standards
  - Biomarker Qualification
  - Standards for Microarray and Proteomics-Based Identification of Biomarkers
- Qualifying Disease- and Disorder-Specific Biomarkers
  - Asthma, pregnancy, CV, infection, cancer, autoimmune ds, ...
- Safety biomarkers
  - Vaccine, gene therapy, immune response to cell and tissue products, cardiac toxicity...

Topic 1: BETTER EVALUATION TOOLS

- Advancing the Use of New Imaging Techniques
  - Performance Standards for Imaging Displays
  - Using Medical Imaging as a Product Development Tool
  - Imaging Biomarkers in Arthritis, CNS, CV ds, Cancer, COPD
  - Noninvasive Therapeutic Monitoring
  - Imaging Implanted Devices

Topic 1: BETTER EVALUATION TOOLS

- Improving Predictions of Human Response from Disease Models
  - Improving Extrapolation from Animal Data to Human Experience
  - Better Model of Wound Repair
  - Better Animal Disease and Tissue Injury Models
  - Better Disease Models for Predicting
  - Biological Product Toxicity

TOPIC 2: STREAMLINING CLINICAL TRIALS

Creating Innovative and Efficient Clinical Trials and Improved Clinical Endpoints

- Advancing Innovative Trial Designs
  - Design of Active Controlled Trials.
  - Enrichment Designs.
  - Use of Prior Experience or Accumulated Information in Trial Design.
    - Adaptive Trial Design
    - Non-Frequentist Methods

TOPIC 2: STREAMLINING CLINICAL TRIALS

- Advancing Innovative Trial Designs (*cont'd*)
  - Development of Best Practices for Handling Missing Data.
  - Development of Trial Protocols for Specific Therapeutic Areas.
  - Analysis of Multiple Endpoints

TOPIC 2: STREAMLINING CLINICAL TRIALS

- Improving Measurement of Patient Responses
  - Measuring Disease-Related Symptoms.
  - Measuring Patient-Centered Endpoints.
  - New Trial Design in Oncology.
  - Improving Efficacy Endpoints for Infectious Diseases

TOPIC 2: STREAMLINING CLINICAL TRIALS

- Streamlining the Clinical Trial Process
  - Development of Data Standards.
  - Consensus on Standards for Case Report Forms.

TOPIC 3: HARNESSING BIOINFORMATICS

Data Pooling and Simulation Models

- Identification and Qualification of Safety Biomarkers
- Virtual Control Groups in Clinical Trials
- Adverse Event Data Mining
- Multiple Complex Therapies
- Modeling Device Performance
- Clinical Trial Simulation
- Failure Analysis
- Natural History Databases for Rare Diseases

TOPIC 4: MOVING MANUFACTURING INTO THE 21ST CENTURY

Manufacturing, Scale-up, and Quality Management

- Manufacturing Biologics
  - Improving Manufacture of Influenza and Other Vaccines
  - Characterizing Cell Therapies.
  - Novel Approaches to Characterizing and Standardizing Biological Products.
  - Detecting Contamination in Biological Products.
  - Enabling Manufacturing Changes for Well characterized Proteins
  - Tissue Engineering
  - Vaccine Potency

TOPIC 4: MOVING MANUFACTURING INTO THE 21ST CENTURY

- Manufacturing Devices
  - Device Interaction with Blood Flow
  - Development of a Biocompatibility Database
- Manufacturing Drugs
  - *Identifying Safety Effects of Excipients.*
  - Manufacturing Novel Dosage Forms.
  - Developing Standards for Spectroscopic Instruments
- Characterizing and Qualifying Nanotechnologies.

TOPIC 5: DEVELOPING PRODUCTS TO ADDRESS URGENT PUBLIC HEALTH NEEDS

- Rapid Pathogen Identification
  - Improving Anti-Microbial Product Testing
  - Screening Donated Blood and Tissue
- Better Predictive Disease Models
  - Animal Models to Test Bioterrorism Countermeasures
  - New Small Animal Models for Vaccine Testing
  - New Tissue Models

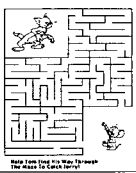
TOPIC 6: SPECIFIC AT-RISK POPULATIONS

Unlocking Innovation in Pediatric Products

- Better Extrapolation Methods and Best Practices in Pediatric Trial Design
- Drug Metabolism and Therapeutic Response
- Diagnosing Depression Subtypes
- Animal Models for Maternal Vaccines
- New Therapies for Juvenile Diabetes

우리나라에 미치는 영향

- Routine development works are being outsourced
  - Non-Core Countries
- But all the critical tools of development will be created and owned by Core Countries



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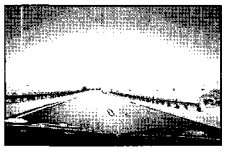


We still have some opportunities – 1

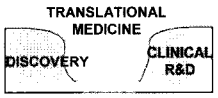
미국에도 이런 숙제들이...

- Stakeholders consistently tell
  - Few academic programs to train product *development professionals.*
  - Need for better trained
    - Physician investigators, Pharmaceutical scientists, Pharmacokineticists
- Need for an integration of quantitative skills into the medical school curriculum

We still have some opportunities – 2
미국에도 이런 숙제들이...

