出國報告(出國類別:會議)

CMR International Institute for Regulatory Science

--「*Regional Alignment in Asia Pacific: What Needs to be in the Regulatory Science "TOOLKIT" to Enable Good Regulatory Decision Making?*」

亞太地區區域聯盟:如何促進良好的法規決策

服務機關：行政院衛生署食品藥物管理局
藥品及新興生技藥品組
姓名職稱：鄒玫君組長

派赴國家：日本東京
出國期間：100 年 1 月 24 日至 1 月 28 日
報告日期：100 年 4 月 22 日

內容摘要：（二百至三百字）

CMR International Institute for Regulatory Science 以"What needs to be in the regulatory science "TOOLKIT" to enable good regulatory decision making?"為題，一天法規單位閉門會議，一天擴大產業參與會，一天產官學研高階主管閉門會議，為行之有年，頗受重視之平台會議。FDA, EMA, PMDA 乃至亞太各國法規單位高階主管、產業代表皆受邀參加，台灣在會中介紹 TFDA 成立後藥政進展，APEC LSIF RHSC 台灣主導之 Best Regulatory Practice 計畫，倡議 APEC PER Scheme 審查報告交換意見。 會中 CMR 報告內部組織改組，各國強調藥物經濟學之 Health Technology Assessment 於新藥研發規劃中日益重要，CMR 推動 Good Review Practice 中計分卡 (Score Card) 和 Benefit/ Risk frame work for communication 計畫，並願意配合台灣推動 APEC PER Scheme 計畫，兩岸醫藥衛生合作協議於會中多人高度關切。

目 次

一、目　的：

CMR 下之 CIRS (center for innovation in regulatory science)乃一非營利機構，專職研新藥研發、上市、生命周期法規科學管理，每年一度邀請產、官、學、研高階主管閉門會議，深入討論上述領域各國發展、國際趨勢，進而對該公司之研究策略提出建言，本次會議主題為「Regional Alignment In Asia Pacific: What Needs To Be In The Regulatory Science "Toolkit" To Enable Good Regulatory Decision Making?」，藉此會議，可迅速掌握議題全球脈動，推廣台灣成果，充分和各界互動，進而在相關亞太區域議題主導。

二、過　程：

1. 本次大會，台灣由財團法人醫藥品查驗中心執行長陳恆德醫師及職與會。

2. 本次職受邀於 1 月 26 日發表演講（如附件一），除介紹台灣 TFDA 成立後之組織現況及藥政最新進展外，並就台灣在 APEC LSIF 中主導之 Best Regulatory Practice 計畫，提出交換審查報告之優點分析，說明未來應透過審查的經驗交換、強化溝通與資訊的分享及建立審查人員交換機制等議題，與各國分享交流，以促進藥品法規國際協和化。

3. 陳恆德醫師於主持分組討論 "Sharing Assessment Reports for the Review of New Medicines" 時，提出 CDE NDA 審查報告乙份(事前經禮來公司同意)為範例，說明 APEC PER (Pharmaceutical Evaluation Report) Scheme 之交換審查報告，將可促成各法規單位之 good review practice，於報告格式、審查流程、風險管理、個案爭議點, 充份交流，並善用有限之審查資源，加速審查時效，CDE 報告以英文撰寫，內容詳實，頗受各國好評，並由禮來公司與會代表 Patrick O'Malley 代表該組報告 CMR /CIRS 亦表示將考慮是否加入推動。

4. 於 1 月 27 日會議結束後，CDE 陳恆德醫師及職和 CMR 執行長 Lawrence Liberti ， Health Canada Supriya Sharma (Therapeutic Product Directorate，Director General)，APEC LSIF RHSC 主席 Mike Ward 召開會議後討論，CMR CIRS 同意一個月內依台灣報告之 APEC PER Scheme 寫成說

帖(附件二)，於 3 月初 APEC LSIF Planning Group Meeting 之華盛頓 D.C 會中討論，此將使台灣推動之 APEC 計畫，得以更宏觀的推動。

5. 大會中，多人表示對 2010 年 12 月 21 日簽署之”兩岸醫藥衛生合作協議”未來發展高度關切，職即時請大會印製該協議產業界翻譯之英文稿供與會人士參考，各方皆認為此協議將有助於中國大陸於法規現代化，提升台灣在區域新藥研發中扮演之樞紐角色。

6. 會中多人提及藥物經濟學的 Health Technology Assessment （HTA）日益重要，歐盟 EMA 和英國 NICE 已有對產業界聯合新藥研發諮詢的例子，台灣 2007 年前，將 HTA 設組於 CDE 中，正符合此大趨勢，近日中國大陸亦將來訪該組。

7. CMR 提及內部改組，原單位稱"International Institute for Regulatory Science"，2011 年 1 月 1 日起新單位稱為"Center for Innovation in Regulatory Science"，除延續原計畫外，將拓展對 HTA 及 Emerging Market 法規科學重點，CMR 並於會中提出對 Good Review Practice 之計分卡"Score Card"，讓法規單位和業界對某一 NDA 個案互評，以求改進，另亦提出"Benefit/Risk frame work for communication"，以研究為何不同法規單位對同一套資料做出不同決定之原因，此建議已得到 EMA 之支持。

8. KFDA 提到審查人力不足、薪水低、工作重、缺醫師審查員等，但有審查員送出國 1-2 年訓練制度，近日內部改組"National Food and Drug Evaluation Institute"，收納原做研究人員，改支持審查，對國際法規之採納，乃從其寬者，逐步落實，使國內廠商有過渡期。

