Data standardization and advancing regulatory science

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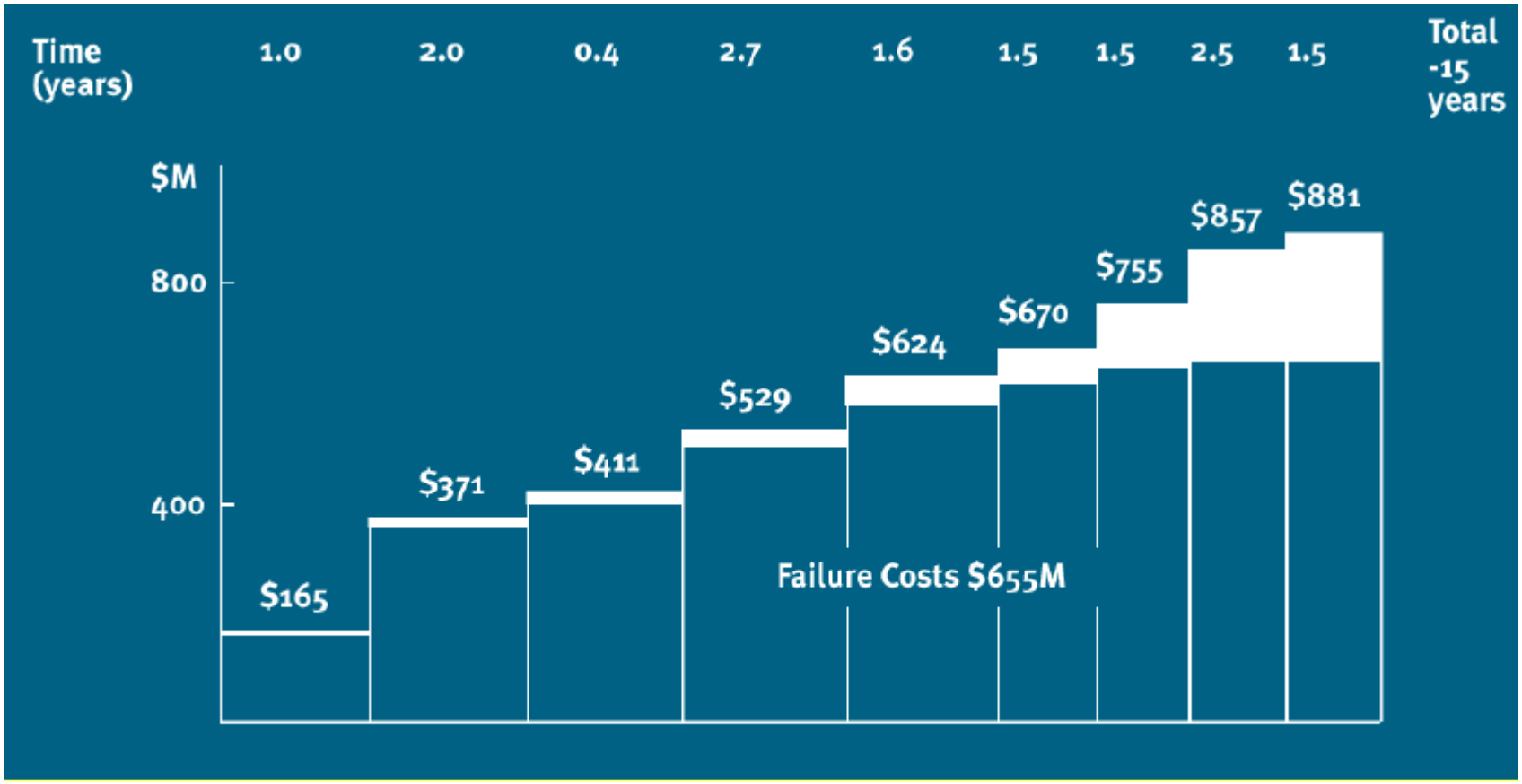
Current Situation

