論文のためには使えるかもしれないですが，社会に対して貢献できないのです。何故なら非GCPのデータは，医薬品としての承認を得るためのデータとしては世界中の規制当局から認められません。ということで，「臨床研究」をやればやるほど何が起こるかということを考えなければいけません。医薬品産業というのは，他の産業，自動車産業や電子産業とは異なり，垂直統合型の産業構造を持っていません。すなわち，例えばiPhoneなどはパッケージングされています。いろいろな部品が入っていて，パッケージング化してアップル社が売っている訳です。ところが，部品部品の特許を置換するものが使えれば，iPhoneではなくても，いろいろなスマートフォンが販売されるようになっています。

医薬品産業は，強力な物質の特許というものがありますと，これが1つのマーケットを形成し得ます。ということで，特許出願後に25年間，exclusiveにデータが保護されますが，25年間たった瞬間にジェネリック医薬品が入ってきて，売上ベースで90%以上売上が落ちてしまう，ということになる訳です。ということで，簡単にいえば，25年間の中で，出願してからいかに早く開発をして，いかに早く患者さんに届けるかということが，患者さんへのdrug availabilityという観点，そして産業化という観点，両方から非常に重要な訳でございます。ところが，この「臨床研究」という，治験以外の制度というものがありますと，ここでとられたデータというものは，GCP上でありませんので，承認のデータには使えません。ですから，「臨床研究」をやればやるほど，25年間のデータ保護期間が短くなっていってしまうのです。そうしますと，当然のことながら，産学連携もしづらいことになりますし，もう1回このデータをとり直すことになりますから，非常に無駄が多いということになってしまっています（表4）。

では，アメリカはこういうことをどういうふうに解決してきたのかといいますと，簡単にお話をしますと，薬というものに関して，Food, Drug, and Cosmetic Actという薬事法がありますが，これが，薬は安全で有効であるということを規定して，その検証をするために臨床試験という制度がつくられました（表5）。

この臨床試験という制度を担っているのがIND（Investigational New Drug）という制度です。これが今日のシンポジウムのキーワードですが，この制度というのは，アメリカの場合には，国家が認めていない，いかなる薬を臨床試験として使う場合であっても，必ず行政当局が審査をするという制度です（表6）。皆さんは，「これは当然ではないか」と思っているかもしれませんが，日本にはこの制度はありません。なぜかと言うと，日本の場合には，臨床試験の前の審査と終わって承認する審査，2回審査があるのですが，承認のための審査は行っていますが，臨床試験の入口に当たっては治験として行っている場合はPMDAが審査しますが，

表4　日本の臨床試験の特徴と問題点（まとめ）

- 臨床研究，治験というトラックの違い
  →(1)手続きに混乱　(2)被験者保護　(3)医薬品機構の審査事例が蓄積しないため経験値が不足　(4)国内データベースが完備されない　(5)特許の期間を無駄している
- 開発薬事の人材と価値観のインキュベーションの必要性（企業，行政，アカデミア）
- 臨床研究を行う医師・医学教育の改善が必要

2007年8月3日　医薬品における産官学の連携組織　資料　京都大学・川上浩司

表5　FDAによる医薬品審査・認可の歴史

- 1906年　Food and Drug Act（Wiley Actor Hey burn Actともよばれる）→ラベル標記の適正化
- 1938年　Food, Drug, and Cosmetic Act→安全性検証の義務化
- 1962年　FD&C Act補足→有効性検証を義務化
- 1983年　Orphan Drug Act稀少疾患に対する医薬品開発を促進（税制優遇，承認後7年間の優先販売権，研究費助成）
- 1992年　PDUFA法，MDUFA法により，審査官の人件費を申請手数料から充当→審査体制（規制と支援）を強化
- 1992年　重要な医薬品に対する優先審査制度の導入
- 1997年　FDA近代化政策　採択
- 2003年　FDAクリティカルパスイニシアティブ発表→規制側からの研究・開発・産業支援を明確化
- 2004年個別化医療関連の通知（ファーマコジェノミクス等）発布

表6　IND制度とは

- Investigational New Drug applications
- 人間（患者）にFDA未承認のいかなる医薬品を投与する場合にもINDパッケージを作成，申請することが義務付けられている

「臨床研究」と言われているものの場合には，GCPに関する部分を担保するための審査というのは行われていない訳です。ですから，IND制度というものは日本にありません。

IND制度がある中で，行政がどのように審査をしているかと言いますと，簡単にお話しすると，「医薬品そのものの審査，医薬品が適切にコントロールされて規格がつくられ，製造されているかどうか」です。2点目が，pharmacology toxicologyと言いますが，非臨床試験が適切に行われているかです。この2つをもって初めて，倫理的に妥当性がある，人間を対象として介入というものがなされる，と認知されています。それぞれに対して，いわゆる医薬物の規制はGMP，非臨床試験のGLPという規制事項がありまして，国はこういったことを審査するのです。GMPとGLPがある上で初めて人を対象とした試験，いわゆる臨床試験というものが行われます。臨床試験というものはGCPによって行われている，ということになります（図5）。

GCPは，各医療機関のIRBが守っていまして（表7），つまり，大学で行っているような研究成果というものが，最終的に企業に引き継がれることが非常にシームレスに行われるようなことを応援するIND制度，あるいは医療機器のIDE制度というものがございます。つまり，大学で行われた臨床試験のデータは，GCPで行われていますので，すべからくそれが引き継がれて，製薬企業が承認申請に使うデータとすることができる。そして，世界の患者さんにな

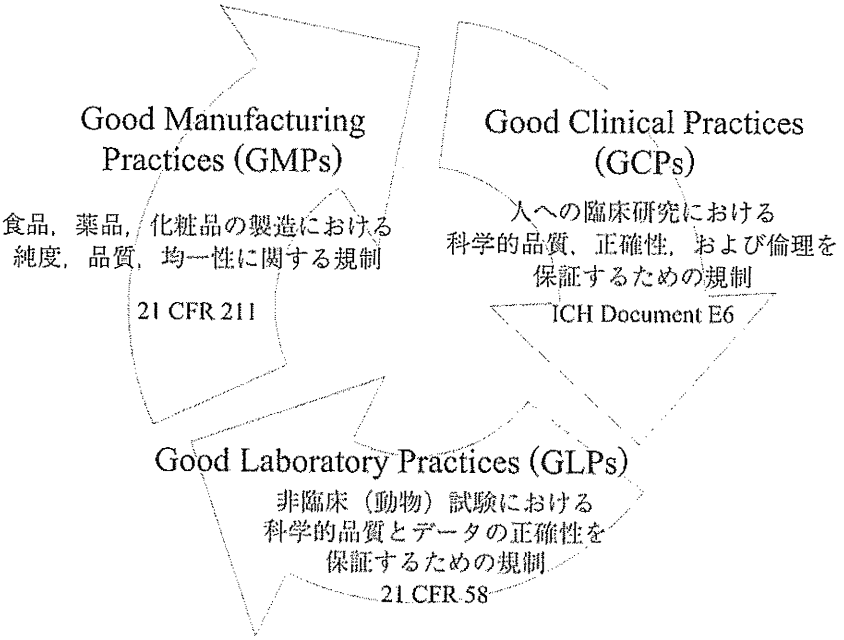


図5

表7　IRBの規制当局OHRPの役割

□保健福祉省（Department of Health and Human Services : HHS）の下部組織であり，HHSの政策と各組織のIRBの監督権限を有する。
□臨床研究に参加する被験者を保護することを目的に，HHSに政策の新しい企画や情報提供を行うとともに，施設の申請に応じて施設を連邦認証（FWA）する権限を持っている。

