Hitachi's Solutions Regarding Latest Trends in Pharmaceutical Regulations and Pharmaceutical Industry

Junichiro Tomimatsu
Kazuhide Furihata
Sei Murakami, Ph.D
Junko Ito
Eiichi Isoda
Haruhiko Araki
Jun Taniguchi

OVERVIEW: As an industry that provides products for protecting the public's health, the pharmaceutical industry is required to observe a great many regulations. Regarding these regulations, which have traditionally been set up individually according to different countries and regions, The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was set up in 1990 as a trilateral partnership between the regulatory authorities of Japan, the USA, and the European Union (EU). Since then, in cooperation with the main trade organizations of the pharmaceutical industry, the ICH has been standardizing regulations on drugs. In recent years, the pharmaceutical industry of Japan has steadily expanded into overseas markets and, consequently, has faced challenges concerning compliance with internationally standardized regulations. Moreover, accompanying the popularization of computers and the electronization of drug-application procedures, the improvement of regulations concerning this digitization is being continued. At the same time, as records and signatures required by pharmaceutical regulations become digitized, standards for assuring their reliability are being established. Orchestrating its collective strength and applying the experience it has accumulated up till now, Hitachi is supporting the pharmaceutical industry in its efforts to comply with the latest pharmaceutical regulations.

INTRODUCTION

HITACHI's relationship with the pharmaceutical industry goes way back to the 1940s, when the mass production of penicillin started immediately after the Second World War. Since becoming engaged in the construction of the first domestic culture plants for

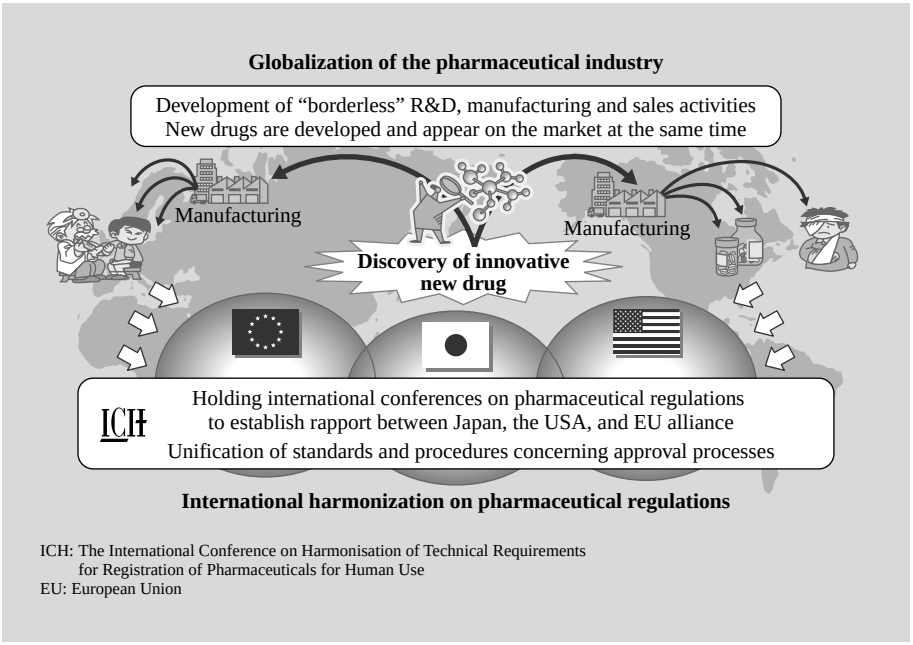


Fig. 1—Globalization of Pharmaceutical Industry and International Harmonization on Pharmaceutical Regulations. Globalization of the pharmaceutical industry does not just mean expansion of business operations, it means the realization of the fundamental philosophy of the ICH—namely, "providing better drugs more quickly to even more patients." Through the steady progress of international harmonization on pharmaceutical regulations between the alliance of Japan, USA, and EU, new drugs are being developed and launched simultaneously onto the world's markets.

manufacturing penicillin—by providing manufacturing facilities, analysis equipment, and computer systems—we have continually helped the pharmaceutical industry to support the rich and varied well-being of peoples' everyday lives.

In Japan, following the establishment of the present Pharmaceutical Affairs Law in 1960, GMP (good manufacturing practice)—which originally arose as a self-imposed guideline by the pharmaceutical industry—was established. After that, in the 1980s, for assuring ethical practices and reliability concerning research and development, the GLP (good laboratory practice) was established as a performance standard for nonclinical studies regarding safety, and the GCP (good clinical practice) was established as a performance standard for clinical trials. Furthermore, keeping up with the times, Pharmaceutical Affairs Law has been revised, and regulations regarding pharmaceuticals have been modernized. To support the pharmaceutical industry under these circumstances, Hitachi has been making great efforts to support compliance with these regulations.

At the present time, the pharmaceutical industry is reaching a turning point. That is to say, it is not only expanding globally but, at the beginning of the 21st century, it is also facing up to the proposition of "providing better drugs more quickly to even more patients" as it meets major challenges posed by reform of pharmaceutical legislation. Several years have passed since the 1990s, and efforts made to tackle this proposition head on—through international cooperation on pharmaceutical legislation—are bearing fruit. Moreover, at the same time as posing major challenges, this mighty swell of international effort looks like bringing about big chances for the pharmaceutical industry (see Fig. 1).