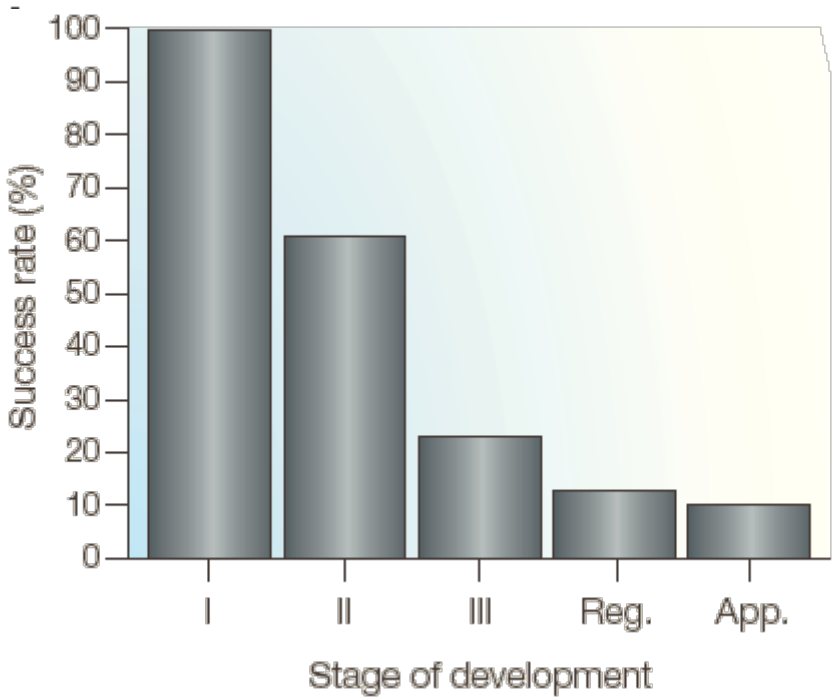
Cost of drug development



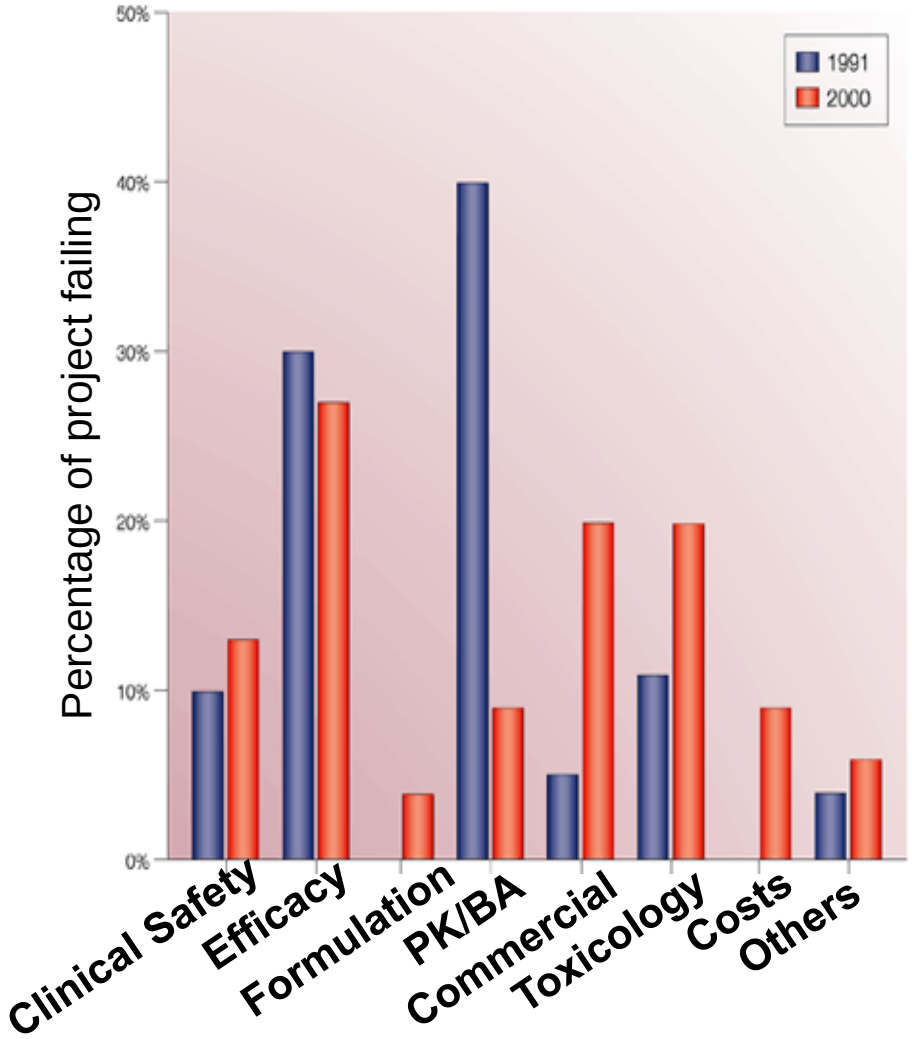
Korn D. and Stanski D.R., (Eds.). Drug development science: Obstacles and opportunities for collaboration among academia, industry and government. Report presented at An Invitational Conference Organized by the Association of American Medical Colleges and the Food and Drug Administration; January 13-14, 2005; Washington, DC.