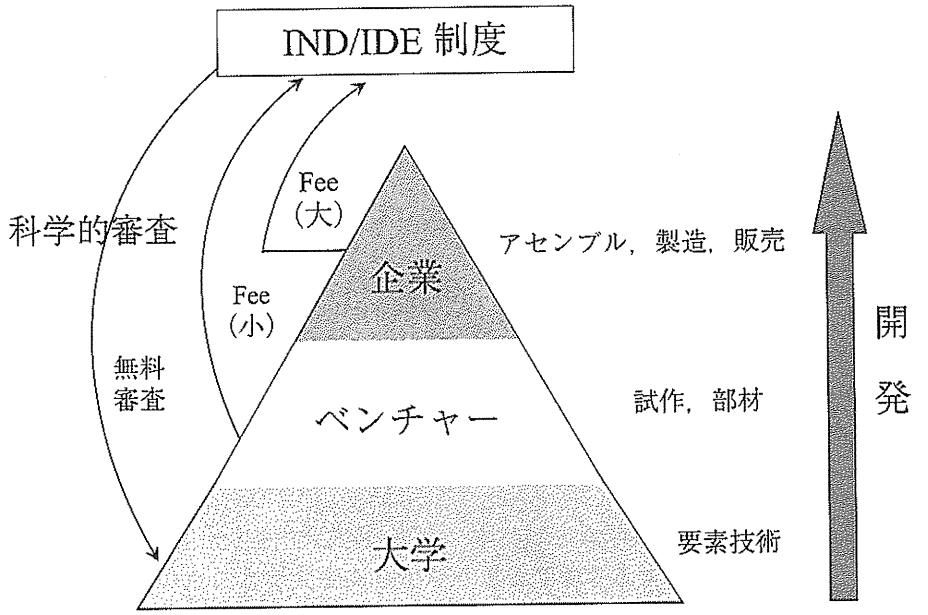
FWA（Federal Wide Assurance）米国連邦保証制度

るべく早く届けることが可能であるということになっています（図6）。

アメリカだけではありません。こういう制度を持っているのは，実はヨーロッパも同様でして，2004年5月以降は，欧州理事会の決議で，EC Clinical Trial Directiveというものが制定され，この中では，企業だろうが，アカデミアだろうが，同じように各国審査を受けないと臨床試験に入ってはいけない，GCPであるということが規定された訳でございます（表8）。

ですから，我々の今回のシンポジウムの目的というのは，大学で行われている研究の成果というものが速やかに国民に届けられるためには，当然のことながら，制度的にGCPが運用されて，そして，それが正しく行われなければいけない，ということだと思っています。すなわち，大学で行われる臨床研究と言われているものが底上げされて，品質が整わないと世界で使えないのではないかということが問題意識な訳でございます。

ですから，こういうことが制度的に行われることが可能かどうかということが今日のテーマでございまして，GCP，大学の臨床研究の成果というものがどうやって社会にアダプトできる



出展：川上浩司　2008 年 5 月 22 日　民主党・医薬品産業政策研究会
2008 年 3 月 12 日　自民党本部・国家戦略本部

図 6　米国における医薬品行政と社会・産業との関連

表 8　臨床研究に関する EC 臨床試験指令

- 1996 年の ICH 合意による ICH-GCP に基づき，2001 年 5 月に欧州議会および欧州理事会指令（以下，EC 指令という）として公布，各 EU 加盟国は 2004 年 5 月までに国内制度を整備
- 臨床試験の実施において，以下の事柄を規定
  - 商業スポンサーか非商業スポンサーか，承認申請目的か否かに関わらず，試験実施前に，倫理審査委員会の審査に加えて規制当局の承認審査が必要
  - 被験者の保護としての賠償・補償（compensation, indemnity）措置
  - インフォームドコンセントの在り方
  - 副作用報告の在り方，特に，重篤未知疑いのある有害事象（SUSAR）の規制当局および倫理審査委員会への報告等

かということも皆さんに今日お考えいただくきっかけとなればと思っております。
どうもありがとうございました。

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RESEARCH NOTE

Medical device development in crisis: A movement for technology innovation in health and medicine in Japan

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ABSTRACT

Japan is currently confronting a serious decline in medical device innovation. We identified some of the many barriers posed by the current clinical development system in Japan, as they relate to academia, industry and regulatory agencies: a scarcity of medical engineering and bioengineering scientists, two separate categories of clinical trials in Japan, a high level of uncertainty in any R&D schedule, leading to stagnation in the development of medical devices. We propose a new clinical development system (CDS) to stimulate medical device development in Japan, with a central body to facilitate the CDS process with appropriate coordination of interdisciplinary and translational research, and through rational public funding arrangements. With the recommendations, a new organization (Council on Health Research Promotion) has been established in the cabinet of office of Japan, and is expected to work in an effective and efficient manner.

Keywords: Clinical development; innovation; Japan; medical devices; regulatory affairs; research and development policy

INTRODUCTION

Medical devices that are used in medical practice for the prevention, diagnosis, treatment of disease and injuries, the correction of physical deformities of the body, and their innovations have improved healthcare worldwide. Japan, the United States (US), and the European Union (EU) are the three largest producers and

consumers of medical devices in the world (USITC 2007). In the global medical device market, technologies developed in Japan have contributed to important novel medical devices being brought to market: for example, the endoscope and ultrasound-based diagnostic devices in the past. In 2007, Japan's medical device market was ranked second in the world (USITC 2007); in 2005, Japanese industry was responsible for 10% of world medical device production. However, Japan confronts a significant decline in medical device innovation – e.g., medical devices (Fig. 1) – importing a significant proportion of its therapeutic medical devices from the US and EU, including high-tech medical devices such as cardiac pacemakers and drug-eluting stents (MHLW 2007).

However, research and development (R&D) for new devices is generally similar in the US, EU and Japan. During the development process, basic research involves searching for and developing the basic ideas for devices, and applied research involves testing the construction materials and performance of the prototype. In general, a physician and/or an engineer conceives of a device to solve an as yet unsolved clinical problem, initiates the patent process, and builds a prototype (Maisei 2004). Unlike drug development, preliminary laboratory and animal testing may be in part replaced by preclinical and exploratory clinical research. For example, in the US the preclinical stage generally takes 2–3 years, depending on the nature of the device, and it may cost US$10–20 million before the device is ready for clinical testing (Kaplan et al. 2004). After the preclinical stage, the safety and efficacy of a device are tested via one or more clinical trials.

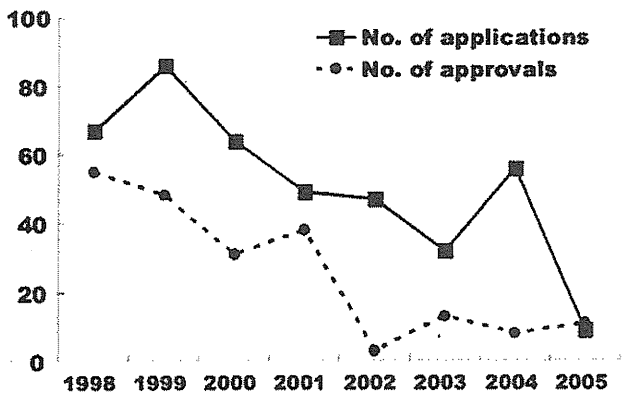

FIGURE 1: ANNUAL NUMBERS OF NEW MEDICAL DEVICE APPLICATIONS AND APPROVALS IN JAPAN BETWEEN 1998 AND 2005

During the period, implementation of the amended Pharmaceutical Affairs Law involved establishment of an independent agency (PMDA) and revision of the regulatory approval system.

Source: PMDZ Annual Report 2007.

The Japanese government has known the problem for several years. Since innovation and a strong commitment to research and development are principal competitive factors, the Japanese public and private sectors have made several attempts to remedy the situation for medical device development (Tsuji & Tsunami 2008). In 2003, the Ministry of Health, Labour and Welfare (MHLW) announced a plan of action to improve the international competitiveness of the Japanese medical device industry. The Medical Engineering Technology Industrial Strategy consortium (METIS) was organized by industry and academia, based on the National Industrial Technology Strategy of Japan formulated in 2000. In the response, the Ministry of Economy, Trade and Industry (METI) and the Ministry of Education, Culture, Sports, Science and Technology (MEXT) have provided more basic and applied research funds for medical engineering research.