The rest of this report first describes the trends in international legislation related to the pharmaceutical industry, and then discusses the efforts of Hitachi in supporting the pharmaceutical industry as it faces this turning point.

TRENDS IN REGULATIONS ON PHARMACEUTICALS

Main Domestic and Foreign Regulations

Since pharmaceuticals could have a fatal effect on peoples' lives, through development and manufacturing and up to sales, various regulations are imposed. In Japan, at the apex of Pharmaceutical Affairs Law, laws are enforced by the government ordinances or the Ministry of Health, Labour and Welfare ordinances. In the USA and European Union (EU), legislation is

TABLE 1. Main Pharmaceutical-related Regulations in Japan, USA, and EU
Since pharmaceuticals could have a fatal effect on peoples' lives, through development and manufacturing and up to sales, various regulations are imposed.

Classification		Japan	USA	EU
Law		Pharmaceutical Affairs Law	FDC Act, PHS Act	Legislation in each member states
Main regulations for separate fields	GLP	1997 Ministry of Health and Welfare, Ordinance No. 21	21 CFR Part 58	EudraLex Vol. 3B
	GCP	1997 Ministry of Health and Welfare, Ordinance No. 28	21 CFR Part 312 (IND) 21 CFR Part 314 (NDA) 21 CFR Part 601 (BLA), etc.	EudraLex Vol. 3C
	Application for approval	1961 Government Ordinance No. 11 1961 Ministry of Health and Welfare, Ordinance No. 1		EudraLex Vol. 2 (NTA)
	Safety monitoring	1997 Ministry of Health and Welfare, Ordinance No. 10 (GPMSP)		EudraLex Vol. 9 (Pharmacovigilance)
	GMP	1999 Ministry of Health and Welfare, Ordinance No. 16	21 CFR Part 210, 211 (cGMP), etc.	EudraLex Vol. 4
	Distribution	—	—	Council Directive 92/25/EEC (GDP)

GLP: good laboratory practice
GCP: good clinical practice
GPMSP: good post-marketing surveillance practice
GMP: good manufacturing practice
FDC law: Food, Drug, and Cosmetic Act
PHS law: Public Health Service Act
CFR: Code of Federal Regulations
IND: investigational new drug application
NDA: new drug application
BLA: biologic license application
cGMP: current GMP
NTA: notice to applicants
GDP: good distribution practice

enacted in a similar manner, as shown in Table 1. As well as the regulations shown in Table 1, more detailed standards have been established as guidelines. In this manner, regulations have traditionally been established by each country or region. As a consequence, in the case of either drug manufacturing or sales, pharmaceutical manufacturing businesses have established in-house operating rules according to compliance with these separate regulations.

In recent years, however, pharmaceutical manufacturing has continued to develop into a global business year after year. And although breakthrough drugs have been created as a result, from the viewpoint of businesses wanting to bring these drugs to all the countries of the world, two deep-rooted problems listed below are being faced.

(1) In line with regulations in different countries and regions, a huge number of applications for approval must be created and translated. Consequently, not only are huge costs generated at application times but excessive time is taken to get products onto foreign and regional markets.

(2) Even in the case of affiliated companies, separate operation rules must be established according to different locations, making cost reduction difficult.

In particular, as regards to the time taken to get products onto markets, not only are problems being faced by businesses, but also voices are being raised from the viewpoint of the public benefits of so-called "providing better drugs more quickly to even more patients".

International Harmonization on Regulations

Aiming for collaboration on regulations through the unified efforts of major pharmaceutical-industry organizations and the regulatory authorities of Japan, the USA, and the EU, "The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)" was inaugurated in 1990.

At the ICH—which is focused on the four key propositions "quality," "safety," "efficacy," and "multidisciplinary"—a lot of EWGs (expert working groups) have been set up and studies are being vigorously pursued. In November 2003, with Japan acting as the host nation, ICH6 (the Sixth International Conference on Harmonization) was held in Osaka.

Up till today, the international collaborative efforts of the ICH have made various achievements in the five main fields summarized below:

(1) Safety

Guidelines for nonclinical studies for verifying the safety of drugs, such as various toxicology studies and safety-pharmacology studies were drawn up. In Japan, these ICH guidelines are reflected in the GLP ordinances and related notifications.

(2) Efficacy

Under the ICH E6 guidelines drawn up in 1996, international cooperation concerning GCP was attempted. In Japan, GCP regulations made public in 1997 were based on the ICH E6 guidelines. At the same time in the USA, the FDA (Food and Drug Administration) announced similar GCP guidelines. As for the EU, although the unification of GCP guidelines was delayed because of the different circumstances in member states, in accordance with European Parliament Directive 2001/20/EC, GCP guidelines based on ICH E6 became compulsory for all member states (excluding counties that joined the alliance in 2004) on May 1st, 2004.

(3) Quality

In 2000, the ICH Q7A guidelines—GMP for Active Pharmaceutical Ingredients—were established. The details of these guidelines have already been acknowledged by each member of the trilateral alliance between Japan, the USA, and the EU. In Japan, the ICH Q7A guidelines are being enforced as a supplement to existing GMP regulations. Moreover, in fields other than bulk drugs, investigations on implementing GMP guidelines are continuing.