9. EMA 提及 Scientific Advice 對新藥研發成功率有正面影響，絕大部份建議皆被 CHMP 最後 NDA 審查團隊接受。

10. 新加坡 HSA 報告送件審查、藥品管理電子化。

11. UK MHRA 提及病人參與新藥查驗登記決策之風險/利益評估乃趨勢，且上市後要監測藥品安全有效性。

12. 加拿大強調 GRP 對審查員之內部訓練。

13. 產業界強調全球同步研發、送審已為主流，因此法規協合更形重要，但要奠基於法規科學上。

三、心　得：

生技製藥乃一法規密集之國際產業，但又須經各國法規單位個別審查，方能上市。因此在 ICH 國際法規協合大原則下，各國如何建立法規科學之審查能量、流程、原則，則為時時須更新現況、掌握大趨勢的一重要課題，CMR 年度法規科學會議，則為一行之有年，頗受重視之平台會議，歷年來美 FDA、歐盟 EMA、日本 PMDA 乃至亞洲各國法規及各跨國大藥廠高階主管都例行受邀與會，例如 EMA 剛卸任執行長 Thomas Lonngren 受邀為 keynote speaker、美國 FDA 駐北京辦公室主任 Christopher Hickey、APEC LSIF RHSC 主席 Mike Ward 等人，台灣由職代表與會，並於會上介紹我國 TFDA 成立後之藥政最新進展，以及我於 APEC LSIF 中主導之 Best Regulatory Practice 計畫現況；另財團法醫藥品查驗中心執行長陳恆德醫師，並獲邀擔任於「Sharing assessment report for the review of new medicines」之主持人，我國藉此機會充分與各國藥政官員及製藥相關與會人士交流互動，同時討論之議題，亦備受重視。

四、建議事項：

1. CMR 年度法規科學平台會議，乃重要平台，宜派高階主管與會，長期深耕，主導議題，擴大國際合作，行銷台灣。

2. 建立之人脈、議題，宜落實於平日互動、策略調整，此乃台灣在許多國際關係受限下之生機。

3. 兩岸合作議題逐漸發酵，宜適時於各國際場合中報告，可使台灣於新藥研發之產業價值鏈地位重新定位，加速拓展各國法規單位雙邊關係。

4. CMR 可長期為 APEC LSIF RHSC 台灣主導之 APEC PER Scheme，GRP Workshop 之合作夥伴。

五、附　　件：

附件 1. 專題演講簡報

Sharing Assessment of Regulatory Approval or Assessment Reports – Could This be an Effective Way for Agencies in Asia Pacific to Use Regulatory Resources?

Jan. 25, 2011

Meir-Chyun Tzou, Ph.D.
Director, Division of Drugs & New Biotechnology Products, TFDA

Dilemma for Regulatory Agency

- Limited regulatory resources with overwhelming workload and increasing complexity and expectation from all stakeholders
- Build-in uncertainty for drug safety – "Drug Lag" vs "Drug Withdrawal"
- Safety beyond the boarder – global drug development, supply chain, ethnicity, safety signal

Potential Solution to Avoid Duplicate Assessment

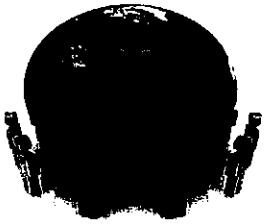
- Standardization: ICH, GHTF, PIC/S
- Mutual recognition: EMA, ASEAN
- Bilateral agreement among countries
- Partnership in Harmonization: APEC, Tripartite, ICH GCG
- Administration requirement: CPP

Why not Sharing Assessment Report?

- Confidentiality data of company esp. CMC data
- Different review approach, template and regulatory consideration
- "Lack of confidence" or "Strong ego" in assessment

Why not Just use FDA/EMA/PMDA Assessment Report on the Web Site?

- Good reference but can be better – Ethnic sensitivity, accumulated safety data, different indication approved, life cycle management of drug



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Advantage of Sharing Assessment Report

- Transparency, Efficiency, Predictability, Consistence
- Improve Good Review Practice – Review quality, template, process, peer group interactions
- "Compare and Contrast" from different, spot check the concerns risk/benefit decision
- Share responsibility and liability via public private partnership

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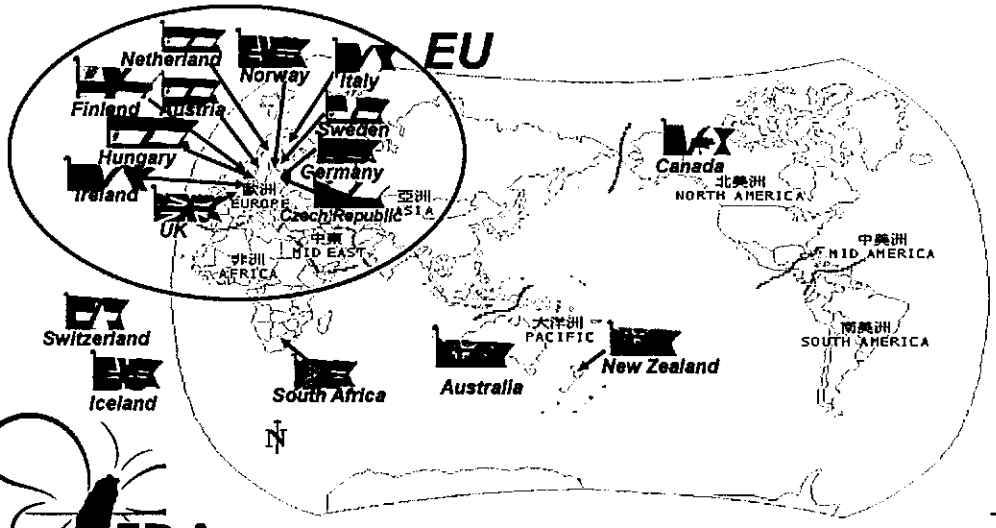
APEC "Best Regulatory Practice Project" (I)

- A 2-year APEC project leaded by Taiwan cosponsored by Canada, China, Indonesia, Korea, Malaysia, Mexico, Peru, Philippine, Thailand and US
- "Partnership in Harmonization" is the key
- Build up capacity of regulatory science via GRP workshop on drug and medical device targeting on regulators

APEC "Best Regulatory Practice Project" (II)

- APEC PER (Pharmaceutical Evaluation Report) Scheme for sharing of regulatory assessment report – follow the successful
- Example of PER Scheme (1979-2000) and them EMA centralized procedure

A Model in the Past: PER Scheme 1979-2000 - EFTA as secretariat



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Current Status for Sharing Reports

- E1: Lilly agreed that Taiwan can share CDE's assessment report of Atomoxetine for ADHD to regulators in the GRP workshop for drug in Nov. 2010
- Concept endorsed by PhRMA & EFPIA and presented in many regional conferences
- Taiwan – China Cross-Strait Medical and Health Care Cooperation Agreement

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Pilot study for APEC PER Scheme

- Select a few marketed products approved by several regulatory agencies to exchange NDA assessment reports with the permission from the license holders
- Evaluate the experience of these "case studies" in GRP, review template and administrative requirement
- Preliminary interest from PhRMA SGD Committee, EFPIA ICH GCG Regulatory Forum, some RA (Health Canada, TGA, etc.) and Individual companies (Eli Lilly, Novartis, etc.)