Consecutively, the dialog between the public and private sectors was held with the aim of reforming the structure of the pharmaceutical and medical device industries in April 2007. MHLW, METI and MEXT launched a 5-year strategy plan for supporting the development of innovative drug and medical devices (McCurry 2007). In FY 2008, the budget for the 5-year strategy is US$86.9 billion (US$804 million/year), and these activities are to be ongoing administrative programs administered by MEXT, METI and MHLW. Furthermore, a separate special program termed 'super medical designated area' for development of innovative medical technology was proposed in April 2008 by the Council on Eco-

nomic and Fiscal Policy under the jurisdiction of the Cabinet Office of Japan (CAO). This program intends to support research and development of projects including induced pluripotent stem (iPS) cell-related area, regenerative medicine products, and medical devices.

With strong social demand for health-care services being forecast for Japan's aging society, many companies are interested in medical device innovations. However, there remain critical difficulties in implementing the clinical development of medical devices, despite the directed approaches described above (ACCJ 2006). Here, we identify some of the many barriers posed by the current clinical development system in Japan, as they relate to academia, industry and regulatory agencies, and then recommend an approach to stimulate medical device development in Japan.

Methods

We investigated R&D process for medical devices in Japan. Clinical development process and marketing of medical devices are controlled by the Pharmaceutical Affairs Law (PAL) in Japan. Legislative amendments of the PAL taking effect in 2005 have significantly restructured the regulatory approval process (e.g., USITC 2007).

To gather knowledge of the actual situation on medical device development in Japan, six structured interviews were conducted from April–June 2007. In total, 17 interviewees were chosen from related parties including regulatory agency (4), think tank (2), academia (engineering and medicine) (5), hospital (1), and medical device industry (5). Subjects of these interviews were determined to cover barriers to medical device innovation posed by the current clinical development system in Japan: 1) medical devices meeting demands and their market sizes; 2) solutions for technical problems on medical device development; 3) policy priority for promotion of medical device innovation; 4) improvement plan for enhancement of international competitiveness on medical device industry; 5) regulatory affairs for medical device; and 6) use of medical device in medical institutions. These interviews took approximately two hours and were recorded using an IC recorder. Each interview was transcribed verbatim and the responses were analyzed. Responses were analyzed by categorizing segments of the transcripts into topic areas, then classifying them using material categories. The responses were verified by literature information including public guideline and reports.

Results and Discussion

Specific barriers to medical device innovation in Japan

Based on the results of interviews, the typical process, major flaws and actual players for medical devices development were summarized (Fig. 2). The Japanese regulatory situation was quite notorious for causing a high level of uncertainty in any R&D schedule, leading to stagnation in the development of medical devices. From a business point of view, Japan's slow and complicated review system is regarded as a barrier to medical device development. For example, a 1–3-year delay in obtaining regulatory approval means that the company faces significant costs before obtaining market approval, and this additional cost may be added to the price of the product in the Japanese health insurance system (JCII 2007). US industry officials estimate that complying with changes in Japan's regulatory system since 2005 has cost US companies US$350 million (USITC 2007). This is due mainly to the duration of the Japanese regulatory review process, resulting from there being too few medical device reviewers in the Pharmaceutical and Medical Devices Agency of Japan (PMDA) (28 reviewers in April 2007). This is less than 10% of the number of reviewers in corresponding US organization, the Center for Device and Radiological Health (CDRH) of the Food and Drug Administration (FDA). In addition, PMDA reviewers do not have requisite experience in medical device technology, as many reviewers originally specialized in pharmaceuticals, and there are very few medical doctors in the medical device division.

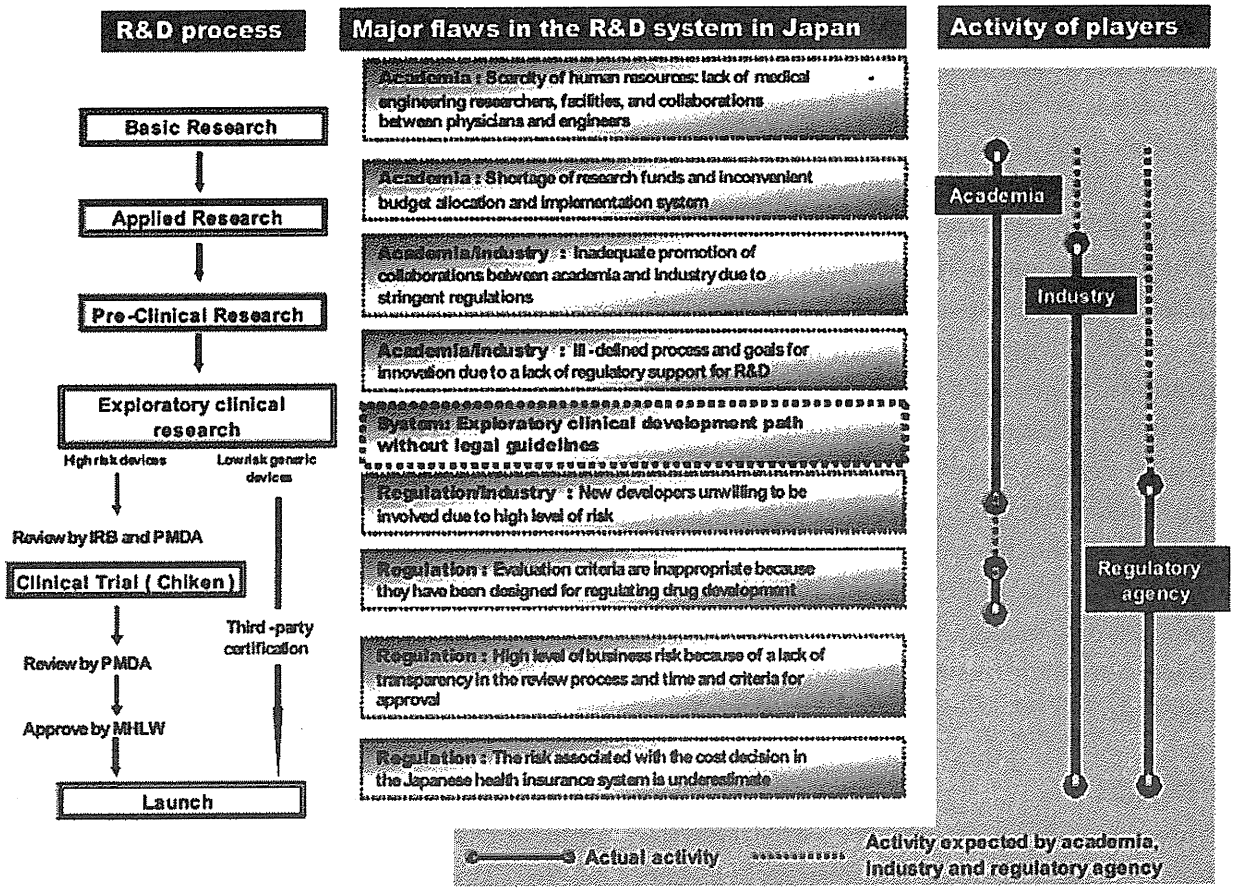

FIGURE 2: CURRENT JAPANESE R&D SYSTEM FOR MEDICAL DEVICES

Specific problems with the process, and the activities undertaken by academia, industry and regulatory bodies are detailed.