Teshirogi I, 11th Kitasato-harvard Symposium, 2011

Stage and Reasons to fail drug development



Kola I et al, Nature Rev Drug Discov, 3: 711-715, 2004



Frank R et al, Nature Rev Drug Discov, 2: 566-580, 2003

Globalization of clinical development

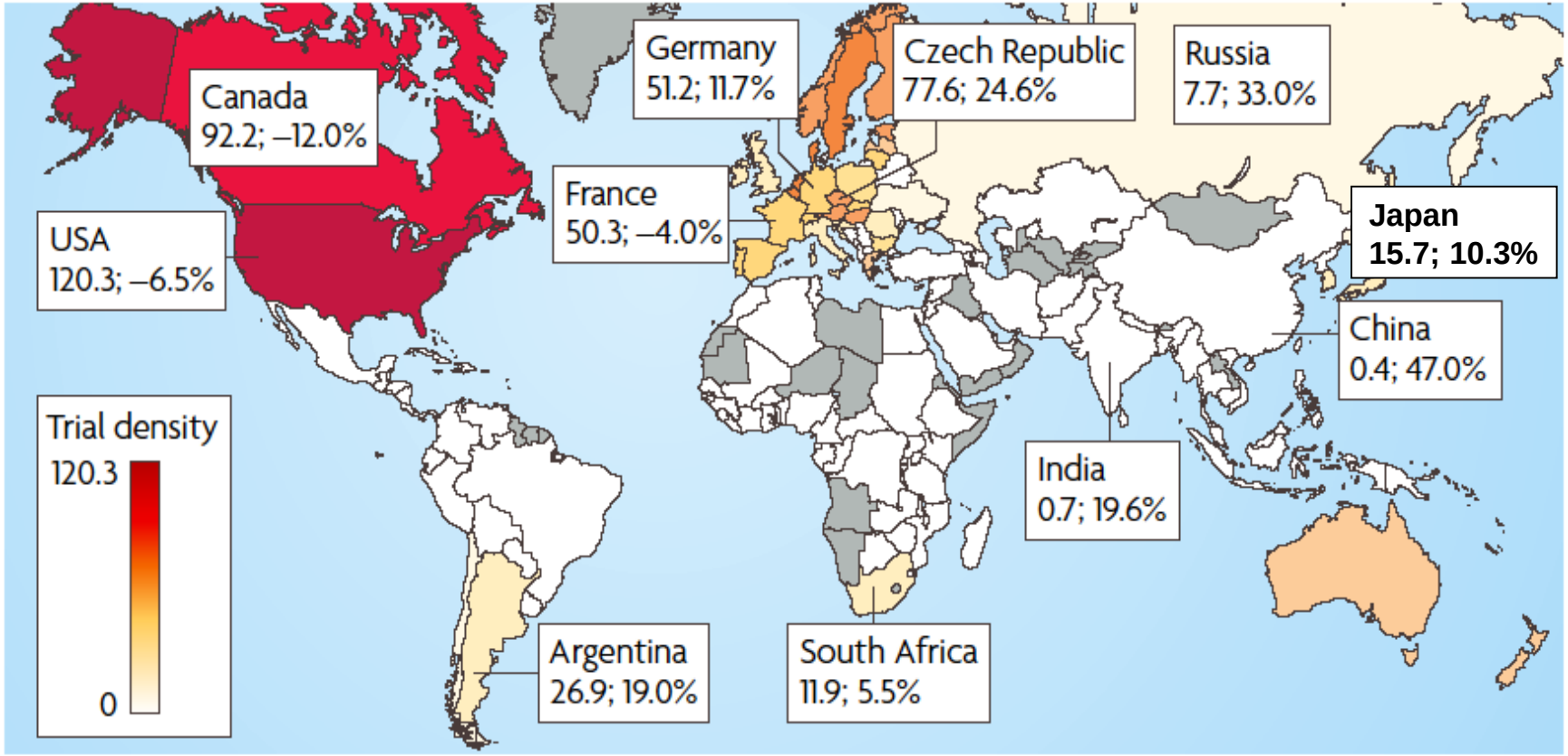
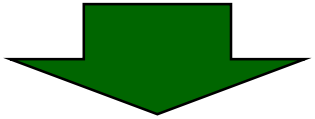


Figure 1 | **Density of actively recruiting clinical sites of biopharmaceutical clinical trials worldwide.** Density is in per country inhabitant (in millions; based on 2005 population censuses); darker orange/red denotes a higher density. The trial density and average relative annual growth rate in percent is shown for selected countries. The countries in grey had no actively recruiting biopharmaceutical clinical trial sites as of 12 April 2007. **Nature Rev Drug Discovery, 7: 13, 2008**

Current Situation of Drug Development

- Huge increase of development cost
  - Failure costs, additional requirements etc.
- Low success rate
  - High failure rate, especially in later stage
  - Scientific limitation (many unknown factors)
- Globalization
  - International harmonization and cooperation



- ✓ A lack of innovative drug
- ✓ Delayed development
- ✓ Unmet-medical
- ✓ A lack of s[illegible] evidence in a population or a region