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A Pilot Case Study of APEC PER Scheme

- Atomoxetine (STRATTERA®)-Eli Lilly, NDA approved in 2006
- A selective norepinephrine reuptake inhibitor
- Indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD)
- Letter from Eli Lilly: CDE/TFDA's regulatory information (except CMC) can share with DRAs in this workshop

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CDE Review Team

- Project manager
- CMC
- Pharmacology/Toxicology
- Pharmacokinetic/Pharmacodynamic
- Clinical
- Statistical
- Primary reviewer plus secondary reviewer in each section
- Supervisor

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CDE Electronic Database: Life Cycle Management

案件案號			藥品組									藥品組	
TFDA文號	CDE案號	藥品名 (成分名)	待辦	移案 CDE	收文 登記	審查 作業	補件 作業	審查 作業	報告 完成	意見 回覆	業審 會	呈判 發文	結案
3501565	91IND12107 1	Strattera (Atomoxetine Hydrochloride)											✓
3501566	91IND12107 2	Strattera (Atomoxetine Hydrochloride)											✓
3501708	91IND12107 3	Strattera (Atomoxetine Hydrochloride)											✓
3501754	91IND12107 4	Strattera (Atomoxetine Hydrochloride)											✓
9701248	97IND01002	Strattera (Atomoxetine Hydrochloride (LY139603))											✓
1626101	94NDA07052 1	Strattera 10 mg (Atomoxetine)				▶							
1626101	94NDA07052	Strattera 10 mg (Atomoxetine)											✓
9401560	94NDA09071 1	Strattera 60 mg (Atomoxetine)											✓

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Reviewer's Training and Quality Control

- Review team :

- Consultation with a group of 100 domestic experts and 5 oversea contracted consultants with FDA experience
- Regular case discussion, review guidance discussion and drafting
- Structured training and evaluation program for primary and secondary reviewers

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Review Conduct

- Review template with consistent formats, logical rational and discussion for regulatory decision
- Data bank can refer to all previous interactions and similar cases for an integrated and consistent review
- A team approach with adequate communication with sponsors and academia

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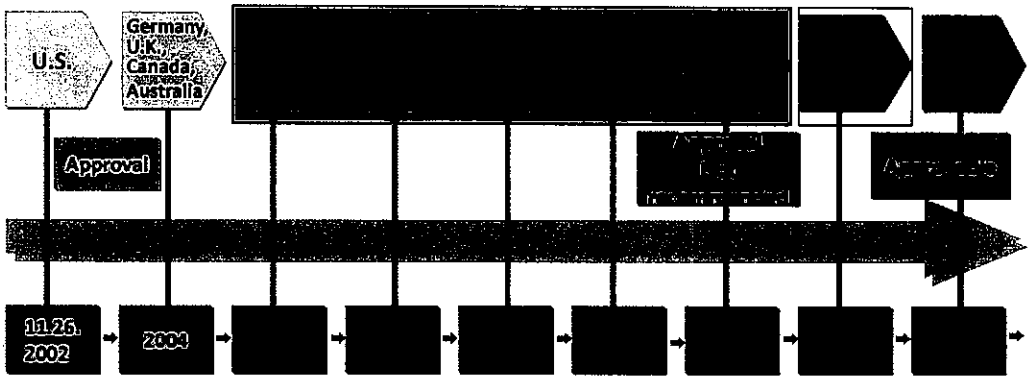
Review Process (continue)



transparent review process for sponsor

*: searchable from CDE website

#: searchable from DOH website

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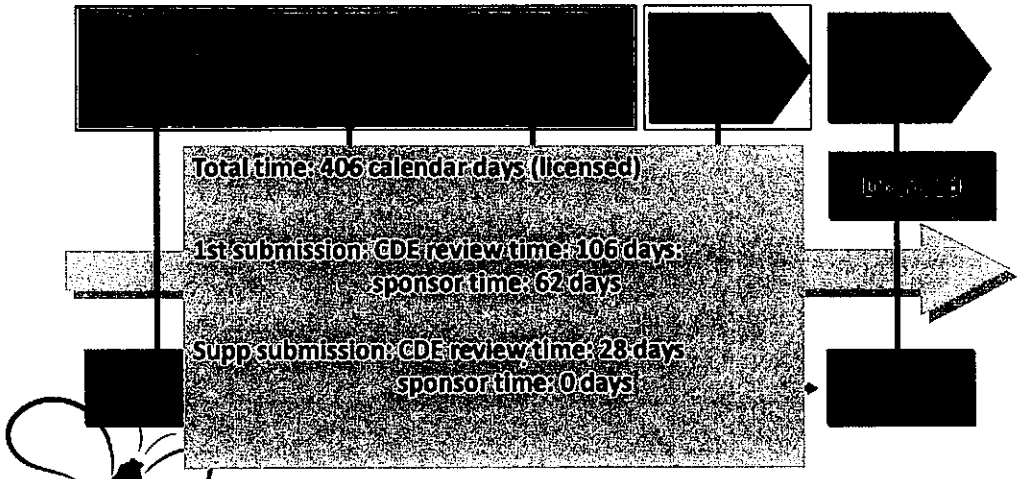
Review Process (continue)



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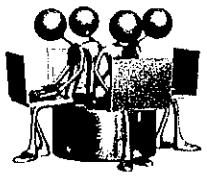
Request for More Data