There are two separate categories of clinical trials in Japan (Tsubouchi et al. 2008). Exploratory clinical development is allowed to be done outside GCP guidelines (Mechanical Social System Foundation 2007) and as a result, to ease the regulatory burden much exploratory clinical research by academic scientists involves clinical trials performed outside the jurisdiction of the Pharmaceutical Affairs Law (PAL). However, there are scientific and ethical concerns about performing clinical research without legal guidelines to protect human subjects. Furthermore, clinical data obtained from clinical research performed in this way cannot be used to support an application for regulatory approval. Therefore, developers need to perform additional clinical trials under PAL if they desire regulatory approval.

Barriers exist between basic and pre-clinical research stages. Since the discovery and development process for new devices may depend on input from physicians and engineers, good communication between physicians and engineers is a basis for developing promising concepts for devices. In Japan, however, scarcity of medical engineering and bioengineering scientists is a major barrier due to lack of support for human resource development in biomedical engineering. Group culture in academia and the absence of inter-disciplinary integration in the Japanese scientific community also results in poor communication between physicians and engineers (Industry Institute Foundation 2007). Academia may also be less concerned than industry about bringing a product to market, causing ill-defined processes and goals for innovation of medical devices in Japan by interviews.

Incoherent national R&D strategies which are legislated by different ministries reduce investment effect on promotion of medical device, resulting in low Japanese government funding in R&D. Subsequently, science and technology policy has yield-

ed a deficiency in human resources and inefficient and irrational research funding patterns. Further, little integration exists between research programs undertaken by academia and industry.

Recommendation for medical device innovations

We found two critical barriers: (i) ill-defined processes and goals for innovation due to the lack of regulatory support for R&D; and (ii) lack of cooperation among industry, government and academia with respect to development of the innovation. Since the Japanese critical barriers essentially result from flaws of R&D system, we here discuss appropriate R&D system to realize medical device innovation in Japan.

Firstly, we recommend a new clinical development system (CDS) to reform ill-defined processes and goals for innovation of medical devices (Fig. 3). This system must provide a user-friendly gateway for any clinical development of medical devices, involving the relevant physicians and engineers in academia and industry. To encourage the invention and development of useful devices and to protect patient safety, the system will include frequent regulatory consultation in the pre-clinical and clinical phases, just as the US FDA does in their Investigational Device Exemption (IDE) system (FDA-CDRH 2003). Consequently, present clinical research involving unapproved medical devices should be terminated and instead PAL-compliant clinical trials should be performed, and regulatory support, including frequent consultations beginning from the initial phase of development, must be provided to academic researchers and industry.

In the CDS, frequent consultations should be emphasized to reduce review times for novel med-

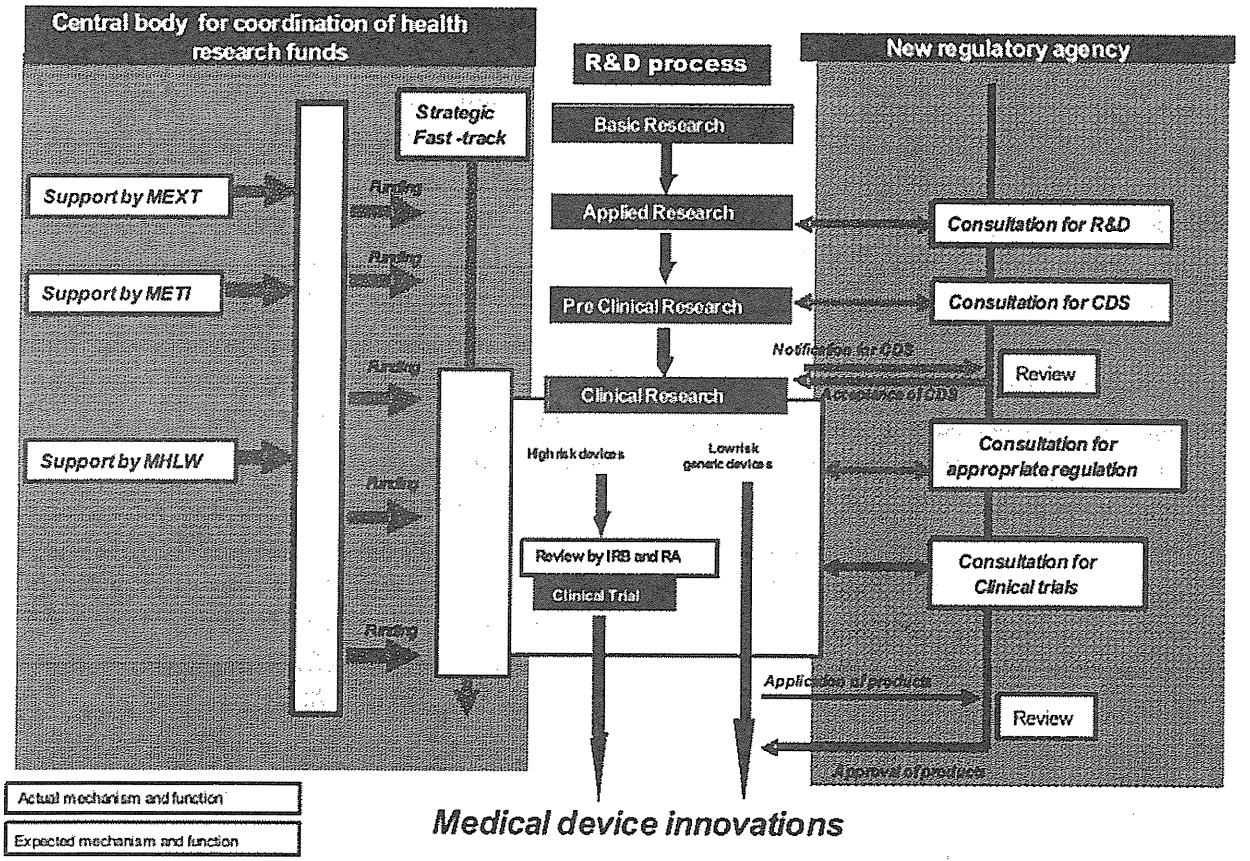

FIGURE 3: RECOMMENDED STRUCTURE OF A NEW JAPANESE CLINICAL DEVELOPMENT SYSTEM (CDS)

The system would involve two functions: (i) clarification of the processes and goals for innovation, with regulatory support for R&D; and (ii) provision of an R&D platform provided by a central body, with the mandate of facilitating cooperation between industry, government and academia.

ical devices. Such communication between regulatory agency and applicants was a key point to clarify defined process and goals of medical device development because such delay in review process is often introduced when applicants respond to reviewers. For example, the PMDA's review time is currently always longer than that of the FDA, but median review times for new medical device applications do not differ substantially between the PMDA and FDA (USITC 2007). Therefore, it is implied that frequent consultations are essential to break down the communication barrier between reviewers and applicants in Japan. In fact, FDA provides pre-IDE program to facilitate initiation of clinical trials, and this contributes to reduce delays of review time due to poor communication in the US (JCII 2007). In Japan, PMDA also provides various consultation programs, but these programs do not perform well because considerable effort (documents) and cost (consulting fee) are required for the consultation (USITC 2007). Therefore, importance of the frequent, inexpensive and user-friendly consultations should be emphasized in the CDS.

In addition, the system should also mandate appropriate stepwise regulatory actions for each device development stage. In many countries, including Japan, Good Clinical Practice (GCP) guidelines dictate that clinical trials are required for regulatory approval of high-risk devices such as implantable pacemakers. In Japan, under the Quality Management System (QMS), quality assurance procedures during the manufacturing process are scrutinized when the license application is submitted. However, many companies are facing a regulatory hurdle such as multiple stringent GMP/QMS inspections conducted by regulatory agency and public sectors at the early stages of development. For early versions of the product, which will be used for iterative testing to identify necessary improvements and modifications, an appropriately low level of manufacturing quality control should be allowable, which may be improved to meet stringent GMP/QMS criteria at a later stage of development.