(4) Multidisciplinary

Up to this day, as a unified format for the technical and scientific documents affixed to the applications for approval that had been separately established in Japan, the USA, and the EU, the CTD (common technical document) was devised and finally agreed upon by the affiliate members in 2002 (see Fig. 2). At present, in Japan and the EU, it is stipulated that the preparation of supporting data abides by the CTD format. In the USA, the CTD format is being strongly recommended. In addition, eCTD, that is, the electronic format of CTD—which utilizes XML (extensible markup language)—was devised and received final approval in November 2003. And taking the lead in the world, Japan's Ministry of Health, Labour and Welfare has given official approval to launch completely electronic approval applications by eCTD from April 1st 2005.

(5) Collaborative studies on efficacy and multidisciplinary

As advanced drugs with powerful efficacy are developed, cases of serious side effects—caused by

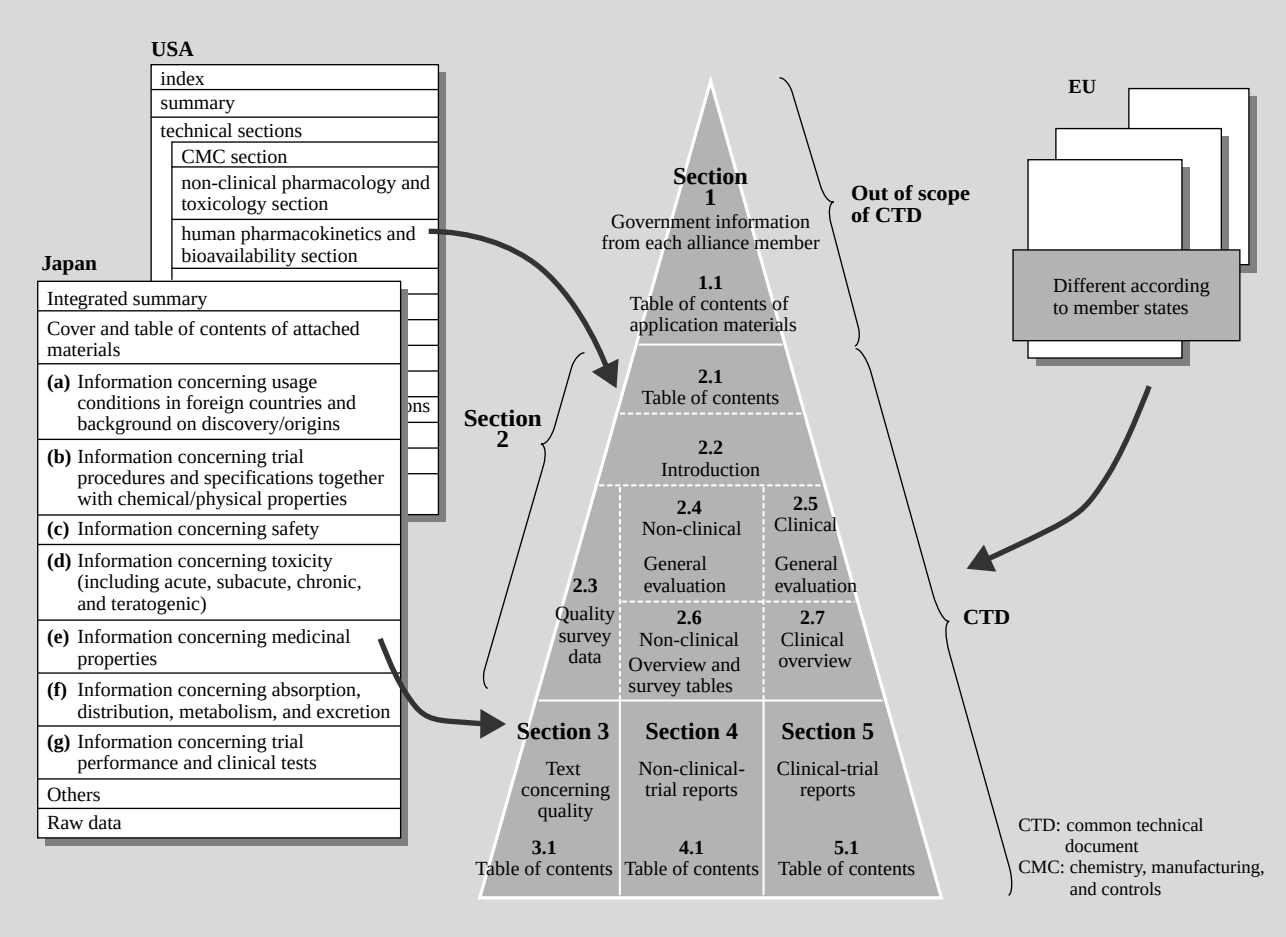


Fig. 2—Overview of Unified Format for Application for Authorization of Pharmaceuticals.
The format of materials for application for authorization of pharmaceuticals is unified as a standard called the "Common Technical Document" or CTD.

constitutional predisposition, disease complications, and simultaneous dose of drugs—are being increasingly seen. In some cases, rare constitutions and diseases are acting as the trigger. Under such complicated circumstances, by means of nonclinical and clinical studies before application for authorization, it is difficult to spot such side effects being generated. For swiftly gathering and sharing information on monitoring of drug safety after products are marketed (known as "pharmacovigilance"), electronic standards for ICSRs (individual case safety reports) were established. Although trials using electronic ICSRs have already started in Japan, the USA, and the EU, some technical uncertainties have been pointed out, so ICSRs are currently still under study.