- PSURs – FDA approved in 2002, EMA in 2004
- Registration trial report conducted in Chinese Taipei – IND in Taiwan in 2002: placebo controlled, DB, RCT for 6 wks in 106 children and Adolescence in 2 hospitals → Result statistic significant for superiority



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Review Report (I): Mostly in English Except Cover Page in Chinese

Confidential 94NDA07052~71-Strattera® 10 mg

Table of Content

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Review Report (II)

Review Report (III)

Review Report (IV)

Any Special Issue or Local Concern

- **PK/PD**
- Atomoxetine metabolized by CYP2D6
- Difference in the proportion of population with CYP2D6 PM status: 5-10% in Caucasians and 0-2% in Asians, but Asian have 24% IM (Intermediate Metabolizer)
- The AUC of PM was 10-fold higher than EM
- No dose adjustment for IM and PM in terms of safety from clinical trial

Any Special Issue or Local Concern?

Clinical

1. Severe liver toxicity noted after drug approval in the US
2. Warning issued for severe liver toxicity (2008)
3. Black box warning issued for suicide ideation (2006)
4. QT prolongation side effect noted after drug approval

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Concurrent Review in US

- Cardiovascular events discussed at a Feb. 9-10, 2006 meeting of FDA Drug Safety and Risk Management Advisory Committee

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More Data Submitted

- Liver toxicity: 373 reports received in 3,710,000 patients. Mostly mild abnormality with severe toxicity very rare.
- Suicidal ideation: 669 reports from Nov 2002 to Nov 2005. The rate of 0.013% was not higher than the rate of suicidal attempt and self injury in general population.
- QT prolongation: 27 cases from Nov 2002 to Nov 2004. No TDP case found.

FDA

Decision Made By AC

- Approval recommended with warnings and data added to drug label on liver toxicity, suicide ideation, CYP2D6

1. 肝毒性方面：自 2002 年 11 月至 2005 年 11 月，據估已有 371 萬人使用過本藥，共接獲 253 件與本藥使用可能初步相關之報告，本藥導致肝毒性之機會不大，但可能造成極少數嚴重之案例，此點尚不足以完全否定本案之申請（以目前之 Risk/Benefit Ratio 看來），但務必詳列相關警語於仿單上。
2. 自殺意念方面：自 2002 年 11 月至 2005 年 11 月，據估已有 371 萬人使用過本藥，共接獲 490 件可能和用藥相關之自殺相關報告，較之於一般族群之 suicide ideation or attempt 的機率，該數字是否顯著增高仍難認定，但仍應仿 FDA 核准仿單之作法，詳列相關警語於仿單上。
3. 慢代謝型者（Poor Metabolizer (PM)）之血中濃度可高過快代謝型者（Extensive Metabolizer (EM)）十倍，故理應仿肝功能障礙者調降劑量。不過因臨床試驗中顯示 PM 者對本品仍可耐受，且我國 PM 之族群比例小於西方人，而在用藥時亦無法得知該病人是否係屬 PM，故勉強可同意毋需特別針對 PM 者調低劑量之作法，但因 PM 者在諸多副作用之發生率上的確高於 EM，而且我國 PM 之比例雖低，但 IM（Intermediate Metabolizer）之比例則高於西方人（即 EM 之比例低於西方人），故建議仿單中用法用量一欄加註："由於 PM 及 IM 之病人，使用本藥將有較高之血中濃度與副作用之發生機率，而我國之 IM 族群比例較西方人為大，故在調高劑量時宜特別審慎，注意病人之副作用發生情況，且不可超過前述之最大每日總劑量"。

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Future Perspectives on Pharmaceutical Regulatory Issues

- **Sharing review experience**
  - exchange review reports of IND/NDA/IDE/PMA/BLA
  - ethnic issue study by retrospective data surveillance
  - establish *bridging study* review consensus.
  - Fast tract review for IND/NDA, Joint IRB
- **Enhance pharmaceutical regulatory networking**
  - joint training program, e.g., GRP, GCP inspections
  - communication and information sharing, e.g. ADR report
  - potentially harmonize the review process, report format, data requirement
- **Establish reviewer exchange program**

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Thank You for Your Attention

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附件 2. CMR CIRS Proposal of APEC PER Scheme for APEC LSIF

Proposal Title: *The Development of a Framework for Sharing Assessment Reports of Market Authorisation Applications Among APEC Member Economies*

Sponsors:

Dr Herng-Der Chern, Executive Director, Center for Drug Evaluation, Taiwan, R.O.C.

Dr Michael Ward, Manager, International Programs Division, Health Canada

Background:

All mature National Regulatory Authorities (NRAs) and many evolving agencies produce an "Assessment Report" (AR) designed to summarise the key data within the market authorisation application (MAA), to highlight likely benefits and potential risks of the new product, and to provide a rational scientific justification for their ultimate regulatory decision. These ARs become important repositories of knowledge which, if organised in a consistent manner, can be used by other NRAs to provide additional input into their detailed review, or to serve as a proxy upon which a more streamlined decision process can be built to accelerate patient access to key therapies.[1]

NRAs, especially those within the rapidly emerging APEC economies, are seeking ways to expedite the scientific review of MAAs while ensuring a high level of certainty regarding the product's quality, efficacy and safety especially as these relate to their specific constituents. In some NRAs, limited resources constrain the ability to readily review all dossiers in a timely manner. All strive to reduce the 'drug lag' in their jurisdiction and to address the evaluation costs to both companies and regulators, especially through more efficient use of experienced reviewers and regulatory affairs personnel, of which there is a global shortage.

One approach to facilitating this process involves categorising MAAs using a "risk-based' approach, through which those products that may be associated with more difficult benefit-risk profiles or which may pose unique problems to a particular region's constituents would be the targets of a NRA's more comprehensive review. Many NRAs currently use this approach, using the CPP to facilitate the review process; the review of these products could be enhanced by understanding the findings and rationale for

approval/non-approval from other NRAs. Therefore, sharing knowledge about a product across NRAs could reduce duplicative efforts, allowing each NRA to focus on their areas of expertise, and permitting each NRA to concentrate their resources on products that may have a unique impact on their constituents. [2] Observing the questions and answers addressed by other NRAs during prior assessments of the product could also reduce duplication of information requests to sponsors and potentially shortening the review process.