This proposed system will impose a further burden on Japanese regulatory agencies because they will need to process more clinical trial applications from academia and industry. Therefore, a new regulatory agency is emphasized for user-friendly consultation and good evaluation of medical products. In relation to this recommendation, the role of PMDA was intensively discussed by the legislators of Japan's Liberal Democratic Party and the Japanese government decided to set up a central office for medical innovation (Council on Health Research Promotion: CHRP) in the cabinet office of Japan in 2009.

Secondly, to manage the involvement of the relevant governmental ministries, a new central body should be established to coordinate public research funds (Fig. 3). This support would comprise developing relevant guidelines, and provide information from a regulatory standpoint to academic researchers and small venture companies engaged in developing device prototypes, to facilitate development and transfer of the concept to larger medical device companies.

This central body would be authorized to plan and evaluate R&D strategy for medical device innovations, and submit budget requests to the Ministry of Finance, like the UK Office for Strategic Co-ordination of Health Research (Cooksey 2006). The central body with appropriate powers could facilitate the CDS process through appropriate coordination of interdisciplinary and translational research, and through rational public funding arrangements to support synergistic relationships and translation of research.

The discontinuous review systems (e.g., the PMDA does not review products before they are in their final form) and lack of industrial promotion are also barriers to successful medical device development in Japan. Therefore, implementation of the recommendations described here will substantially reduce several risks associated with the clinical development of medical devices, and will help avoid a crisis in the Japanese medical device industry.

Concluding Remarks

Thus, we recommend a new clinical development system (CDS) with a central body to stimulate

medical device development in Japan. Consequently our recommendations were being considered by various Japanese governments and political parties, including the Liberal Democratic Party of Japan. In this context, the Council on Health Research Promotion (CHRP) has been already established as a central body in the CAO to coordinate public health research funds since July 2008. The CHRP consists of knowledgeable persons and ministers of State for Science, Technology, and Innovation Policy (SSTIP), MEXT, METI, and MHLW, although detailed structure and function of the organization is still under discussion. On another front, the CDS is also currently under the intensive discussion by the Minister of State for Regulatory Reform (Council of Regulatory Reform, Cabinet of Office) as Japanese IDE system from October 2008 (CAO-CRR 2008). Currently, under the admission of the Democratic Party of Japan, the role of the CHRP is unclear; however, the importance of development of new medical devices is strongly imposed by academic researchers and industries. We believe that our recommendations are likely to be adopted with public awareness of the current situation and an understanding of the importance of clinical research.

Acknowledgements

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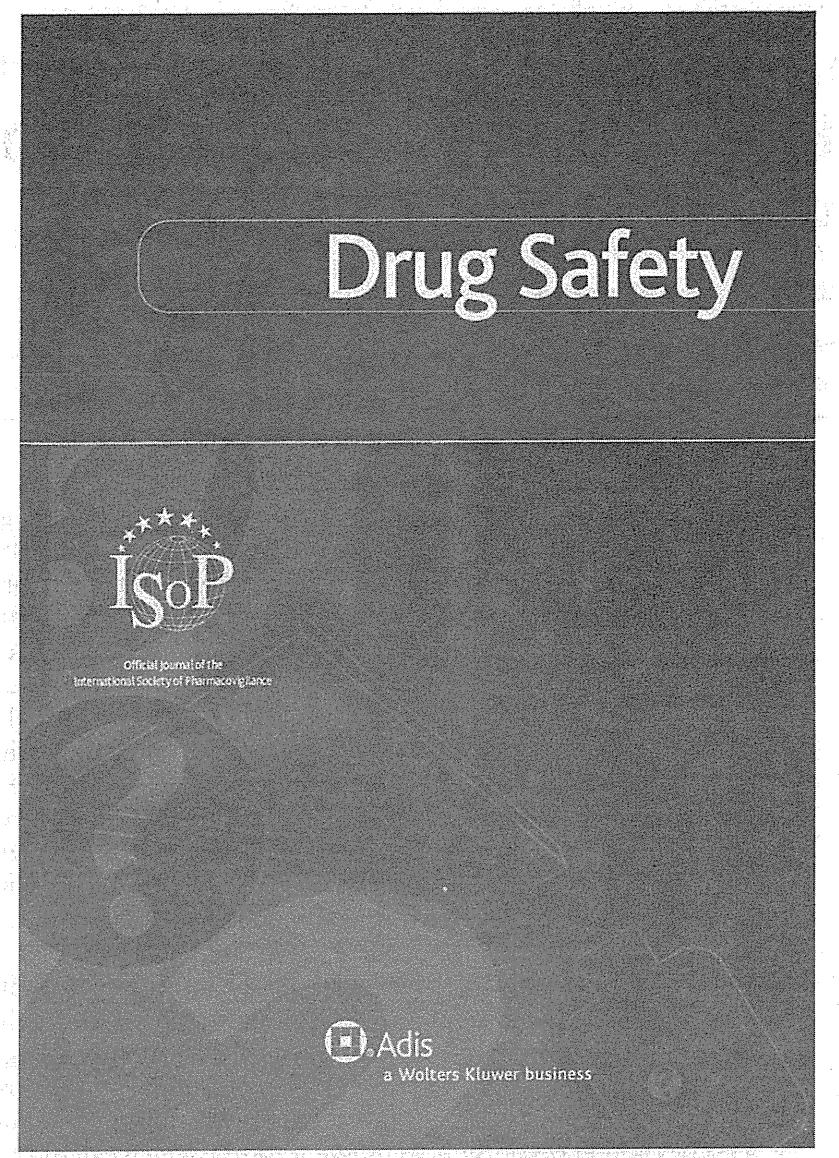

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Development Safety Update Reports and Proposals for Effective and Efficient Risk Communication

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Abstract

The periodic safety reporting to regulatory authorities is globally harmonized for postmarketing medicinal products by the International Conference on Harmonisation (ICH) guidelines, and is being extended for investigational drugs. To facilitate effective safety risk communication regarding investigational drugs, and to reduce duplicate periodic reporting to the US and EU by sponsors during development programmes, standardized Development Safety Update Reports (DSURs) are to be implemented in the near future.

In this current opinion article, after extensively reviewing the relevant report from the CIOMS VII Working Group and the ICH draft guideline regarding DSURs, we discuss an effective and efficient approach to its application. To ensure effective risk communication, we recommend that DSURs be made available to all the ethics committees and participating investigators around the world for the purpose of continuing review during ongoing clinical trials.

Furthermore, in order to maintain the consistency and integrity of safety information throughout the life-cycle of a drug, we believe it would be substantially more prudent and efficient to start a single, integrated, life-cycle periodic safety report covering both development and postmarketing, as proposed by the CIOMS VII Working Group, rather than maintain separate DSURs and Periodic Safety Update Reports, which can overlap considerably in content. To this end, we believe that the international regulatory community should undertake the new initiative for integrated periodic reporting immediately.

1. Periodic Safety Reporting during Drug Development

1.1 Safety Risk Communication for Investigational Drugs

Risk communication with regulatory bodies, investigators and ethics committees regarding an investigational drug is carried out during development programmes using several internationally well established tools, including the investigators' brochure (IB) and expedited reporting of suspected unexpected serious adverse reactions (SUSARs). Additionally, regulatory bodies in the EU and US require different annual reporting on investigational drugs from sponsors under local regulations, namely the EU Annual Safety Report

and the US FDA Investigational New Drug Annual Report. These reports overlap slightly in content but differ substantially in purpose, scope and timing of data-lock points, creating costly inefficiency and redundant work for sponsors. Because of the gap in reporting periods and the difference in purposes between these annual reports, it has been pointed out that, for example, EU regulators might receive different safety messages regarding a particular investigational drug at different timepoints from FDA regulators.[1,2]

These issues prompted a new initiative by CIOMS for developing a unique, standardized content and format for periodic safety reports on investigational drugs. In August 2006, the CIOMS VII Working Group published *The Development Safety Update Report (DSUR): Harmonizing the Format and Content for Periodic Safety Reporting During Clinical Trials*.[1] The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) step 2 consensus guideline (E2F) on the DSUR, based on the CIOMS proposals, was issued for public comment in June 2008.[2]

In this present current opinion article, while we argue for the significance of harmonized periodic safety reports during development phases, we present extensive discussion on the draft ICH E2F guideline and the CIOMS VII Working Group report to help improve the current, malfunctioning risk communication and to promote safety risk management during clinical development programmes. In particular, we discuss the following subjects:

- effective use of DSURs to improve the current risk communication system;
- efficiency brought about by introduction of integrated periodic safety reporting throughout the life-cycle of a drug.