As for collaborative efforts other than ICH, MRAs (Mutual Recognition Agreements)—set up before the inauguration of the EU to promote trade within European countries—still play an important role. In the wake of the international collaborative efforts on pharmaceutical regulation by the ICH, in 2002, pharmaceutical GLPs and GMPs were included in the MRAs concluded between Japan and the EU. This means that regulations from one country can be considered equivalent to the home-land regulations of another country, and inspections regarding GLP and GMP in pharmaceutical businesses and facilities of the other countries' pharmaceutical businesses can be abbreviated or omitted. As for drugs produced domestically, since GMPs in the EU have many accompanying documents called "Annexes," the coming into effect of MRAs was postponed, and investigations were continued up until MRAs came into full effect on May 29, 2004.

In addition to the above circumstances, the revised Pharmaceutical Affairs Law enforced from April 2005 will also play an important part in international harmonization on pharmaceutical regulations. In Europe and the USA, marketing (i.e. wholesales) of

drugs has to be authorized. On the other hand, in Japan, "manufacturing" has to be authorized. As regards the revised Pharmaceutical Affairs Law, manufacturing and marketing in Japan that is to say, "manufacturing" includes commissioning to others but does not include being commissioned by others; and "marketing" includes selling, leasing, and awarding drugs (excluding bulk drugs) are authorized by the Ministry of Health, Labour and Welfare. By making the framework for drug authorization in Japan equivalent to that in the EU and USA, importation of drugs and commissioning of manufacturing can be made quicker than ever.

Regulations Regarding Electronization

In addition to application for approval by eCTD, growing demands for improving efficiency of various activities by means of computerization have become a matter of course in today's golden age of computing. However, in regards to GxP (i.e. generic terms for GLP, GCP, and GMP), to assure safety and quality of drugs, storage of various records and documents is obligatory, and the authenticity and reliability of this information —be it electronic or not—must be maintained.

In accordance with demands from the pharmaceutical industry, as a standard for assuring the necessary security when digitizing records and documents required by GxP guidelines, application documents, and signatures and seals provided, federal statute "21 CFR Part 11" (code of federal regulations, title 21, part 11) was enacted in the USA as the world's first such regulation. (Hereafter, 21 CFR Part 11 is simply referred to as "Part 11"). Up till now, adequacy of this regulation, including laws for unifying security standards related to electronic records and signatures, was judged in each individual field. To expand the scope of application of Part 11 not just for drugs but also other products regulated by the FDA (such as medical devices, food, and cosmetics), this regulation is currently being re-examined.

In Japan, under individual guidance and notification from the Ministry of Health, Labour and Welfare, computer use and electronization of records in each field are getting allowed. Moreover, firmly focused on the going on-line of various notifications according to the "e-Japan strategy" and the computerization of applications by eCTD, common guideline for electronic records and signatures were proposed in June 2003. And in August 2004, the final guideline—final draft according to solicited public comments—have been put under review by the Ministry.

Next-generation GMP

With the rapid advances made in manufacturing technology and computer technology, the improvements in quality-control engineering in the manufacturing world—particularly, chemicals, semiconductors, and certain food products—have been striking. In the pharmaceutical industry, when scaling up from pilot plants to mass production, efforts to improve quality by trial and error, various ideas, and activities in the manufacturing plant have been continuing for many years.

However, current GMP and authorization systems were established before quality-management systems such as the widely known ISO9000 standards and computer technology that surpasses today's simple automation were made public. Consequently, utilization of advanced technology can not help being limited.

As regards the FDA's "cGMP for the 21st Century," although quality and reliability of pharmaceutical products are assured, problems facing the implementation of new concepts and innovative technologies are being faced head on. Furthermore, modern concepts such as quality systems and risk management are being absorbed, studies that attempt to evolve GMP are being pushed forward, and new concepts like "comparability protocol" and "PAT (process analytical technology)" are being hammered out.

ACTIVITIES OF HITACHI

The environment surrounding the pharmaceutical industry—one that includes advance of genome-based drug discovery, reduction of medical expenses and penetration of EBM (evidence-based medicine)—is rapidly changing. Under such an environment, while following trends concerning regulations, pharmaceutical companies are focusing on the main themes listed as follows:

(1) Research, clinical development, and regulatory affairs: improving efficiency of drug discovery and speeding up putting new drugs on the market
(2) Production departments: improving production efficiency and strengthening quality management
(3) Marketing: developing strategic promotions

With these themes in mind, Hitachi is providing solutions spanning research and clinical-development departments up to sales departments (see Fig. 3). Each solution is implemented in order to reflect trends concerning regulations in the pharmaceutical industry. In addition, offering a wide range of support—from

