エンス・サミット），厚生労働省の改革は待ったなしの必要性に迫られている。

今後の展望：産官学連携に向けて

川上氏は私見としながらも，PMDAあるいは日本版FDA（新組織）の創設により，臨床試験（治験および臨床研究）の審査・認可業務の一元化が望まれると述べ，京都大学の創薬・バイオ人材養成プロジェクトの取組みを照会しつつ，産官学連携の道を提示して講演をまとめた。

Future Perspectives: Collaboration among Industry, Regulatory Agency and Academia

"Although it is my personal opinion", says Prof. Kawakami, "I propose that PMDA or another new organization just like Japanese FDA, should consolidate the double pathways into one". By introducing a collaborative way among industry-regulatory agency-academia, which is currently planned at Kyoto University, he rounded up his lecture urging the necessity for the Japanese regulatory agency's urgent improvement.

〈川上浩司氏のプロフィール〉

筑波大学医学専門学群卒，横浜市立大学大学院医学研究科頭頸部外科学卒，医学博士。米国FDAの生物製剤評価研究センター（CBER）にて細胞遺伝子治療部臨床試験（IND）審査官，研究官を歴任後，米国内で大学，研究施設，企業からFDAに提出された遺伝子・細胞治療，癌ワクチン等に関する臨床試験の審査業務および行政指導に従事，その後，東京大学大学院医学系研究科 先端臨床医学開発講座客員助教授を経て，2006年3月より京都大学大学院医学研究科薬剤疫学分野の2代目教授として就任（初代教授は福島雅典氏）。認可行政システム，先端医療に用いる新規医薬品・生物製剤の研究開発，臨床試験，市販後評価を通じて，当該製剤の薬理・薬効・副作用などをレギュラトリーサイエンスとして科学的に研究し，そのエビデンスに基づいて社会と対話をしていくことを基本理念としている。

現在，京都大学大学院医学研究科 薬剤疫学分野教授，および，シンガポール国立大学薬学部準教授を兼任。

Koji Kawakami, M.D., Ph.D.

Professor, Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University

After graduating from Tsukuba University School of Medicine, Japan (MD), served as Postdoctoral Fellow at CBER/FDA (USA) during 1999-2001.

Acquired PhD degree from Yokohama City University Graduate School of Medicine, Japan. Then worked as a Visiting Associate (IND Reviewer and Researcher) at CBER/FDA from 2002 to 2004. Appointed as Associate Professor, Department of Advanced Clinical Science and Therapeutics, Graduate School of Medicine, The University of Tokyo.

Currently, Professor, Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Japan (since 2006), also Adjunct Associate Professor, Pharmacy Department, National University of Singapore (since 2005).

Email: kawakami-k@pbh.med.kyoto-u.ac.jp

細胞治療や遺伝子治療の審査関連，INDに関するより詳細なFDAの考え方については下記のガイドラインを参照：
For more details, please visit the following:

- Guidance for Reviewers: Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy INDs.
  http://www.fda.gov/cber/gdlns/cmcsomcell.htm
- Guidance for Industry: INDs–Approaches to Complying with cGMP During Phase I (January 2006)
  http://www.fda.gov/cber/gdlns/indcgmp.htm
- Guidance for FDA Review Staff and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy INDs.
  http://www.fda.gov/cber/gdlns/gtindcmc.htm

RECIIS
Electronic Journal in Communication, Information and Innovation in Health
[www.reciis.cict.fiocruz.br]
ISSN 1981-6286

Original Articles

Clinical Research in Japan: Ways to Alleviate Unnecessary Regulatory Burdens

Koji Kawakami
Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University.
kawakami-k@pbh.med.kyoto-u.ac.jp

Hiroko Yamane
Graduate Institute for Policy Studies, Tokyo.
hiroko-yamane@nifty.ne.jp

Resumo

For drug discovery and development today, synergy between pure science, clinical research, and the organization of clinical trials is essential. In Japan, there is a delay in the institutional response to this need. This paper identifies one of the bottlenecks in the Japanese regulatory process. Clinical research undertaken by university researchers and medical doctors are not integrated into the Japanese drug approval procedure. Therefore, their efforts and research data are wasted in the inherently unpredictable nature of long and costly biomedical research. Collaborative efforts between companies and researchers/medical doctors should be encouraged through institutional incentives, by integrating university and medical clinical research *ab initio* into regulatory process. In order to achieve this, it would be necessary to promote commercial exchange of database information and short-term employment of researchers in those projects leading to regulatory approval.