Furthermore, we hope that our discussion will attract greater public attention to the regulatory system on drug development safety, and trigger wider discussion among the international regulatory community as well as the representatives of trial investigators and ethics committees, on the basis that although these parties are primarily responsible for managing the safety of individual patients, they have thus far rarely been involved with the bigger picture.

1.2 Comparison between the Report of the CIOMS VII Working Group and the Draft International Conference on Harmonisation (ICH) E2F Guideline

DSURs are intended to be a common standard report to "notify regulators and other interested parties (e.g. ethics committees) at regular intervals of the evolving safety profile of an investigational drug and actions proposed or being taken to address safety concerns" during clinical development.[2] The CIOMS VII Working Group further stated that "by design, [DSURs] will enable a seamless transition for communicating safety information to relevant stakeholders, starting at the early clinical development stage and [...] continuing throughout the post-approval period". The DSUR table of contents was developed in alignment with that of established PSURs for marketed drugs (table I).[2,3] Where possible, commonalities in the table of contents between the proposed DSUR and the PSUR were retained. Furthermore, the concept of safety risk management during development is fully reflected in the detailed instructions in the proposed DSUR guideline, in accordance with the proposal by the CIOMS VI Working Group, 'Management of Safety Information from Clinical Trials'.[4]

Several recommendations made by the CIOMS VII Working Group were not reflected in the draft ICH E2F guideline (table II). For example, both the CIOMS VII Working Group and the draft ICH E2F guideline recognize the value of providing an executive summary of a DSUR to ethics committees and trial investigators where the local legislation requires, although only the CIOMS VII Working Group suggests disclosure of the full report upon request. Additionally, one chapter of the CIOMS VII Working Group report is devoted to the goal of a single periodic safety report covering the lifecycle of a drug from development to post-launch, and incorporating the current PSURs within its scope. However, a compromise on this

Table I. Comparison of table of contents between the Development Safety Update Report (DSUR) proposed by the International Conference on Harmonisation (ICH) E2F draft guideline and the current Periodic Safety Update Report (PSUR) for marketed drugs[a] (reproduced by kind permission of the Council for International Organizations of Medical Sciences.[1] © CIOMS)

Proposed contents of the DSUR[2]	Corresponding contents of the PSUR[3]
Title page	Title page
Executive summary	Executive summary
Table of contents	Table of contents
1. Introduction	1. Introduction
2. Worldwide marketing authorization status	2. Worldwide market authorization status
3. Update on actions taken in the reporting period for safety reasons	3. Update of regulatory authority or MAH actions taken for safety reasons
4. Changes to reference safety information	4. Changes to reference safety information
5. Status of clinical trials ongoing and completed during the reporting period	7. Studies 7.1 Newly analysed company-sponsored studies 7.2 Targeted new safety studies planned, initiated or continuing during the reporting period 7.3 Published safety studies
6. Estimated exposure 6.1 Cumulative subject exposure in clinical trials (phase I–IV) 6.2 Patient exposure from marketed setting	5. Patient exposure
7. Presentation of safety data from clinical trials 7.1 General considerations 7.2 Interval line listings of serious adverse reactions (SARs) 7.3 Cumulative summary tabulations 7.4 Deaths in the reporting period 7.5 Subjects who dropped out in association with any adverse event in the reporting period	6. Presentation of individual case histories 6.1 General considerations 6.2 Cases presented as line listings 6.3 Presentation of the line listing 6.4 Summary tabulations 6.5 MAH's analysis of individual case histories
8. Significant findings from clinical trials during the reporting period 8.1 Completed trials and any interim analyses 8.2 Ongoing clinical trials 8.3 Other therapeutic use of investigational drug 8.4 New safety data related to combination therapies	7. Studies 7.1 Newly analysed company-sponsored studies 7.2 Targeted new safety studies planned, initiated or continuing during the reporting period 7.3 Published safety studies
9. Relevant findings from non-interventional studies	
10. Relevant findings from other studies	
11. Safety findings from marketing experience	Included in point 6. 'Presentation of individual case histories'
12. Other information 12.1 Non-clinical data 12.2 Long-term follow-up 12.3 Literature 12.4 Other DSURs 12.5 Significant manufacturing changes 12.6 Lack of efficacy 12.7 Phase I protocol modifications	8. Other information 8.1 Efficacy-related information 8.2 Late-breaking information
13. Late-breaking information	
14. Overall safety assessment 14.1 Evaluation of the risks 14.2 Benefit-risk considerations 14.3 Conclusions	8. Other information 8.3 Risk management programmes 8.4 Benefit-risk analysis report 9. Overall safety evaluation 10. Conclusion
15. Summary of important risks	Not explicitly covered by PSUR according to ICH E2C (R1)

a Contents are numbered according to the applicable ICH guidelines.

MAH = Marketing Authorization Holder.

Table II. Comparison regarding expected audience of Development Safety Update Reports (DSURs) and separation from Periodic Safety Update Reports (PSURs) for the postmarketing phase

Reports and guidelines	Ethics committee and trial investigators as recipients of DSUR	DSUR as a separate document from PSUR
CIOMS VII report[1]	Executive summary provided where national legislation requires periodic submission of safety information on an investigational drug to ethics committees, institutional review boards or investigators, and a full document delivered upon request	Ultimate goal is to implement an integrated life-cycle periodic safety report covering the scope of the DSUR and PSUR, but current recommendation is to create two stand-alone documents – one for investigational drugs during development (DSUR) and one for postmarketing (PSUR)
ICH E2F draft guideline[2]	Executive summary only for submission to ethics committees and other stakeholders, if required by local regulations No description on full report	No description for integration with the PSUR Create two stand-alone documents – one for investigational drugs during development phase (DSUR) and one for postmarketing (PSUR)
Our proposal	Executive summary submitted to all ethics committees and participating investigators across the board A full report readily available upon request to trial investigators and ethics committees	Introduce a single, life-cycle periodic safety report pertaining to both development and postmarketing as soon as possible Require update of outdated PSUR guidelines to comply with most recent concept of risk management

ICH = International Conference on Harmonisation.

point appears to have been reached, considering "the significant and complex challenges a unified safety update report would present, such as requiring changes to existing practices and requirements", presumably the current, long-standing PSUR practice. Thus, the temporal focus of the CIOMS VII Working Group is a stand-alone DSUR in a step-by-step approach towards their ultimate goal.[1] In contrast, the draft ICH E2F guideline included no suggestion regarding an integrated DSUR-PSUR report. We consider the above points as being of high relevance to effective risk communication and rational use of resources. In this current opinion article, we discuss two proposals regarding DSUR recipients and the DSUR as a separate document from the PSUR.

2. Proposals

2.1 Ethics Committees and Investigators as Development Safety Update Report (DSUR) Recipients

The CIOMS VII Working Group considers that "the DSUR is intended for submission exclusively to regulatory authorities. However, where national legislation requires periodic submission of safety information on an investigational drug to Ethics Committees, Institutional Review Boards, or investigators, the CIOMS VII Working Group recommends that only the DSUR Executive Summary be provided, with a full DSUR available upon request".[1] Furthermore, the ICH E2F draft guideline recommends that "where local authorities ask for periodic submission of safety information on an investigational drug to ethics committees, institutional review boards, or investigators, the DSUR executive summary should suffice, supplemented with line listings of serious adverse reactions (SAEs) as warranted".[2] Thus, even though they are primarily responsible for managing the safety of trial participants, not all the ethics committees and trial investigators around the world receive the executive summary, and a full report might be available only if requested.