Review models

Types of evaluation

Primary review
- Single complete, independent review
- Examples: FDA, PMDA new drug reviews

Secondary review
- Partial, focused evaluation carried out after a primary evaluation has been undertaken elsewhere
- Examples: EU mutual recognition and decentralised procedures

Tertiary review
- Acceptance of a review carried out elsewhere
- Examples: New GCC process; objective of the EU Mutual recognition procedure

Review process

Shared/Joint review
- Collaboration between different agencies on the same product
- Example: EMEA centralised process

CPP exchange
- Use of evidence of regulatory status and quality in country of export
- Support for secondary and tertiary reviews

Sharing the burden of assessing MAAs is not a novel concept, having been pioneered by the PER Scheme more than 20 years ago. Secondary and Tertiary reviews (see box) depend upon obtaining information on primary assessments carried out elsewhere and, building confidence in such reviews. The **PER Scheme** for the exchange of *Pharmaceutical Evaluation Reports* was an important part of the 'evolution' of such processes among the more developed agencies. Set up by EFTA, in 1980 the scheme allowed assessment reports to be exchanged initially between European countries and later extended to Australia, New Zealand, South Africa and countries emerging from the Soviet bloc. This was an 'open' exchange scheme in which industry retained the rights to see the reports, to comment and (on very rare occasions) refuse to allow release of the report.

Translation of the reports was an industry obligation. The PER scheme promoted the development of evaluation guidelines, assessment checklists and templates and mutual confidentiality agreements. During its existence, *the scheme shortened assessment times by a mean 40 days and reduced, by an estimated 30%, and* the resource requirements of recipient authorities. The scheme had strong support from industry and increased understanding and co-operation between agencies. The scheme was abandoned primarily because the EU participants found it redundant once European Pharmaceutical Evaluation Reports (EPARs) were developed and available to agencies. There are opportunities to be further explored for the exchange of evaluation reports

in the Asia Pacific Economic Community (APEC) region and to learn from past experiences [3]. Today, many NRAs informally rely on the FDA's Summary Basis for Approval (SBA) and EPAR and using ARs from mature agencies can serve as a good reference; however, the use of regional ARs can provide more specific experience regarding ethnic sensitivity, accumulated safety data, different indications, and the life cycle management of drug [4]. It is key to bear in mind sensitivities that the industry may harbour regarding this sharing of ARs: these include issue surrounding intellectual property protection and other confidentiality topics, a perception that expecting a NRA to use another NRA's AR may paradoxically add to the overall review time, etc. Therefore, the goals of this project must clearly communicate the benefits to NRAs, industry and ultimately, patients.

The review of selected (ie, less risk-prone) products could be streamlined by relying on reviews conducted by other competent authorities. Sharing ARs could enhance the transparency of decision-making within a NRA. At the APEC Good Review Practice Workshop on Pharmaceuticals (Taiwan, ROC; Nov 3-6, 2010) the participants noted that tools and methodologies that all regulatory agencies can share (including best practices, the use of a common AR template etc) was a priority among reviewers, but all agreed that there was the need to first set a common baseline regarding these activities. The APEC "Best Regulatory Practice Project" strives to use ARs to help improve Good Review Practice – encompassing quality, template, process, peer group interactions.[4]

It is the goal of this project to support the above initiative through the development of a formal framework (in this context defined as the tools and guidelines for their us) by which NRAs of APEC member economies can facilitate the preparation and sharing of ARs to accelerate access to new medicines by focussing resources on the most critical products.

Objectives:

- To establish best practices for the risk stratification and use of assessment report information from other NRAs and
- To establish if it would be possible to promote the use of such information by NRAs within the APEC region.

The overall objective of this programme is to build a framework (tools and guidelines) to facilitate the sharing of AR among APEC member economies. **In order to accomplish this, it will be important**

- To determine if the development of a model Assessment Report (AR) is appropriate and what the common elements would be required to build confidence in their acceptance
- To understand how APEC NRAs create and use ARs in their medicines approval processes
- To identify best practices to guide the sharing and use of the AR by NRAs
- To understand NRA transparency initiatives and how the AR plays a role in improving efficiency, transparency, and predictability

Methods:

This programme is envisioned in three stages: **survey, research** and **pilot**.

In order to accomplish the goals of this proposal, a baseline understanding of how ARs are now being used across the APEC NRA community is required. **A survey** of NRAs is proposed to accomplish this task. This survey is described in more detail under "*Initial Activities*" below.

The survey responses will be supplemented by **further research**. This will investigate:

- Processes used to prepare ARs, especially by mature agencies around the world
- How SOPs support the use of ARs

The results of the survey and research will help determine if the develop of a model AR is appropriate activity whose return-on-investment will benefit the member economies. This will be tied to a detailed assessment of each member economy's interest and stated goals of participating in parallel or shared dossier reviews and to determine how a model AR would facilitate this process.

ARs may take several forms, based on the needs of the end audience. Generically, a full AR, complete with internally document Questions and Answers regarding the product's review, forms the most comprehensive report.