Keywords

Biotechnology, biologics, drug development, regulatory science, clinical trial

1. Introduction

Across the world, the advent of genomics, genetics, and proteomics has posed a massive challenge to university researchers, pharmaceutical companies, and regulators alike. For drug discovery and development, the paradigm change in the late 1990s was radical. A wide range of new in-vitro technologies and techniques for animals and humans replaced traditional chemical manipulation, requiring not only more sophisticated investments, but also further education in science, basic research, and biotechnology. For companies, a massive increase in regulatory requirements both in the pre- and post-launch periods resulted in significant changes in risks and benefits. For regulators, the need to ensure non-toxic, safe and effective drugs has led to significant delays in developing new criteria for judging whether medical inventions submitted for examination are indeed safe and effective. Concomitant to these difficulties, risks of over-regulation inadapted to actual needs have increased.

Since such a paradigm shift occurred, drug development has become closely linked to, and dependent on, the advancement of science and basic research. The new domain of research that arose from such a drug discovery process can be called "bio-pharmaceuticals" and it includes molecular-targeted

drugs against causal genes of diseases. Thus, researchers and companies have been drawn to work in the fields which are more or less common.

This paper attempts to identify bottlenecks in Japanese regulation and proposes ways to eliminate what seem to be archaic overlaps. In doing so, we aim at exploring the complex issues involved in fostering inventions in medical research that regulatory authorities may face, particularly in countries where universities and commercial companies had little in common before the introduction of bio-pharmaceuticals.

2. Common fields: biologics

According to the definition given by the Center for Biologics Evaluation and Research (CBER) at the U.S. Food and Drug Administration (FDA), biologics are materials derived from "living sources", such as cells/tissues and genes of humans, animals and/or microorganisms. Most biologics are manufactured using biotechnology, including gene manipulation.

They may offer effective means to treat a variety of medical illnesses and conditions that presently have no other treatments available. Examples of such treatments are cellular and gene therapy, vaccines, allergenics devices such as HIV test kits, and xenotransplantation.

In Japan, in comparison to the U.S. and the U.K., basic research in such fields as cell and tissue therapy, blood substitutes, and gene therapy has been relatively successful, whereas the development of therapeutic classes utilizing the technologies which are more closely related to genetics are lacking, as shown in Table 1.

Japanese regulatory paths, which are highly complicated for all fields of pharmaceuticals, are even more complicated for biotechnology products derived from cells, genes and tissues, which are regulated very strictly. For example, before submitting a clinical trial

Table 1: Comparison of Biologics under Development -Japan and U.S. (U.K.)

Biologics	Japan	USA (*UK)
Gene Therapy	**Anges MG** HGF vascular disease(angiogenesis) {P2 in Us,P3 in Japan}	**Introgen** Adenovirus-p53 (head&neck cancer) {P3}
	Oncolys BioPharma Telomelysin®(hTERTp-Ad5,for vaious solid tumors) {P1 in US}	
Cancer Vaccines	**GreenPeptide, Co.** Peptide vaccine- "Tailormade"{P1 in Japan}	**Vical, Inc** Malignant melanoma DNA vaccine(HLA-B7) {P2}
		Cell Genesys GM-CSF(GVAX) for prostate cancer {P3}
Cell&Tissue Therapy	**BCS, Inc** Autologous skin regeneration {preclinical}	***Intercytex (UK)** Topical woundcare product for persistent choronic wounds {P3}
Blood Substitutes	**Oxygenix, Co.,Ltd.** Artifical Red Blood Cells(OXY-0301) {preclinical}	
RNAi		**Alnylam Pharmaceuticals** Direct RNAi™, ALN-RSV01(respiratory syncytial virus) {P1}
		Sirna Therapeutics, Inc.** Sirna-027(siRNA for AMD) {P2} (** acquired by Merck in Oct. 2006)

application to the regulatory agency, the applicant must first apply to the same agency for review regarding the chemistry, manufacturing, and control (CMC) of the product. Thus, biotechnology therapeutics must go through multiple review processes before entering the clinical trial stage.

The hope Japanese industries placed in the future of Japanese biotechnology was, for a certain period of time, overwhelming. Approximately $ 1 billion was invested in the field by 2004 to create a "mini-bubble". However, the expectations fell dramatically because the efficacy of the investment was difficult to achieve. It appears that this disappointment came from the impression that regulatory mechanisms and institutional structure are not functioning favorably for the rational use of resources.