Currently, safety information regarding an investigational drug can be relayed to investigators and ethics committees in several ways, namely as an IB and an expedited individual case summary report (ICSR).[5] Recently, the CIOMS VI Working Group proposed periodic reporting with interval line listings of SUSARs, as a substitute for a barrage of expedited ICSRs.[4] Safety risk communication in clinical trials should be established by maintaining transparency of safety data, rapidity and consistency of assessment, and periodicity and clarity of messages throughout all

development programmes. However, whether the current communication tools satisfy all of these criteria is unclear.

An IB is a comprehensive compilation of findings on an investigational drug, and is submitted to an ethics committee when seeking approval to begin a new trial. It is developed and reviewed for update annually according to Good Clinical Practice standards, and updated as significant new information becomes available by sponsors, although the requirements for annual updating is subject to local regulations.[4] However, a revised IB does not necessarily contain the latest safety information from ongoing clinical trials, because such results are not declared as 'locked'. A complete set of results from a clinical trial is included in the revised IB only after the data has been validated and analysed. Occasionally, annual revision may thus be delayed until analysis completion or 'when significant results become available' (figure 1), reducing the periodicity of IBs. Furthermore, this 'dictionary' contains information accumulated from early developmental stages; too much to be efficiently processed. Readers struggle to identify important updates in safety information and the relevant risk assessments. Thus, an IB lacks periodicity in communicating newly emerging risks associated with an investigational drug, and clarity in effectively conveying the sponsor's perspective on those risks. Nonetheless, an IB is submitted annually to ethics committees for continuing review of clinical trial activities, despite the above disadvantages. In fact, submission of revised IBs to regulatory authorities during an ongoing study is not necessarily required.

When a SUSAR case associated with an investigational drug is reported to the sponsor, an expedited ICSR is issued according to existing ICH standards.[5] The report is delivered to

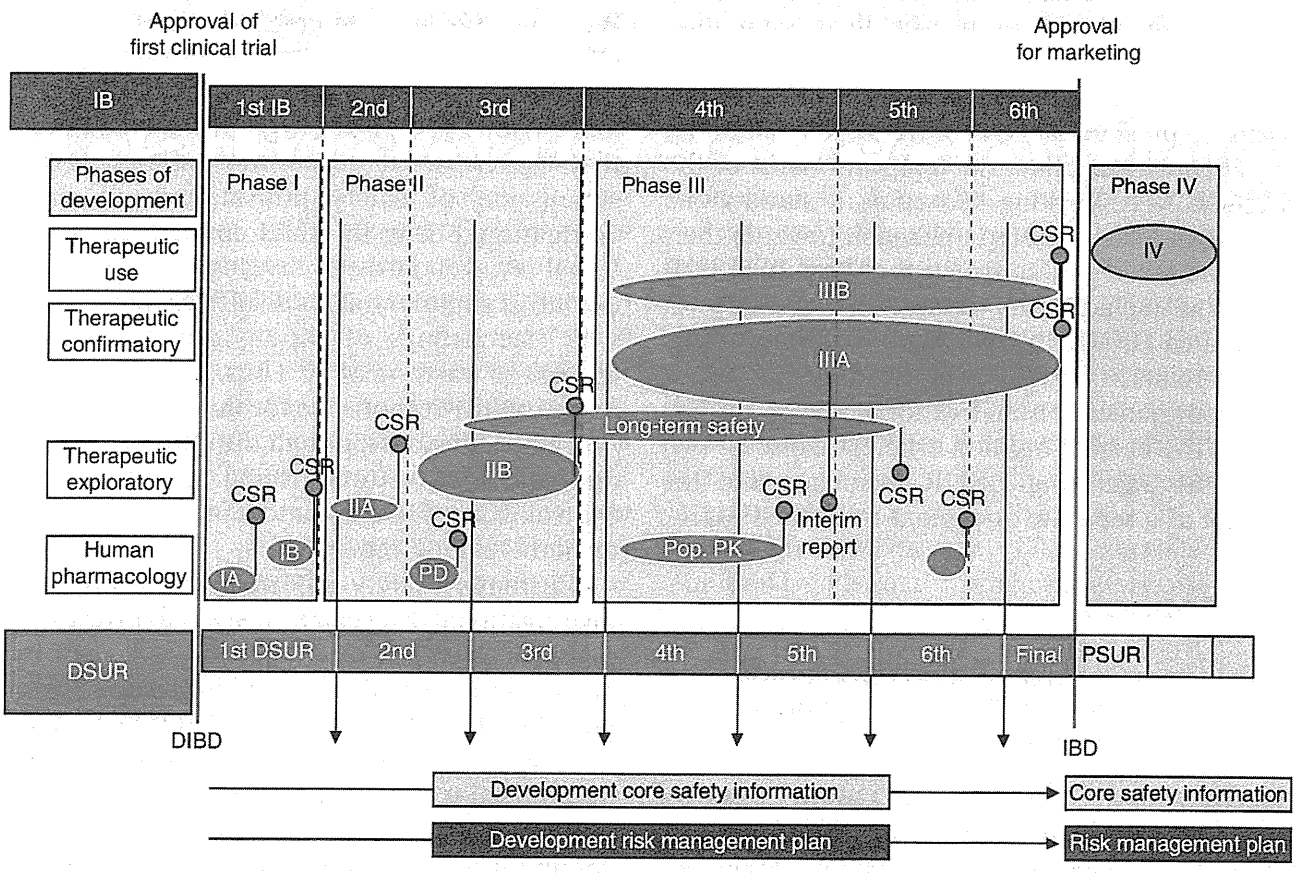

Fig. 1. Periodicity of Development Safety Update Reports (DSURs) and Investigators' Brochures (IBs) in a model development programme. Vertical dotted lines indicate data-lock points for IB revisions, and vertical solid lines indicate data-lock points for each DSUR. **CSR** = Clinical Study Report; **DIBD** = Development International Birth Date; **IBD** = International Birth Date; **PD** = pharmacodynamics; **PSUR** = Periodic Safety Update Report; **Pop. PK** = population pharmacokinetics.

regulators, trial investigators, and ethics committees within a locally determined timeframe. As reported by the CIOMS VI Working Group,[4] in this era of global multi-tiered and parallel development, ethics committees and trial investigators are overwhelmed with paperwork for processing ICSRs for various investigational drugs dispatched one after another from pharmaceutical companies. The original intent to expeditiously convey important risk information is lost, and investigators may overlook relevant safety findings. The CIOMS VI Working Group proposed replacing sporadic ICSRs with periodic interval line listings of unblinded SUSAR cases, along with a brief summary from the sponsor on the up-to-date safety profile.[4] This appears to improve upon current practices with regard to reducing the burden on investigators and ethics committees to process a large quantity of ICSRs while keeping trial investigators and ethics committees abreast of recent unblinded SUSAR cases, but remains to be implemented with a new global consensus on harmonization.