Need another approach

Role of Regulatory Science in drug development

Regulatory Science Bridge

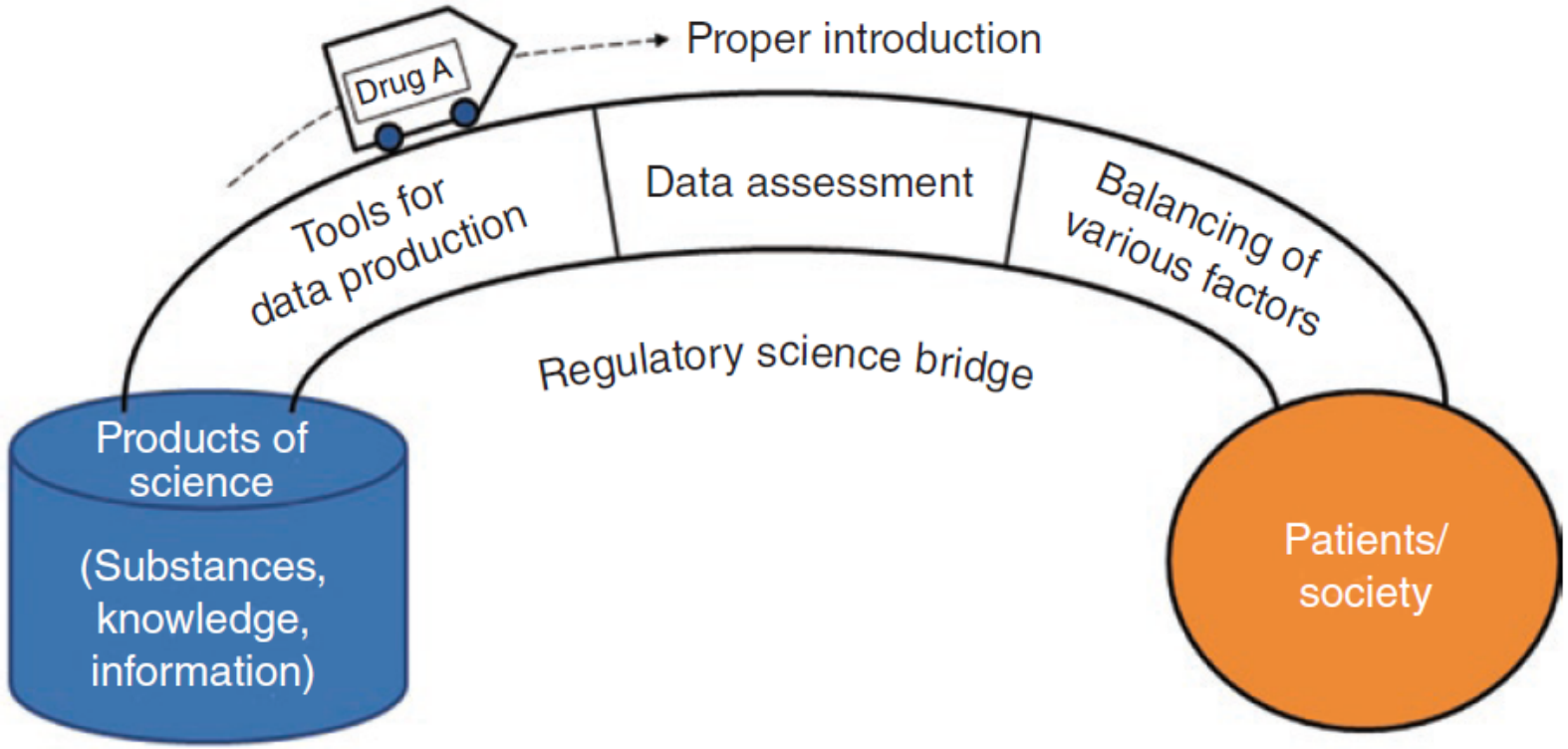
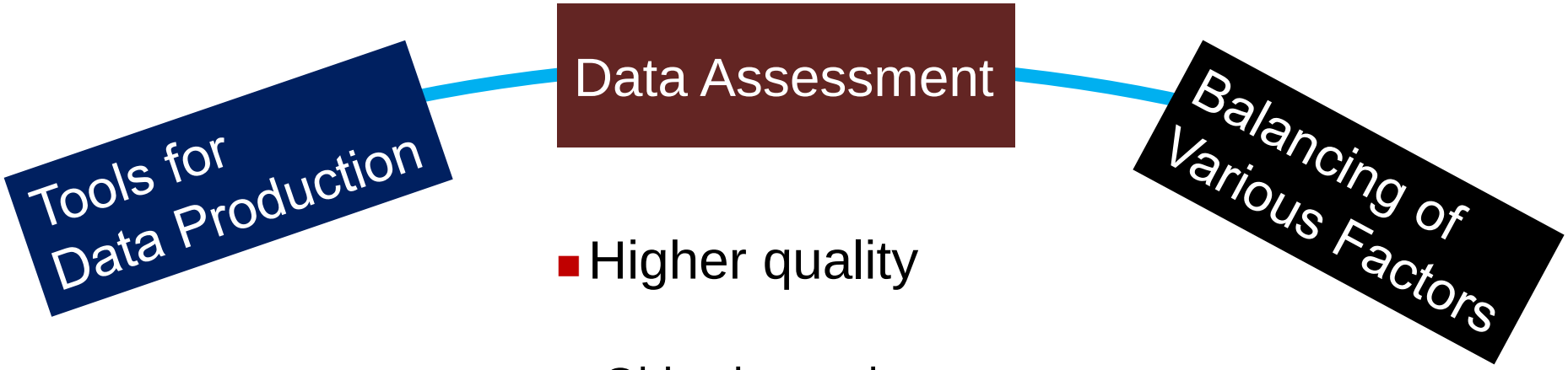


Figure 1 The regulatory science "bridge" as a means to introduce products of science to patients and to society. Regulatory science performs three functions: providing tools for data production, a basis for data assessment, and methods for balancing various factors. All three functions are indispensable to a proper introduction of a new product of science (here, "Drug A").

Tominaga T et al, Clin Pharmacol Ther, 90: 29-31, 2011

Details of 3 Factors in Regulatory Science



- Higher efficiency
  - Biomarker
  - M&S
  - Adaptive Design

  and more

- Higher quality
  - Objective and Quantitative assessment etc.
    - What is Benefit?
    - What is safety?

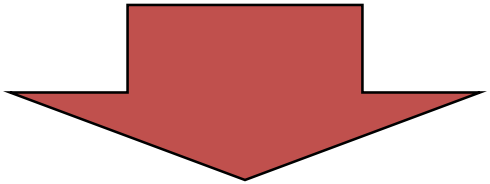
- Better balance
  - Better methods for benefit/risk assessment
  - Medical and social needs
  - Patients voice

Need alternative approach and more research

Importance of the electronic data standard for advancing regulatory science

Why data standard is important?

- Only limited data are available from one study or one organization
- Wasteful, if expensive clinical data are not utilized effectively
- More effective to analyze data from relevant multiple studies or products



- To maximize data value and facilitate proper analysis
  - Data should be acquired, submitted, archived in same structure and format

Data in a clinical trial

Medical Inst

Sponsor

Regulatory Agency

Out of control,
if these data were collected in
different standards among studies

HL7

Protocol (eProtocol)

Data

PRM

CRF aCRF

Data Capturing and Processing

Data

Study Data (SDTM)

Metadata

Data

Submission

Data

Analysis Data (ADaM)