3. Regulatory paths in Japan

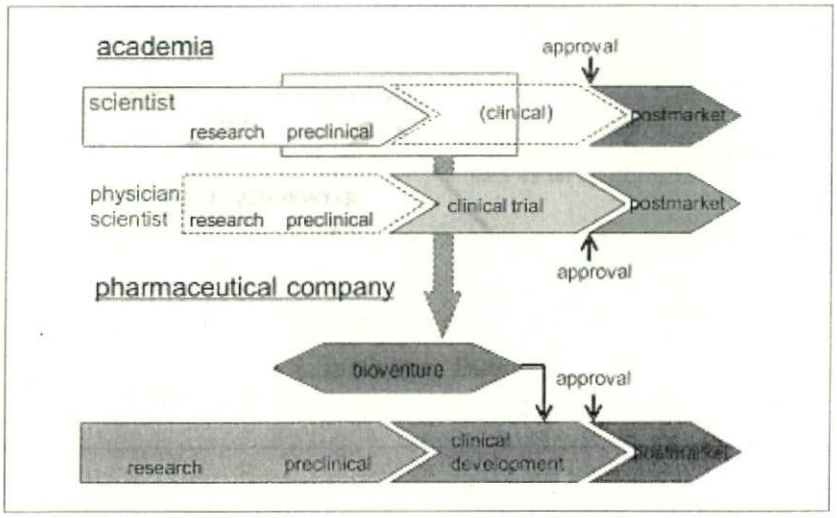
The process of discovering, developing, and obtaining regulatory approval for a medical invention involves "pre-clinical" and "clinical" stages. The pre-clinical stage consists of exploratory research, with a view to identifying drug candidates. These candidates are then further tested and developed until sufficient information is acquired, through both in-vitro and animal studies. The clinical stage requires a series of human clinical studies. The process may lead to regulatory approval, which has become increasingly rare. In the context of the pre-clinical stage, it may be difficult to distinguish between exploratory research and development, on the one hand, and testing to obtain regulatory approval, on the other.

In this process where science, medicine and industry intermingle, one of the difficult questions is who leads the process of applying for clinical trials amounting to drug approval. In the U.S., companies, academia, and bio-venture companies from universities are called "sponsors", and all of them can submit an Investigational New Drug Application (IND) to the FDA. They are subject to FDA control without exception. This provides different stake-holders such as researchers, medical doctors, and pharmaceutical companies with flexibility in drug development.

In Japan, by contrast, under the pharmaceutical affairs law (called "Chiken" in Japanese) clinical trials can be sponsored only by pharmaceutical companies. These trials, to be performed by physicians and researchers, constitute a separate category called "clinical research" of unapproved therapeutics, which is also regulated under the medical affairs law. Generally, the term "clinical research" is understood to be "patient-oriented research" partly comprising medical treatment. However, in Japan, this includes clinical testing not only of approved drugs for the purpose of expanded use but also of non-approved drugs, which is performed only by medical doctors and only in hospitals. Clinical research has become increasingly important for biological and therapeutic drug development, for the purpose of ameliorating the efficacy of the existing drug or enlarging its therapeutic scope. This is partly because recent biological drugs and treatments target individual genetic or other particularities that cause the diseases in question rather than symptoms.

Importantly, those who undertake clinical research cannot obtain any approval from drug regulatory authorities called the Pharmaceuticals and Medical Devices Agency (PMDA). Clinical research may be integrated into the "Chiken" process led by pharmaceutical companies, but this requires that researchers and medical doctors decide in advance on the purpose of their research. Moreover, clinical data obtained from initial clinical research cannot be used in "Chiken" protocol design and drug approval.

Chart 1: The Role of Academia and Pharmaceutical Companies



This system of completely separating clinical research from the drug approval process has two kinds of inefficiencies. If clinical research yields promising results for drug development after years of work, the team has to return to the initial stage of clinical trials to go through the "Chiken" process, as Chart I shows. Secondly, the two separate systems have no common information database to share.

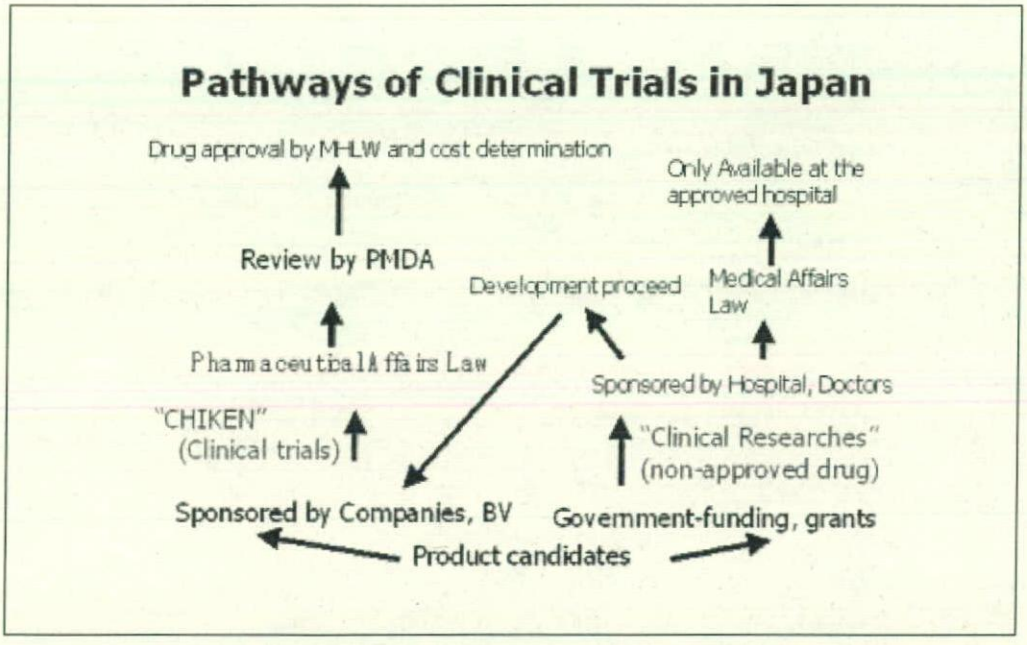
What should be the direction of regulatory reform? First of all, regulatory approval systems should be conceived of on the principle that researchers and medical doctors are given the option to use their clinical data for regulatory approval purposes when they think appropriate, taking into account the inherently unpredictable nature of long and costly biomedical research. This means that any rigidity at the entry level should be avoided. Secondly, collaborative efforts between companies and researchers/medical doctors should be encouraged through institutional incentives. Examples of such incentives include mechanisms for encouraging commercial exchange of database information and short-term involvement or employment of researchers in projects leading to regulatory approval.