An "Executive Report" is often prepared for internal agency use, summarising key aspects of the full AR. From this, a public report redacted of proprietary information, is prepared (ie, the European Public Assessment Report- EPAR; or the US Summary Basis of Approval) is created. Sharing the Full AR and Executive Summary with a second NRA can be accomplished where a MOU is in place, in response to a special request by the NRA and via a request to the sponsor company, which may translate the AR for the second agency. This project will determine the most convenient methods for sharing the relevant types of ARs

The final phase of this project will be a **Pilot programme** using AR exchanges among volunteer member economy NRAs. If approved by the LSIF, a "model AR" would be used in this pilot. The goals of this pilot will be:

- To test the use of a model AR
- To develop SOPs that can be used by NRAs to prepare and share [model] ARs
- To develop guidelines or Industry with respect to the exchange of ARs
- To determine what effect this process has on review/approval timelines
- To develop a training programme for reviewers focused on the use/review and preparation of ARs

Suggested steps in this process include [4]:

- Select a few marketed products approved by several NRAs to exchange MAA assessment reports with the permission from the license holders
- Evaluate the experience of these "case studies" in GRP, review template and administrative requirements
- Pursue preliminary interest from PhRMA SGD Committee, EFPIA ICH GCG Regulatory Forum, some RA (Health Canada, TGA, etc.) and individual companies (Eli Lilly, Novartis, etc.) to participate in such a pilot

Initial Activities- Survey:

This initial survey will set a baseline among participating APEC NRAs in the following areas of interest:

- What is the structure/format/language of ARs from various APEC economies?

- What are the common elements of these ARs? What is their level of details?
- Is a tiered risk-based approach used to prioritise MAA reviews? If so, by what criteria
- Are ARs from other jurisdictions currently used as part of a dossier's review?
- What guidelines are in place to standardise the use of other NRA's ARs?
- Is a model/template followed for the preparation of the AR? Is this guided by SOPs?
- Does the NRA participate in parallel MAA reviews?
- Does the NRA participate in shared MAA reviews (ie where each jurisdiction is responsible for the review of selected portions of the MAA and the results consolidated)? Is this something the agency aspires to conduct?

Other Parties to be Involved:

We propose that the survey and research be conducted by a neutral, independent organisation. Preliminary discussions have been conducted with the CIRS (the Centre for Innovation in Regulatory Science, Ltd.; formerly the CMR International Institute for Regulatory Science), a not-for-profit, London-based organisation that has interacted with APEC and the LSIF for almost a decade. CIRS has indicated their interest in this project and their willingness to provide support as directed by APEC LSIF. The contacts at CIRS are:

Lawrence Liberti, MSc, Executive Director
Neil McAuslane, PhD, Scientific Director
Prisha Patel, MSc, Emerging Markets Portfolio Manager

Timeline:

These activities are envisioned for this project (timeline TBD):

Initial review of this proposal	March 2011
Approval to proceed	

Survey Develop initial survey tool
Approval by Steering Committee
Period to conduct NRA surveys
Compilation and analysis of survey results
Delivery of Survey findings report

Research Develop research parameters
Approval by Steering Committee
Period to conduct research
Compilation and analysis of research results
Delivery of research findings report

Pilot Develop research parameters
Recruit NRAs
Period to conduct pilot project
Compilation and analysis of pilot results
Delivery of pilot findings report
Development of training programme
Implementation of review training programme

References:

1. Walker SW, Lumley C eds. Improving the Regulatory Review Process: Industry and regulatory initiatives. Kluwer Academic Publishers, Lancaster UK. 1996.

2. Gray A. Access to Medicines and Drug Regulation in Developing Countries: a Resource Guide for DFID. DFID Health Systems Resource Centre. 2004.

3. Jefferys D. Overview of Review Options. Presented at the CMR International Institute for Regulatory Science Workshop *Models of best practice for the regulatory review of new medicines*. 5-6 December 2007, Geneva, Switzerland

4. Tzou M-C. Sharing Assessment of Regulatory Approval or Assessment Reports – Could This be an Effective Way for Agencies in Asia Pacific to Use Regulatory Resources? Presented at the CMR International Institute for Regulatory Science Workshop *Regional Alignment in Asia Pacific: What needs to be in the regulatory science "toolkit" to enable good regulatory decision making*. 26-27 January 2011, Tokyo, Japan

附件 **3. Workshop Synopsis** (大會會後摘要報告)

Regional Alignment in Asia Pacific:

What needs to be in the regulatory **science "toolkit" to enable good** regulatory decision making

WORKSHOP
26 – 27 January 2011
Tokyo, Japan

Workshop Synopsis

CMR International
INSTITUTE FOR REGULATORY SCIENCE

The following is a high-level summary of key points from a Workshop conducted by the CMR International Institute for Regulatory Science (the Institute; currently known as the Centre for Innovation in Regulatory Science) on 26-27 January, 2011, in Tokyo, Japan.

Background to the Workshop

Regulatory agencies are rising to meet the challenge posed by the reality in which companies are not only undertaking global clinical trials but are also looking to make their products available to patients worldwide in a timely, often almost simultaneous fashion. In the developing pharmaceutical markets this has put pressure on the evolution of regulatory policy, infrastructure and resources, while in established markets resource implications along with the duplicative nature of some of the work is resulting in an increasing emphasis on collaboration and sharing of resources where possible As more agencies look to take a science-based approach to regulation and risk-based decision making, a common regulatory language is being developed as well as clarity around the resources required to approve and monitor new medicines. This has lead agencies to begin to discuss and work out how to cooperate in order to share information and activities, such as safety data and inspections, as well as exchange of staff. In addition, some agencies are looking to the exchange of assessment reports. Challenges to collaboration include differences in skill sets, experience and processes between agencies. The key question therefore is, what are the underpinning components of good regulatory decision making and what are the regulatory science tools that can be used to ensure a timely, high-quality, predictable and transparent process whilst ensuring an effective and efficient use of resources?

The key question therefore, is what are the underpinning components of good regulatory decision making and what are the regulatory science tools that can be used to ensure a timely, high-quality, predictable and transparent process whilst ensuring an effective and efficient use of resources?

The objectives of this Workshop were to:

- **Discuss good risk-based regulatory decision making** and what the components are that need to be built into the review process
- **Identify current initiatives/approaches** and understand how these are enabling the decision making process from companies and agencies perspective
- **Recommend what should be in the regulatory science "toolkit"** and how best this can be used as part of the regional alignment initiatives

The Workshop and its Syndicate Discussion Sessions provided a comprehensive look at and recommendations for the use of three key tools that can form the basis of a good regulatory decision making strategy: a Quality Scorecard for the assessment of dossiers and their reviews, a simple, standardised benefit-risk framework, and the foundational elements that can underpin the sharing of assessment reports among stakeholders. Each of these was addressed within the broader context of moves towards regionally harmonised regulatory activities.