Metadata

Data

ODM

Data

LAB

Data

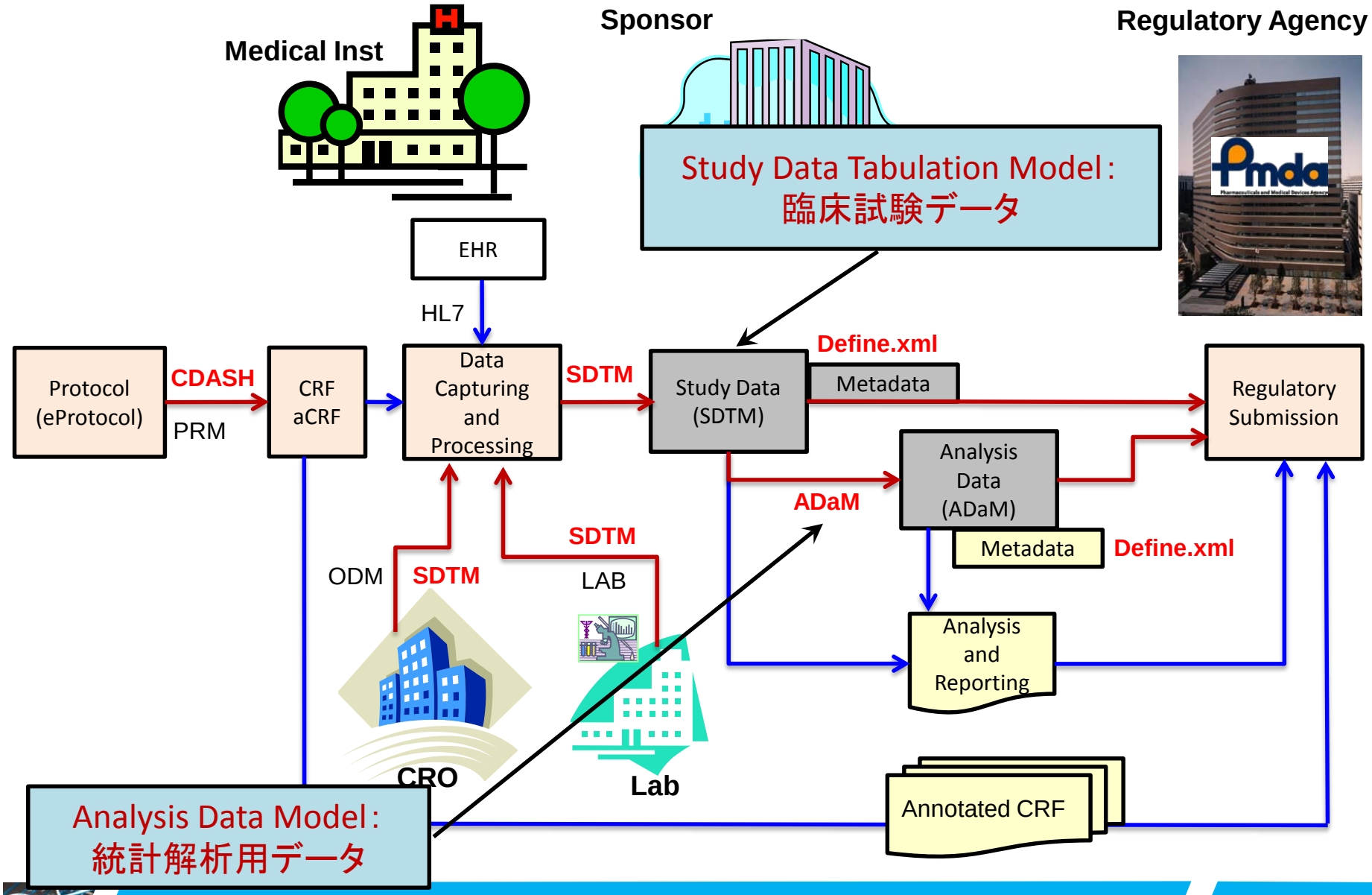
CRO

Lab

Analysis and Reporting

Annotated CRF

CDISC Standards in a clinical trial



Reinforcement of the PMDA system -Task force for advanced review and consultation with electronic data-

Background

1. Japan Revitalization Strategy -JAPAN is BACK-

◆ Strategic Market Creation Plan

Cabinet decision; June 14, 2013

➢Theme 1: Extending the nation's healthy life expectancy"

- The assessment lag "0" for pharmaceuticals and medical devices by accelerating the assessment process by strengthening the PMDA system

2. Health and Medical Care Strategy

Agreement of Chief Cabinet Secretary, Minister of Health, Labour and Welfare and other concerned Ministers; June 14, 2013

◆ Three Basic Plan

- Achievement of a healthy, long-lived society
- Contribution to economic growth
- Global contribution

- PMDA-initiated promotion of research and analysis based on clinical data

Task force for advanced review/consultation

- The special task force was formally established on Sept 1st, 2013
  - "Task force for advanced review and consultation with electronic data“ http://www.pmda.go.jp/english/service/taskforce.html

Accumulation and Utilization of e-Data

NDA submission

e-Submission of data

- Submission of electronic data from clinical and nonclinical studies

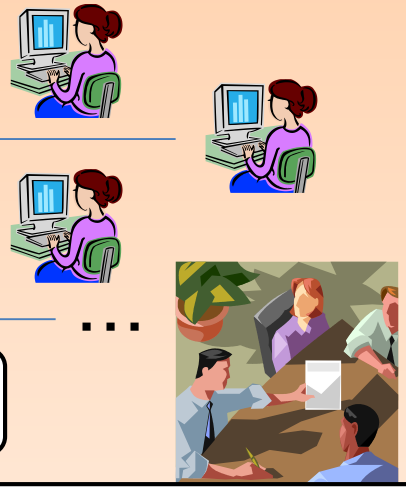
Storage of electronic data in the dedicated server and registration in the database

Visualization and analysis of data, supported by browsing software

Regulatory Review

Use of electronic data

- Accessible, visualized electronic data for each reviewer
- Easy to identify individual clinical case data, drilling down of data
- Operation of various analyses - simple, subgroup analysis for the present



Scientific discussion and decision making on the basis of internal analysis result

Utilization of Accumulated Data

Integration of cross-products information

- Utilization of exhaustive information by therapeutic category for review/consultation
- Internal review on particular theme – e.g.) active utilization of Modeling & Simulation
  - Review on pediatric dosage
  - Preparation of disease model
  - Development of evaluation indicator
- Utilization in preparation of guideline

What the review authority can do with the information of all products.