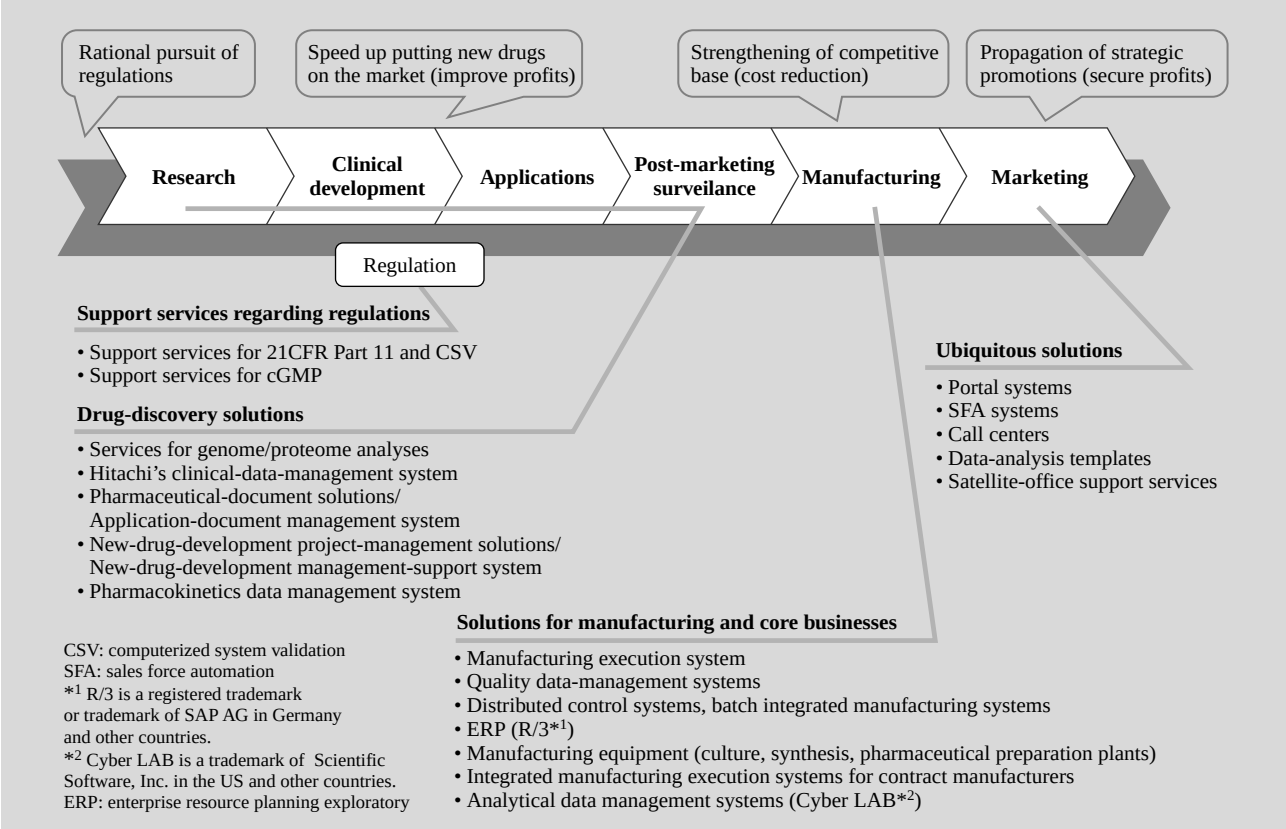


Fig. 3—Hitachi's Solutions and Representative Affairs in the Pharmaceutical Manufacturing Industry. Covering exploratory research to production and launch in the market, Hitachi is developing a broad range of solutions.

information systems and devices to plant machinery, various equipment, and consultation services (mentioned later)—Hitachi is making great efforts to respond appropriately to the needs of the pharmaceutical industry.

The activities of Hitachi are in the fields that regulations have significant impact on, such as (1) the research, clinical trials, and regulatory affairs fields, and (2) the manufacturing field are described in the following two sub-sections.

Activities Aimed at Research, Clinical Development, and Regulatory Affairs Fields

Aiming at making the drug-discovery process more efficient, and knowing the importance of improving business processes in order to shorten development times and meet CTD/eCTD requirements, Hitachi is developing solutions to tackle these challenges.

As regards improving efficiency of operations involved in clinical trials, information exchange between hospitals and drug companies is in the limelight. Mainly done by paper up to now, such information exchange can be done electronically in line with GCP revisions. Accordingly, Hitachi has added an EDC (electronic data capture) function—which gathers case data from facilities such as medical institutions directly through a network—as an option to Hitachi's "clinical-data management system." By utilizing digital signatures based on PKI (public key infrastructure) technology, this system aims to assure security.

Moreover, to improve correspondence with CTD/eCTD requirements and operation efficiency in regulatory affairs sectors, Hitachi is putting forward suggestions for improving the application process, and providing computer systems for supporting them. Processing new-drug approvals by CTD and eCTD does not just involve gathering and sorting out application materials close at hand in the conventional way; instead, it involves efficient methods for advancing the drug-discovery process at the same time as amassing application materials. Hitachi is providing integrated services regarding CTDs. These services range from (1) consulting on format standardization of final reports and (2) rule formulation for document-management operations to (3) operational support for

systems constructed around a core composed of application-document management systems, and (4) operational support after such systems have been set up.

As for the drug-discovery process, long-term activities have been continuing for over 10 years. Today, we consider such activities as "projects," where cases of applying project-management techniques acquired in the construction and IT industries have increased. Management support systems for new-drug development—namely, Hitachi's "new-drug development management solutions"—provide support for managing the new-drug discovery process, from daily scheduling management up to long-term management applying project-management techniques. In recent years, experiments applying portfolio management, which originated in the field of financial engineering, are also being performed, and Hitachi is developing solutions in response to such trends.