GOOD REGULATORY DECISION MAKING: KEY COMPONENTS THAT BUILD PREDICTABILITY

Dr Satoshi Toyoshima, *Senior Advisor, Pharmaceuticals and Medical Devices Agency (PMDA), Japan* reported on the status of the five components of the PMDA four-year action programme for new drug reviews: improving the consulting service and review system; promoting global drug development; improving measures for ensuring public safety and reassurance; strengthening international programs including collaboration with Asian regulators; and advancing regulatory science within the agency, industry and academia.

The holistic paradigm of the United States Food and Drug Administration for ensuring the safety and efficacy of drugs throughout their life cycles was described by **Dr Christopher Hickey**, *Director, China Office, U.S. Food and Drug Administration (FDA), China* which consisted of good review management principles and practices, oversight of post-market drug safety and harmonisation and collaboration with other regulatory authorities

Noting that the quality of regulatory decisions are dictated by their accuracy, predictability and transparency, **Dr Zill Li,** *Emerging Markets Regulatory Strategy and Policy Lead, Merck & Co Inc, USA* detailed the quality measures, continuous improvement initiatives, training and education of assessors and communication efforts being undertaken by thirteen regulatory authorities in the Emerging Markets to meet these goals.

As the Chair of the Asia Pacific Economic Cooperation (APEC) Regulatory Harmonization Steering Committee (RHSC), **Mike Ward,** *Manager International Programs Division, Health Canada* detailed important new developments taking place within APEC in advancing regulatory harmonisation and cooperation, including the ratification of a multi-year strategic plan, moving from individual effort to more collective, coordinated and more effective action. A project plan to be implemented during 2011-2012 includes the development of a training program, a good review practice toolkit and a framework for the use and exchange of regulatory information.

According to **Dr Won Shin,** *Division Director, Korea Food and Drug Administration,* good review practices, training and international and regional cooperation are the most important platforms on which to build trust and partnership across agencies. This partnership is particularly important in the development of the rapidly growing Asian pharmaceutical market, which represents both the largest portion of the global population and an environment that highly encourages research and development.

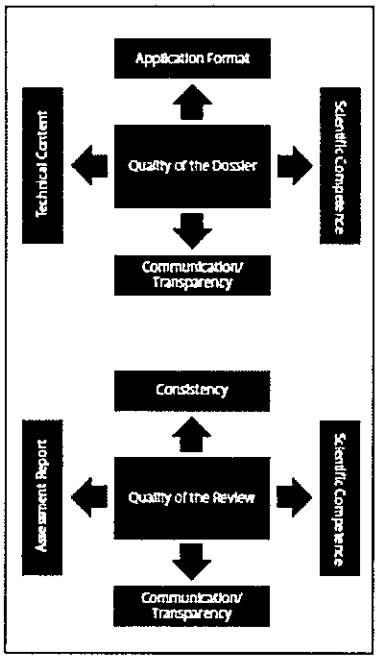
Dr Supriya Sharma, *Director General, Therapeutic Products Directorate, Health Canada* discussed the contribution of Good Review Practices (GRPs) to a well-functioning regulatory review system and to inter-agency cooperation. Although *good regulatory review* is a highly subjective concept for which there is no easy measure, there are ten hallmarks that point to an independent, objective, scientific and timely analysis of information relevant to a marketing application. A good review is knowledge-based, uses critical analyses, identifies signals, investigates issues, makes linkages, considers context, involves consultation, is balanced, thorough, and well documented.

Following the Scientific Advice obtained from a regulatory agency is one of the strongest predictors of regulatory success yet identified; how to best provide this advice in a consistent manner that can drive both regulatory and reimbursement decisions remains a matter of discussion. As the former Chair of the Scientific Advice Working Party (SAWP) of the Committee for Medical products for Human Use (CHMP) **Professor Bruno Flamion,** *Chairman, Belgian Committee for Reimbursement of Medicines (CTG/CRM), Belgium* reported that receipt of unfavourable scientific advice from the SAWP is a negative factor toward achieving marketing authorisation in the EU if the company does not change its development plans accordingly. The SAWP would welcome the opportunity to provide parallel scientific advice with other regulatory bodies and expects that it would be provided in collaboration with key European HTA and payers organisations in the near future.

Measuring Performance Across Regulatory Agencies: Improving Predictability and Regulatory Decision making through the use of Benchmarking and Quality Scorecards

Dr David Jefferys, *Senior Vice President, Global Regulatory and Healthcare Policy, Eisai, Europe Ltd, UK* provided an industry wish list for regulatory performance by an agency: rapid assessment and outcome determination; pragmatic, proportionate, justified decisions; balanced and transparent benefit-risk assessment; and predictability. Judging an agency's performance by metric benchmarking, however, is complicated by the fact that performance targets reflect different country regulatory systems and involve different definitions.

Improving predictability and regulatory decision making regulatory research programme : Scorecards. The Institute has developed two scorecards – one to measure the quality of the sponsor's submission and the second to measure the quality of the regulatory review.



Dr Neil McAuslane, Scientific *Director, CMR International Institute for Regulatory Science*, explained that because no agency works in isolation and because they are being judged by their stakeholders, timely, high-quality, predictable and transparent processes for the measurement of performance such as the Institute's Regulatory Benchmarking and Quality Scorecard programmes can help underpin good regulatory decisions, create a basis for improvement and aid in more predictable decision making.

For example, at Swissmedic, performance measurement is directly related to strategic goals and they have measures related to employees, process, finance, stakeholders and mandate, the results of which are reported as a balanced scorecard. **Dr Petra Dörr,** *Head of Management Services and Networking* reported that benchmarking information can used to support strategic planning discussion with stakeholders, and at Swissmedic such data have been used to support requests for additional resources to maintain global competitiveness.