Contribution to efficient development through review/consultation and GL publication based on further analyses by dry-lab

Merit of use of CDISC standards in PMDA

PMDA plans to request patient level clinical trial data in electronic format which complies with CDISC standards

- PMDA
  - For fast access and easy handling of submitted clinical trial data in many new drug applications
  - For future use of accumulated clinical trial data for cross-products analysis
- Industry/Sponsor
  - For efficient and qualified process to make submission materials
  - For efficient use of medical records of medical institutes for clinical trials
  - For promotion of participating global development and using Japanese clinical trial data for submission to foreign regulatory authorities

Relationship between PMDA and CDISC

- PMDA regularly attend the meetings of CDISC in Japan as observer since July 2013.
  - Japan CDISC Coordinating Committee (J3C)
  - CDISC Japan Users Group (CJUG) SDTM, ADaM
- Contribution of CJUG members to the introductory lecture of CDISC in PMDA
- Presentation by PMDA in International Interchange and Japan Interchange

Proposed timeline for electronic study data system development

- FY2013
  - Surveys, procurement of hardware/software, pilot*

*Electronic data viewing and internal analysis

- FY2014 to FY2015
  - Continue the pilot*; to be in full operation after the Lab is open
- FY2016 (prospect)
  - Submission of clinical electronic data for NDA
  - (With transitional period)
- After FY2017
  - Submission of non-clinical electronic data for NDA
  - (To be discussed)

TENTATIVE
Currently under discussion

FY2013 pilot project (outline)

- Purpose
  - To confirm that the clinical data submitted as a part of approval application for new drugs is appropriately stored and managed with in-house system, and that persons in charge can analyze the stored data by utilizing introduced software.
- Data to be used
  - Clinical data including those of Japanese subjects, which was amassed according to the CDISC standards, and are under regulatory review or going to be filed to PMDA (more than 1 clinical study per 1 product, around 3 products)

Through the pilot project, PMDA will confirm the feasibility of reviewing and analyzing data in CDISC formats, using actual data from clinical trials.

Pilot project updates

- Volunteers for FY2013 pilot
  - more volunteers than expected
  - meetings with sponsor prior to pilot data submission
  - vary in product categories, phases, types, global/domestic
  - datasets
    - compliant with CDISC standards
    - with some additional company-specific variance

- Several volunteers for FY2014 pilot

Thank you for your great support and contribution!!

Pilot project updates

- Tools and training for pilot projects
  - Surveyed and prepared tools/software for data analysis and presentation
    - Feasibility to be tested through the pilots
  - Training on CDISC standards and software
    - ALL new drug reviewers in charge took the trainings
    - To be continuously conducted

Current Activities

- Monthly meeting with pharmaceutical industry association (JPMA, PhRMA Japan, and EFPIA Japan)
  - Japan CRO<clinical research organization> Association just joined to the discussion
  - All procedural and technical issues for data submission have been discussed.
- Information exchange with FDA and EMA
- "Basic principles on e-data submission for NDA" is currently under preparation and will be notified in FY2014

Future

Advanced workflow of review/consultation

Analysis by PMDA

Giving additional scientific value to submitted data

Cooperation with Academia

Regulatory Science

More rational & effective evaluation process for regulatory decision

Practical use of Innovative Medical Products

NDA etc.

e-Submission of study data

Data Accumulation

Database

Sophisticated review

- Each reviewer utilizes innovative assessment techniques

Cross-Products Analysis

- Advanced evaluation methods
- Active utilization of Modeling & Simulation
  - ➢ Disease model
  - ➢ Objective B/R assessment
  - ➢ Identifying AE-related factors etc.