Most importantly, uniform and clear approval criteria should be established by the regulatory authorities. This last element is lacking in Japan, causing a significant waste of information, time, and professional skills. Japanese drug developers (*i.e.*, pharmaceutical companies) are justifiably frustrated because the guidelines are not clear and explicit enough in explaining what is necessary. Furthermore, there is no open door policy in the regulatory agency for any questions.

4. Further exploration

Each country has different administrative traditions for encouraging science, technology, and medical research. Today, synergy between pure scientific investigation, clinical research, and organization of clinical trials is essential in drug discovery and development. Vested interests of each institution (and each person) in the past administrative structure, as well as political struggle on ideological grounds, tend to have disproportionately negative impacts on the advancement of science and technology. Each country should evaluate the efficiency of its own administrative and regulatory systems for drug development in a collaborative and objective manner. The ultimate goal of drug regulatory agencies is to ensure safety and efficacy of drugs and therapeutics and that scientifically sound preclinical and clinical data can be accepted by all regulatory agencies of the world after the approval of multinational clinical trials. This means that "one size fits all" data packages for safety and efficacy should be standardized at the highest level for any serious strategy of drug development.0Inefficiencies in national regulations not based on science or reason should be re-examined as obstacles to sound drug and therapeutics development.

Chart 2: Pathways of clinical trials in Japan



* MHLW - Ministry of Health, Labour and Welfare

Bibliographic references

SPRINGHAM, D. G.; MOSES, V.; CAPE, R.E. Biotechnology: The Science and the Business, Second edition. Amsterdam: Harswood academic publishers, 1999.

Special report from the 3rd DIA multitrack workshop in Japan: Scientific review and clinical development of advanced therapeutics and biologics, Global Outsourcing Review, v. 9, p. 10-15, 2007.

KAWAKAMI, K.; PURI, R.K. Regulatory expectation during product development for tumor vaccines. Developments in Biologicals, v.116, p. 53-59, 2004.

About the authors

Koji Kawakami, M.D., Ph.D

Koji Kawakami, M.D., Ph.D., is a Professor and Chairman of the Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan. He serves also as a Senior Fellow (medicine) of the Japan Science and Technology Agency (JST-CRDS); and an Adjunct Associate Professor of the National University of Singapore (NUS), Singapore. After his training as a head and neck surgeon in Japan, Dr. Kawakami joined the Center of Biologics Evaluation and Research (CBER), United States Food and Drug Administration (FDA) and conducted a number of research projects in cytokine immunobiology, gene therapy, and targeted cancer therapy. In addition, serving as a regulatory product reviewer specialized in tumor vaccine and cancer gene therapy at the FDA, Dr. Kawakami had reviewed investigational new drug (IND) applications submitted from U.S. industries and academic institutes. Currently, Dr. Kawakami is conducting research projects focusing on drug health policy, pharmacoepidemiology, and targeted cancer therapies.

Hiroko Yamane

Hiroko Yamane is a Professor of Law at the National Graduate Institute for Policy Studies (GRIPS) in Tokyo, Japan. The Japanese government created GRIPS in 1997, mainly to train government officials both from abroad and from Japan, through M.A. or Ph.D. programs in Economics and Public Policy (http://www.grips.ac.jp). She specializes in Competition, Intellectual Property Rights and Trade Law. Her areas of study cover competition and regulation, licensing as well as various issues concerning Trade-Related Aspects of Intellectual Property Rights (TRIPS), such as research and development, public health, and biological diversity. Between 2004 and 2006, she was a member of the WHO International Commission on Intellectual Property, Innovation and Public Health (http://www.who.int/intellectualproperty).