Activities Aimed at Manufacturing

To assure efficient production of safe drugs and their stable supply to markets, while complying with GMP, another important theme facing the pharmaceutical industry is continuously reducing costs by improving production efficiency. Moreover, it is necessary to establish efficient production systems in response to the emerging new business model due to revision in Pharmaceutical Affairs Law. At Hitachi, providing support in facing these challenges, we are developing a variety of solutions—such as optimizing design and construction of drug-manufacturing plants, IT systems (manufacturing execution and quality control) for improving operational efficiency, and backbone systems for integrating resource management from production up to distribution.

For drug-manufacturing plants, it is necessary to respond to the conditions appropriate to meet GMP requirements regarding condition of each room, appropriate equipment selection and validation of equipment. With over 50 years of experience, Hitachi has been not only designing and constructing plants but also providing comprehensive backup for GMP requirements. In particular, as regards plants for manufacturing bulk drugs, we are also providing support for meeting the ICH Q7A guidelines.

The revised Pharmaceutical Affairs Law, fully implemented in April 2005, is opening up new possibilities in the field of drug production. By completely commissioning drug-production operations—from production of bulk drugs up to packaging—the options for reducing costs are expanded. On the other hand, for contract manufacturers, it is ever more important to meet challenges like responding to multi-item production, strengthening price competitiveness by establishing low-cost systems, and complying with GMP rationally. Up until now, it has been basically assumed that integrated production-management systems have been constructed with a combination of multiple packaged software. For supporting solutions to propositions imposed on contract manufacturing businesses, on top of providing our manufacturing execution—namely, the Hitachi manufacturing execution system—Hitachi is enabling construction of integrated production-management systems with a single software package.

As well as the above systems, we have pushed forward with Part 11 compliance with our integrated instrumentation system, which works effectively with monitoring and control systems. And we are providing our LIMS (laboratory-information management system) product for improving efficiency of quality-control operations. Furthermore, as regards construction of backbone IT systems based on R/3 architecture, responding to document output matched to actual conditions in Japan, we are attempting further improvement in business-operations efficiency through cooperation with our manufacturing execution system.

FACING NEW CHALLENGES

Expansion of Products Meeting Part 11

In the process for providing various computer systems to the pharmaceutical industry, since 1997, meeting Part 11 has become inevitable. And as regards Hitachi's products, we have added functions that meet Part 11 requirements.

Since Part 11 was announced, starting with HPLC (high-performance liquid chromatography), a wide variety of equipment fitted with functions that meet Part 11 has appeared on the market one after the other. However, the resulting increased management load, for example, due to different user management for each equipment vendor, is causing concern. In response to that concern, by connecting various analytical devices to a network and providing solutions through "CyberLAB KES" system for unifying management, we are lightening the load on individual management systems and making it possible to efficiently meet Part 11.

Starting up Part 11 Consulting Services

In regards to establishing computer systems, it has

become understood that meeting customer requirements to satisfy "Part 11 compliance" faces the common problems described below.

To begin with, simply using software that meets Part 11 is not sufficient to comply with Part 11. That is to say, complying with Part 11 not only means meeting the necessary requirements with capabilities of computer systems, it also means laying down requirements that must meet the operational procedures of pharmaceutical companies. Moreover, confirming whether computer systems used under GxP have sufficient functions and performance must be verified by means of CSV (computerized system validation). And the same applies to functions for meeting Part 11. As regards compliance with Part 11, an integrated action is needed (see Fig. 4).

To comprehensively understand and adhere to the provisions of Part 11 correctly—which is sometimes apt to be seen abstractly—the "spiral model" (put forward as a software-development model in recent years) and the "plan, do, see, act" approach are effective in the case of management systems (see Fig. 5). In the rule-creation step, rather than agonizing over the task as a desk job, it is more efficient to try out interim rules in pilot projects, and to reexamine them according to the pilot results. Even when the rules are implemented corporate wide, it is less risky to enlarge their scope gradually and reconsider them on seeing the result of enlargement as appropriate.

Getting to grips with the challenges mentioned above, Hitachi is utilizing its know-how gained through implementation of computer systems, and has launched consultation services independently of system-integration services, and has gained outstanding results.

Proper Management of IT Infrastructure

As the application range of computer systems gets wider, new problems are becoming apparent. The chances to apply IT infrastructure, such as in-house common networks, shared servers, user-authentication platforms, and distributed PCs, have increased in departments regulated by GxP. As a result, when implementing applications to meet GxP, it is necessary to implement CSV that includes IT infrastructure. Moreover, if the IT infrastructure changes without acknowledging GxP departments, the eligibility of computer systems being used in a certain GxP area might end up being questioned.

As a result of these circumstances, the idea of "IT infrastructure qualification," in which components of CSV concerned with IT infrastructure are standardized, efficiency of CSV is improved when implementing application softwares complying with GxP guidelines —has been studied, mostly by pharmaceutical companies in the USA, since 2002. As a result of trend research in the USA and Europe, new solutions are under development even in these fields. Moreover, Hitachi is aiming at creating synergy between its knowledge as an IT infrastructure integrator and as a service provider.