Sophisticated Consultation

- More evidence-based consultation

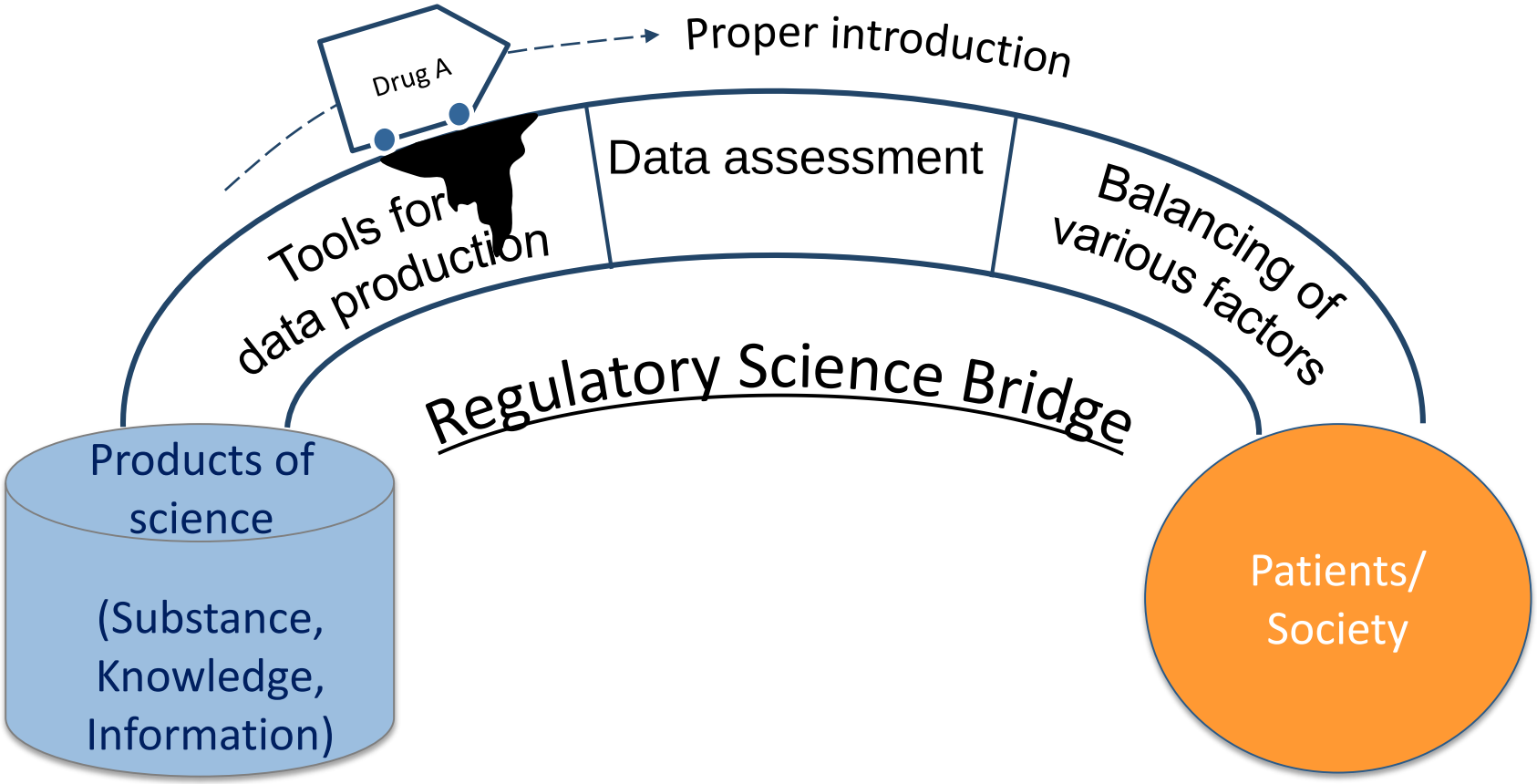
More effective and high quality Review

- More predictable efficacy/safety after approval
- Reduction of applicant's work load
- More scientific regulatory decision

More efficient and Successful Development

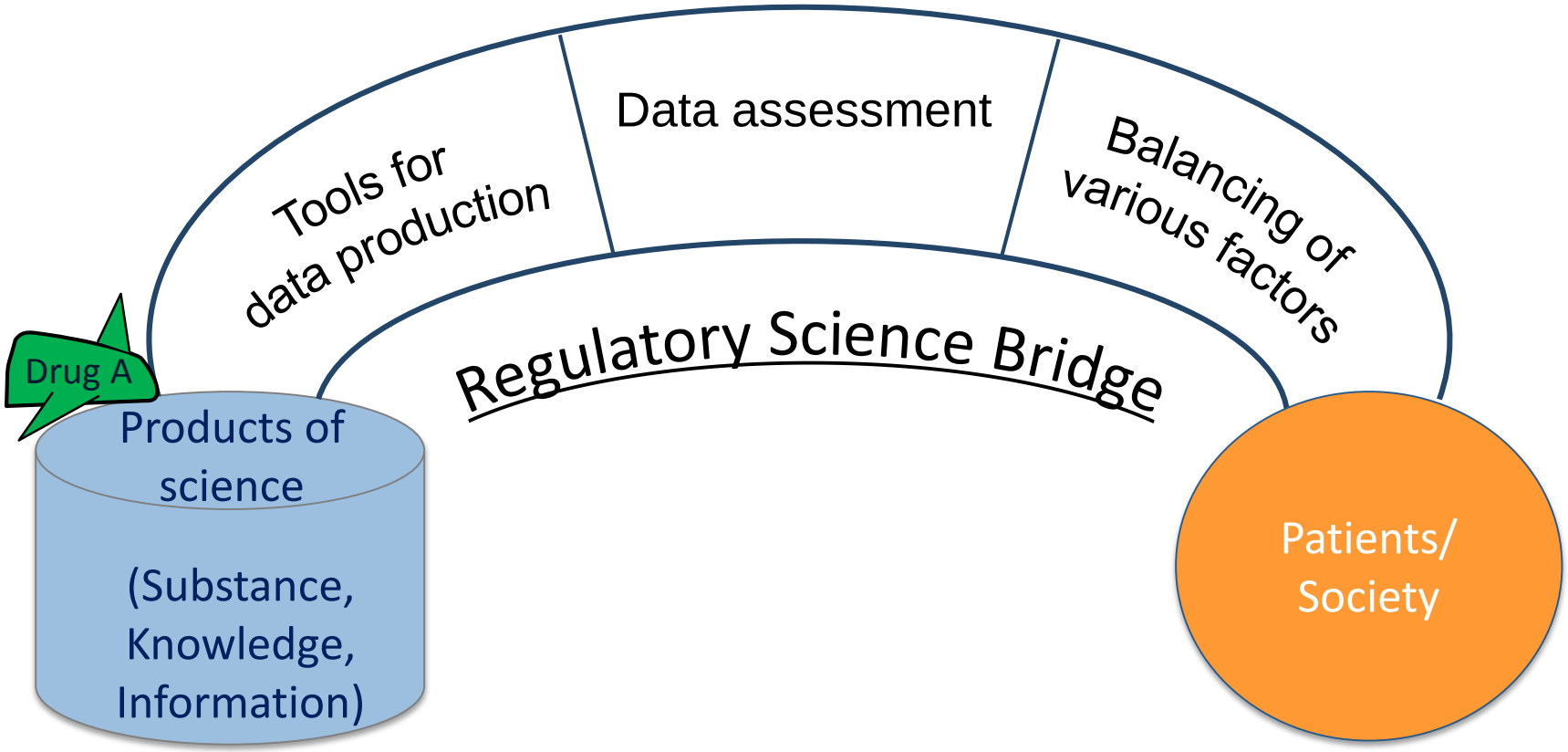
- Epoch-making proposal leading the world
- Proactive publication of guideline