An ICSR also fails to serve as a common tool with global integrity that provides a sponsor's safety assessment on one particular case. Expectedness of adverse events varies depending on the reference documents adopted by local regulations in each country, including an IB, a Summary of Product Characteristics and a package insert. In a multinational study, this difference may result in regulators in different countries receiving ICSRs with different expectedness for a particular case, or even no report at all. To address this issue, the CIOMS VI Working Group proposed using a single reference safety information document for expectedness assessment, namely a Development Core Safety Information (DCSI), which is comparable to company core safety information for postmarketing. The CIOMS VII Working Group report and ICH draft guideline also recommend appending a DCSI to DSURs, and describing any significant changes occurring during the reporting period in the DSUR. Furthermore, by attaching the DCSI to IBs, the recency of IBs may be enhanced because of the more frequent, prompt and independent updates required of DCSIs.[4,6]

The current safety communication tools described above lack either reporting periodicity, data transparency, clarity or risk message integrity. In contrast, a DSUR has accurate periodicity because of the predetermined annual data lock and efficiency in documenting a sponsor's latest comprehensive and integrated perspective on the safety of an investigational drug while focusing on relevant recent data showing any changes from the previous knowledge. The recency of a DSUR would be ensured by its completeness in listing recent SUSAR cases from ongoing clinical trials reported during the covered period in the cumulative tabulation of SAE incidences once the case files are closed, without having to wait for the data lock of the concerned trial. In addition, the focus on interval safety in a DSUR, in contrast to an IB, would be preferable to continuing review of ongoing development activities, and therefore we argue for its submission to all ethics committees and participating investigators across the board (table II).

Transparency in safety communication may be undermined by providing only an executive summary, because of the summary's inherent lack of supporting evidence on which the safety assessments are based. This limitation may be overcome by making relevant information (namely the remaining periodic reports) available to not only clarify events occurring during the interval, but also to bestow a sense of easy access to relevant materials. In the EU, both the ethics committees and regulatory authorities are the target audience of annual safety reports under the applicable regulation. DSURs are developed as replacements for annual safety reports and there would therefore be no definitive reason to stop distributing the equivalent to ethics committees in those countries. It is true that an executive summary may be sufficient during initial review to allow ethics committees to judge whether or not further discussion is necessary. When the committees regard further discussion on the sponsor's recommended actions as necessary, a full DSUR can provide immediate access to the supporting data. Moreover, such reference information on important risks and similar event cases may greatly aid investigators in the early

and appropriate management of adverse event cases and in enhancing their sensitivity to usually overlooked but significant non-SAEs. Objections to distributing full reports stem mainly from the additional burden that reviewing a new voluminous report would pose on investigators. We therefore suggest that sponsors make full DSURs readily available upon request during the conduct of clinical trials via methods such as web distribution under appropriate security control and electronic documentation with hyperlinking, which ensures quick retrieval of documents as the need arises, and easy access from the executive summary to supporting data in the main body of the DSUR without a significant increase in paperwork. Additionally, to further improve development risk communications, it may be worthwhile to conduct a survey on the receptivity and usefulness of DSURs for safety management at study sites after the start of DSUR distribution to reflect feedback from trial investigators and study sites.

It should be noted that the objective of the above-mentioned periodic line listings proposed by the CIOMS VI Working Group, which consist of only expeditiously-reported, unblinded SUSAR cases along with brief updates on the emerging safety profile, differs from that of DSURs. Although DSURs present a transparent overview of interval safety findings for an investigational drug, the CIOMS VI Working Group's proposed line listings lack content essential to ensuring the transparency of a periodic safety report, such as information regarding all SUSAR cases occurring during the period, and tabulated cumulative incidences of SAEs, available safety analyses by study from ongoing or completed clinical trials and information on risk management during the relevant period; these important elements are all available in DSURs.

In summary, we recommend that executive summaries of DSURs should be distributed to all participating study sites around the world on the grounds that they are the most effective tool for strengthening risk communication, and that sponsors should make full DSURs readily available upon request. Further discussion on the role and structure of IBs is required if DSURs are to be submitted to ethics committee review sessions.

2.2 A Single, Life-Cycle Periodic Safety Report Format Pertaining to Development and Post-Authorization Phases

The ICH E2F draft guideline states that "some overlap is expected between the DSUR and PSUR" and contains no description of a single model of periodic safety reporting throughout the life-cycle of a drug (table II).[2] In contrast, the CIOMS VII Working Group presents their goal of "the eventual development and implementation of a single, integrated life-cycle safety report that incorporates the scope of the current DSUR and PSUR, and avoids duplication of information, unnecessary burden and confusion for both sponsors and regulators".[1] We strongly agree with the CIOMS VII Working Group's perspective and further suggest that integrated reporting throughout development and postmarketing be implemented as soon as possible when the periodic safety reports during the development phase start.

Collection of safety data starts before human exposure to an investigational drug and continues into the postmarketing phase. The nature and quantity of available data evolve depending on the developmental stages. All relevant safety-related data should be evaluated within a continual and comprehensive context throughout the life-cycle of the drug, considering the differences in data sources and clinical stages to relate a simple, specific and clear message to all concerned parties. From the perspective of continuing and consistent safety assessment, separating periodic safety reporting by authorization status would not be of great significance as the status varies by country and marketing authorization would be nothing but a landmark during the life-cycle of the drug. Safety data can be collected concurrently from clinical trials and postmarketing experiences for a fair amount of time after the initial marketing authorization. In this peri-approval period, the content of PSURs in any country will be similar to that expected for DSURs in other countries where clinical trials are still ongoing. Both reports deal with a large amount of information from pre-approval clinical trials, along with a comparable portion from emerging postmarketing experiences. The proposed

DSURs and the current PSURs differ with regard to items, order and headings due to differences in applicable guidelines (table I).[1] If a sponsor must create a DSUR in parallel with a PSUR for the same reporting interval, cross-validate them and submit these reports on different schedules according to local regulatory requirements in the recipient countries, inefficiency is inescapable. In addition, it may be undesirable and confusing for a regulatory body to receive two periodic safety reports regarding the same medicinal agent in countries where clinical trials are ongoing after the initial market launch. Therefore, a single, common, integrated periodic update report for each active substance should be pursued to relate a simple, specific and clear safety message with global consistency.

With the effort of the CIOMS VII Working Group, the proposed DSUR format is modelled after the current PSUR format to promote smooth transition to PSURs during the peri-approval period, contributing to the discussion on a common format for integrated report. The CIOMS VII Working Group also expressed their strong belief in the efficiency and utility provided by integration of DSURs and PSURs, and provided the framework for a model integrated periodic safety report, which could accommodate the presentation of both elements for early development compounds, such as non-clinical or clinical pharmacological data, and elements for postmarketing, such as interval line-listings of SUSAR cases for approved indications (table III).[1] As specifying the data sources and authorization status would ensure that readers appropriately understand the significance and quality of various safety findings, refinement in this regard may be necessary for implementation. Thus, we recommend that the international regulatory community should make every effort to realize harmonized life-cycle reporting as soon as possible, rather than maintain parallel production of a separate DSUR and PSUR. In case a sponsor restarts a new development programme for an approved product for an additional indication, for which the development programme has terminated, it would be much more efficient and prudent to use a single integrated periodic

Table III. Proposed table of contents for a model integrated periodic safety report (reproduced by kind permission of the Council for International Organizations of Medical Sciences.[1] © CIOMS)

Title page
Table of contents
Executive summary
Introduction
Worldwide marketing authorization status
Update of regulatory authority, trial sponsor or MAH actions taken for safety reasons (actions taken during the reporting period)
Changes to reference safety information (DCSI and CCSI when relevant)
Patient exposure
market use
clinical trials
Individual case histories from marketing experience (excluding clinical trials)
clinically significant individual case histories
line listings (only for special types of reports, such as SUSARs, and by exception)
summary tabulations (including spontaneous and solicited reports)
Clinical studies
inventory and status of worldwide interventional clinical trials (all phases; approved and non-approved indications, dosage forms, populations)
results from interventional clinical trials
completed (synopsis of results)
approved uses
unapproved uses
ongoing (synopsis of results if interim analysis conducted during reporting period)
approved uses
unapproved uses
line listing (only for SUSARs)
summary tabulations (all serious adverse events from interventional clinical trials; cumulative)
observational and epidemiological studies (including use of registries)
completed
ongoing
targeted new safety studies
completed
ongoing
planned
Other information
efficacy-related information
chemistry, manufacturing and formulation issues

Continued next page