As regards managing IT infrastructure, the ITIL (IT Infrastructure Library)* developed as a

* ITIL is a registered trademark of OCG—the Office of Government Commerce.

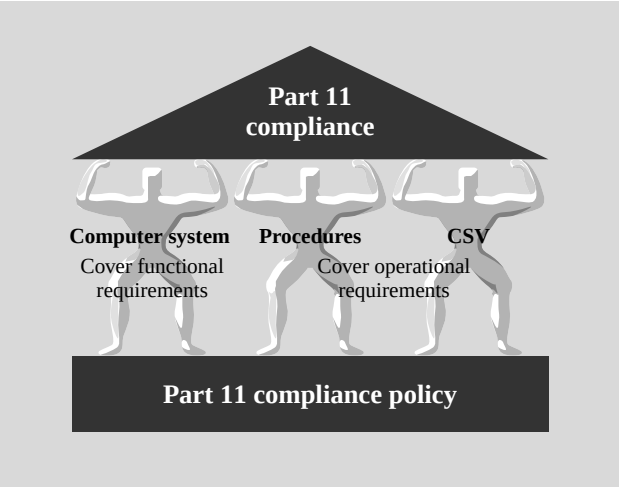


Fig. 4—Supporting "Part 11" Compliance.
Based on Part 11, a trinity of computer systems, operational procedures, and CSV supports compliance with Part 11.

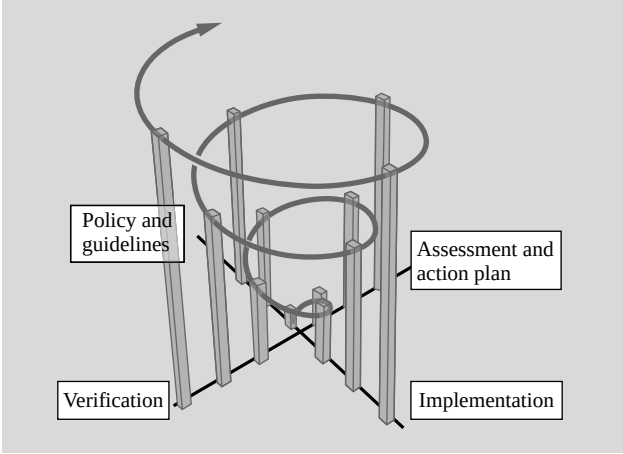
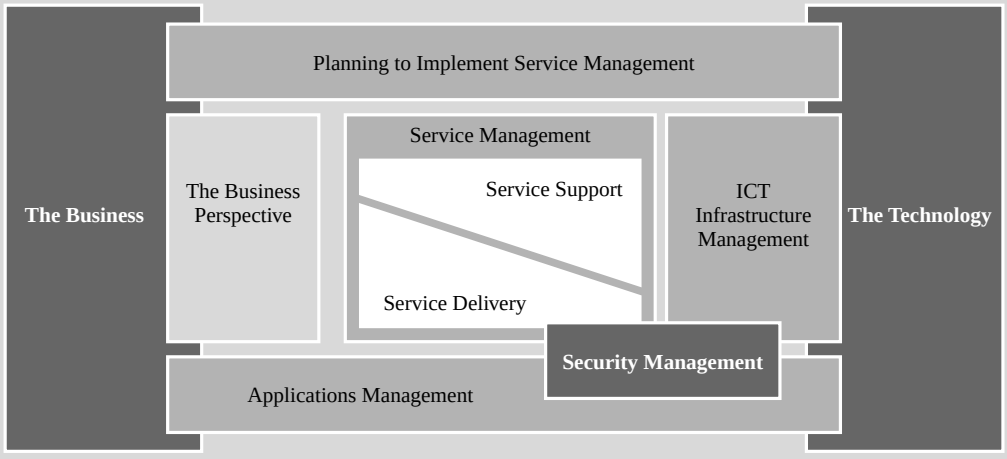


Fig. 5—Spiral Model Expressing Activities for Part 11 Compliance.
The effect of implementing an action plan based on a compliance assessment is verified, and this information is fed back into the corporate policy and guidelines.



ICT: information and communications technology

Fig. 6—Framework of ITIL. ITIL consists of seven books spanning the fields of business and technology.

procurement specification for the UK government, — which is now being studied to be an international standard at the ISO (International Organization for Standardization) as one and only, systemized framework for "IT service management" in the world today—is drawing much attention (see Fig. 6). In Europe and the USA, some companies implemented ITIL corporate-wide, and improved their expenses. Moreover, in the guidelines for IT-infrastructure management created by the GAMP (Good Automated Manufacturing Practice Forum), the body that compiles the de facto standards for CSV, in the published schedule for Autumn 2004, ITIL has a significant influence. As for Hitachi, one of Japan's affiliated founding members of itSMF (IT Service Management Forum — the private body that supports the popularization, publication, and management of ITIL), we are applying our knowledge in making efforts to apply ITIL in the pharmaceutical industry.

CONCLUSIONS

This report described international trends in regulations related to pharmaceuticals and presented Hitachi's efforts in supporting the pharmaceutical industry at the turning point.