Regulatory Science Bridge



Tominaga T et al, *Clin Pharmacol Ther*, 90: 29-31, 2011

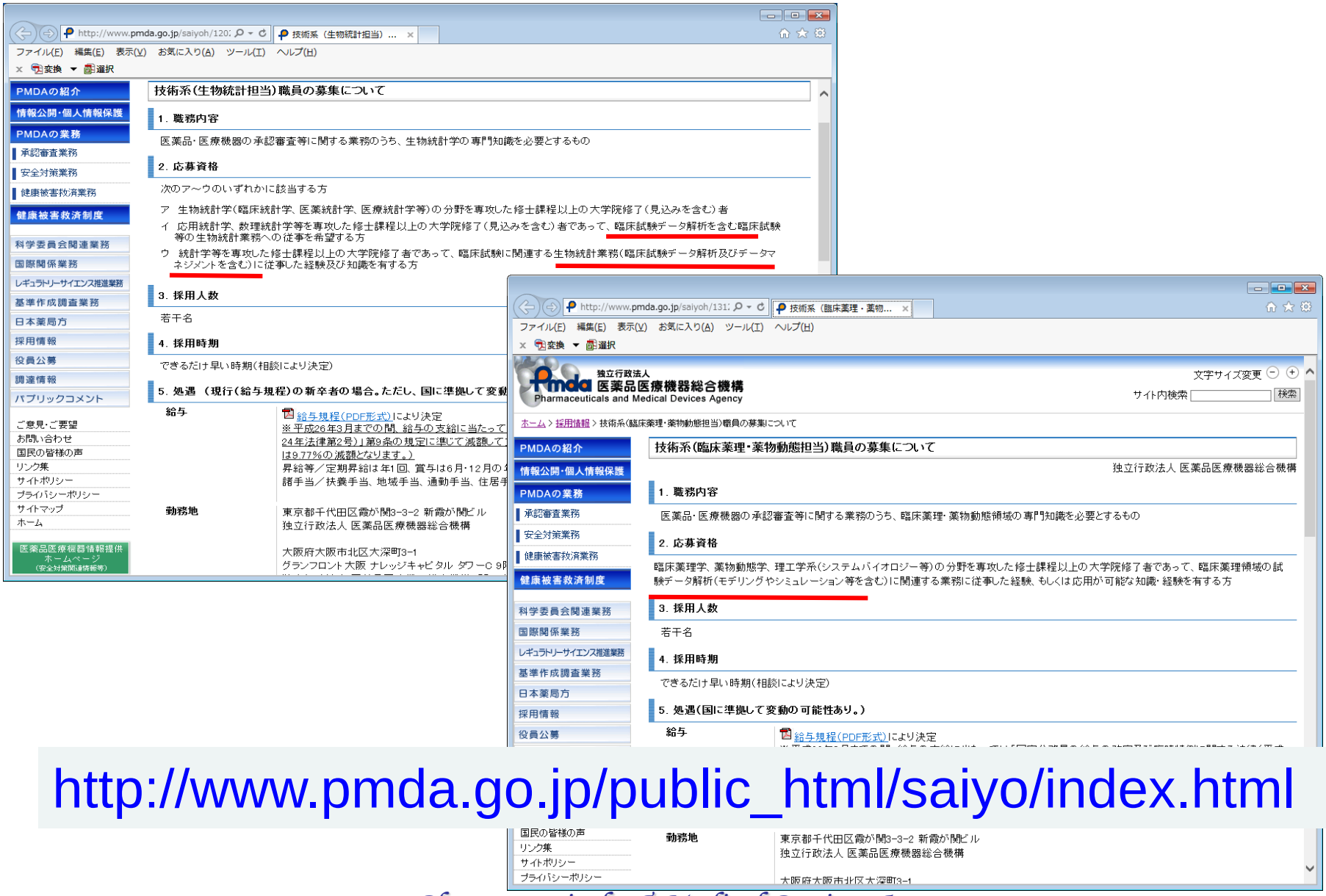
Regulatory Science Bridge



Stronger & More Complete Regulatory Science Bridge will help us in the future drug developments

Tominaga T et al, *Clin Pharmacol Ther*, 90: 29-31, 2011

Staff Recruitment



http://www.pmda.go.jp/public_html/saiyo/index.html

Information

- **PMDA HOMEPAGE (English)**
  http://www.pmda.go.jp/english/index.html
- **E-mail:**
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Thank you for your attention