- Need for a new area of expertise
  - ***experimental medicine***

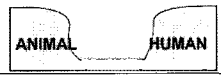
    New types of clinician-scientists, trained in the translational medicine and diagnostics that bridge the discovery and clinical R&D phases, and in clinical trial management.



We still have some opportunities – 3
미국에도 이런 숙제들이...

- Need for another new area of expertise
  - ***animal physiology***

    who understand how animal physiology data predict human responses, and we need *clinician-researchers who can work effectively with both animals and humans*



We still have some opportunities – 4
미국에도 이런 숙제들이...

- ***Lack of Career Models for Multidisciplinary Clinical Researchers (experts in animal + clinical research)***
  - 수련 받아도 대학이나 연구소에 마땅히 갈만한 조직이 마련되어 있지 않음
  - Need for multidisciplinary teams that may cross the lines of traditional academic departments or corporate divisions

What Does The U.S. Industry Say ?

- FDA efforts to stimulate innovation should not detract from improvements in the regulatory process, nor divert resources from marketing application review.
  - New Critical Path standards should replace old standards, not constitute additional requirements.
  - FDA: The goal of the Critical Path Initiative is to modernize standards, not create roadblocks.
  - Needs clarification of the regulatory pathways for certain types of products (e.g., combination products, tissue engineered products)

New Collaborations

- Many of the Critical Path Opportunities on the list cannot be accomplished by one entity alone.
- No single company, university, or governmental agency will have sufficient resources, expertise, or information base to undertake the work.

New Collaborations – Biomarker Consortium

- Consortia organized around common areas of interest—
  - Disease-specific or Marker-specific
  - Technology-specific (a new imaging technique)
- *Also to pool data to identify rare side effects and* safety signals or markers for organ toxicity
  - use of biomarkers to study organ toxicity during animal toxicology testing is a very promising area.
    - The animal-to-human test sequence provides an ideal setting to evaluate new markers of organ toxicity.

New Collaborations

Building an E-Clinical Trial Infrastructure

- **An electronic clinical trial environment that includes more standard data elements, forms, and formats (Topic 2).**
  - **Clinical Data Interchange Standards Consortium, and others**
  - **To meet the needs of all parties.**
  - **For a future of more efficiently administered clinical trials.**

New Collaborations

Creating a Bioinformatics Infrastructure

- **No one company, university, or governmental agency has the necessary information bases to create computer models sufficiently robust to accurately predict product safety and efficacy (Topic 3).**
  - **Useful, but untapped, sources of data**
    - **publicly available data, data from companies, FDA, and/or other parts DHHS.**
  - **New strategies for information sharing and safe information housing will be needed.**

New Collaborations

Collaboration on Specific Diseases

- ***Sylvia Lawry Centre for Multiple Sclerosis Research, Munich Germany***
  - **Compiled the world's largest database (20,000 patients) of clinical information about multiple sclerosis.**
  - **Pharmaceutical companies, clinics, and universities have provided data to the Centre free of charge from the placebo arms of clinical trials.**
  - **Now enabling innovative mathematical modeling of the course of the disease.**
  - **Also partnering with Ludwig-Maximilian University in Munich to take advantage of the University's expertise in information science, mathematics, and medicine.**

New Collaborations

Critical Path Institute

- **Co-founded by the University of Arizona and Stanford Research Inst., (SRI) Intl., with input from the FDA.**
- **Goals are to accelerate the development of safe medical products and foster education and *training in applied research and regulatory* sciences.**
  - **will bring together academic faculty, local clinicians and researchers, and scientific staff from SRI Intl., industry, patient advocacy groups, and others to accomplish**

Similarity to MLB

- 게임의 법칙을 만들고...
  - 신약개발 기법 방법론의 원천적 변화
- 그들만의 리그를 운영하며...
  - 거대 제약기업의 축적된 자료와 경험을 집약하는 방식
- 전 세계로부터 판매 수익을 추구...

For Korean Leaguers

- 임상시험 전문 인력 양성 계획의 수정
  - 교육 과정이나 교육 대상에 대한 새로운 고려
    - 임상시험 관련 대학원 코스에 반영
    - 여러 대학의 협력 교과 과정 운영 고려
      - 소모적 경쟁 지양, 교수 인력의 최적 활용
    - 배출된 전문가들의 진로 문제

For Korean Leaguers

- **Decision Making Through Revising the NTRM**
  - **Critical Path Opportunity List**에서
    - 독자적으로 도전할 만한 분야 (인력 >> 자본)
    - 늦었지만 우리 나름의 데이터를 축적해야 하는 분야
    - 혼자서는 승산이 없는 분야 (자본 >>인력)
      - 국제적 제휴 고려 ?
    - 포기해도 되는 분야 ?

지역임상시험센터 인프라의 최적 활용

X 15 = ?

Six million $ Man

- 상호 협력을 통한
  - 체계적 **CRITICAL PATH RESEARCH**
  - 연구 인력의 양성

It's not an easy job for them, either...