Hitachi has also started to make efforts in regards to PAT (process analytical technology) — the new framework for quality improvement that first saw the light of day in the USA. In regards to chemicals, construction of pharmaceutical plants, and especially culture plants, Hitachi has the top share in Japan, and covering instrumentation, control, and up to analysis equipment, we are one of the integrated manufacturers handling all the components and equipment needed for PAT. We are fusing the collective strength in the device and equipment fields with the intellectual ability of our research centers and our knowledge gained from our accomplishments aimed at other businesses. Moreover, cooperating with the pharmaceutical industry, we aim to contribute to even more growth of drug-quality-improvement technologies that Japan can be proud of.

From now onwards, swiftly sensing the latest trends in regulations, we at Hitachi are making use of integrated, state-of-the-art technologies and, through cooperation with the pharmaceutical industry, we will strive to contribute even more to realizing a healthy, fulfilling life for all.

This paper was translated from a paper that first appeared in Japanese in *Hitachi Hyoron* Vol. 86, No. 10 (Oct. 2004).

REFERENCES

(1) Ministry of Health, Labour and Welfare: Pharmaceutical Industry Vision, Aug. 30, 2002 in Japanese.
(2) Pharmaceutical Affairs Law, August 10, 1960, Law No. 145; latest revision July 2, 2003, Law No. 102 in Japanese.
(3) Ministry of Health and Welfare: Ordinance Regarding Standards in Conducting Nonclinical Studies Related to Safety of Pharmaceuticals, Mar. 16, 1997, Ordinance No. 21; latest revision July 20, 2000, Ordinance No. 127 in Japanese.
(4) Ministry of Health and Welfare: Ordinance Regarding

Standards in Conducting Clinical Studies Related to Pharmaceuticals, Mar. 27, 1997, Ordinance No. 28; latest revision June 12, 2003, Ordinance No. 106 in Japanese
(5) Ministry of Health and Welfare: Regulations for Production and Quality Management of Pharmaceutical and Health-care Products, Mar. 12, 1999, Ordinance No. 16; latest revision May 20, 2003, Ordinance No. 95 in Japanese.
(6) Manager of Evaluation and Licensing Division, Pharmaceutical and Food Agency of Ministry of Health and Welfare: Electronic Specifications of Common Technical Document, May 27, 2004, Issued by Evaluation and Licensing Division, Pharmaceutical and Food Agency No. 0527004 in Japanese.
(7) Evaluation and Licensing Division, Pharmaceutical and Food Agency of Ministry of Health, Labour and Welfare: Collection of Information and Opinion Regarding "Draft Guidance for Utilization of Electro-magnetic Records and Electronic Signatures for Application Regarding Authorization or Consent of Pharmaceuticals and Others," Public Comments on June 4, 2003 in Japanese.

ABOUT THE AUTHORS

Junichiro Tomimatsu

Joined Hitachi, Ltd. in 1983, and now works at the Pharma and Biotech Systems Department, the Total Solutions Division. He is currently engaged in the management of solution business concerning pharmaceutical industry. Mr. Tomimatsu can be reached by e-mail at junichiro.tomimatsu.ee@hitachi.com.

Kazuhide Furihata

Joined Hitachi, Ltd. in 1982, and now works at the Medical Systems Management Department, the Industrial Systems Division, the Information & Telecommunication Systems. He is currently engaged in the management of a pharmaceutical IT solution business. Mr. Furihata can be reached by e-mail at furihata@itg.hitachi.co.jp.

Sei Murakami

Joined Hitachi, Ltd. in 1979, and now works at the Industrial Systems Division, the Power & Industrial Systems. He is currently engaged in the pharmaceutical manufacturing plant engineering. Dr. Murakami is a member of International Society for Pharmaceutical Engineering (ISPE), International Association for Pharmaceutical Science and Technology (PDA), The American Society of Mechanical Engineers (ASME), Japanese Association for Animal Cell Technology, Institution of Professional Engineers Japan, and can be reached by e-mail at sei_murakami@pis.hitachi.co.jp.

Junko Ito

Joined Hitachi, Ltd. in 1985, and now works at the Pharma and Biotech Systems Department, the Total Solutions Division. She is currently engaged in the management of business planning concerning pharmaceutical industry. Ms. Ito is a member of PDA, and can be reached by e-mail at junko.ito.qh@hitachi.com.

Eiichi Isoda

Joined Hitachi, Ltd. in 1993, and now works at the Pharma and Biotech Systems Department, the Total Solutions Division. He is currently engaged in the management of consulting service concerning regulatory compliance of pharmaceutical industry. Mr. Isoda is a member of ISPE, PDA, Drug Information Association (DIA), and can be reached by e-mail at eiichi.isoda.nf@hitachi.com.

Haruhiko Araki

Joined Hitachi, Ltd. in 1995, and now works at the Pharma and Biotech Systems Department, the Total Solutions Division. He is currently engaged in the management of consulting service concerning regulatory compliance of pharmaceutical industry. Mr. Araki is a member of ISPE, PDA, DIA, The Institute of Electronics, Information and Communication Engineers (IEICE), the Physical Society of Japan (JPS), and can be reached by e-mail at haruhiko.araki.yw@hitachi.com.

Jun Taniguchi

Joined Hitachi, Ltd. in 1995, and now works at the Pharma and Biotech Systems Department, the Total Solutions Division. He is currently engaged in the management of solution business concerning pharmaceutical manufacturing. Mr. Taniguchi is a member of ISPE, PDA, and can be reached by e-mail at jun.taniguchi.zv@hitachi.com.