KEY POINTS FROM THE SYNDICATE DISCUSSIONS

- **Scorecards and the Emerging Markets dossier:** Although the general consensus was that Scorecards are an appropriate element of the regulatory toolkit, issues must be considered relative to their application, transparency among agencies and industry and their relative place in the review process.
- **Added complexity of scorecard approach in Emerging Markets:** In addition to rating the quality of the dossiers received from sponsors, health authorities may need to rate the quality of information received from other health authorities (assessment reports).

APPLYING A STANDARDISED BENEFIT-RISK FRAMEWORK TO THE ASSESSMENT OF NEW MEDICINES

This is a clear need for a better understanding of why different agencies come to different conclusions when faced with essentially identical application data; this is a particularly challenging issue for regulatory agencies which are under growing pressure to increase transparency and accountability for their decision making. **Professor Stuart Walker,** *Founder of the Institute,* described the efforts underway to develop an international, structured, systematic and standardised benefit-risk framework as an essential part of the regulators' transparency armamentarium. He presented a summary of the seven steps of such a framework currently being developed by the Institute.

KEY POINTS FROM THE SYNDICATE DISCUSSIONS

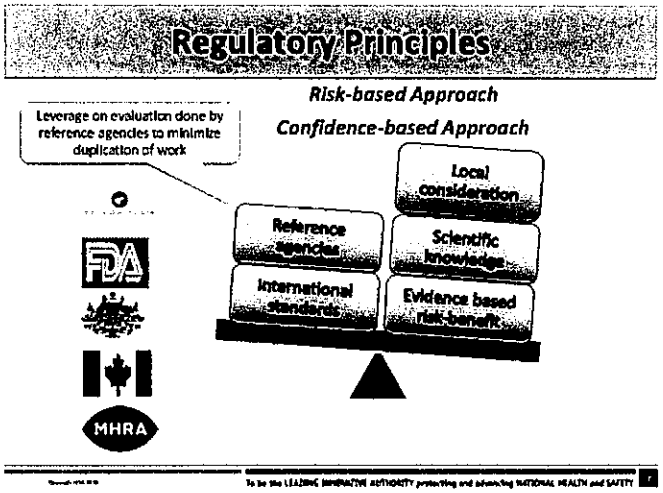
- **A proactive Emerging Markets benefit-risk plan:** Although benefit-risk evaluations are currently part of the regulatory review process in many Emerging Market countries, a formal codification would add structure, could improve overall assessment and facilitate inter-agency exchange of assessment reports. Countries with developing pharmaceutical markets should not wait for the United States FDA and the European Medicines Agency to implement a benefit-risk framework before initiating work in this area,
- **Integrating benefit-risk throughout a product life cycle:** To better understand a medicine's effectiveness, there should be a post-marketing plan to study benefit-risk in "real-world" settings.

SHARING REGULATORY ASSESSMENT REPORTS

During the course of this Workshop, it became clear that streamlining the regulatory process by sharing regulatory assessment reports is a win-win proposition for agencies in the Asia Pacific region. According to **Dr Meir-Chyun Tzou,** *Director, Division of Drugs and New Biotechnology Products, Food and Drug Administration, Chinese Taipei,* such collaboration will save resources, lead to better review quality and earlier approval of and access to medicines. A pilot study of best regulatory practice will be conducted by APEC in 2011-2012 and is co-sponsored by 10 other countries.

Joseph Scheeren, *SVP, Head of Global Regulatory Affairs. Bayer Healthcare, Pharmaceuticals Inc, USA* agreed that regulatory dialogue and sharing regulatory reports has many advantages and will allow a more efficient use of resources and earlier access to medicines. The chief challenges to this sharing will be language and standardisation barriers and a framework for partnership is required.

Dr Christina Lim, *Deputy Group Director, Health Products Regulation Group, Health Sciences Authority (HSA), Singapore* explained that although HSA does use information from other agencies in their decision making, the primary challenges in obtaining the best value for the exchange of regulatory reports are a lack of access to the data set submitted to other agencies in support of an application, the lack of avenues to seek clarification, and industry's expectation that regulatory approval in other countries would lead to HSA approval.



KEY POINTS FROM THE SYNDICATE DISCUSSIONS

- **Differences in format and content of assessment reports:** Assessment reports are highly variable in substance, level of detail. The extent of decision rationale and the details of the question and answers can be lacking.
- **Timing of global applications:** It was felt that although it is the sponsors' intent to achieve approval as quickly as possible, use of completed assessments could lead to delay of submission and approval. Challenges include varying levels of agency development, different visions, and language. Implementation of the sharing of reports requires agency and industry commitment and incentives for both sponsors and regulators should be defined.

CONCLUSION

Professor Robert Peterson, *Executive Director, Drug Safety and Effectiveness Network. Canadian Institute of Health, Canada* concluded the Workshop presentations by reminding the audience that the primary objective of regulatory agencies is the timely, predictable review of new medicines, permitting market entry of products with a positive benefit-harm profile while demonstrating value to national or regional healthcare systems. Strategies to accomplish this objective successfully in an increasingly complex global environment include regional harmonisation, scientific advice prior to submission, measuring performance, and use of GRP and a benefit-risk framework. Strategies for efficiencies meanwhile, include sharing regulatory assessment reports, parallel reviews, multinational regulatory consortia, use of other regulator's decisions and regional safety surveillance

SPECIAL THANKS TO:

The Workshops Chairs
Dr Thomas Lönngren, *Former Executive Director, EMA*
Professor Sir Alasdair Breckenridge *Chairman, MHRA, UK*
Professor Robert Peterson, *Executive Director, Drug Safety and Effectiveness Network. Canadian Institute of Health, Canada*

The Syndicate Chairs
Dr Lucky Slamet, *National Agency of Drug and Food Control, Indonesia*
Mike Ward, *Manager International Programs Division, Health Canada*
Dr Herng-Der Chern, *Executive Director Center for Drug Evaluation, Taiwan, R.O.C*

The Syndicate Rapporteurs
Jerry Stewart, *Regulatory Policy Head Emerging Markets, Pfizer, USA*
Carolyn Maranca, *VP, Global Regulatory Affairs – Asia Pacific and Latin America, Johnson & Johnson PRD, USA*
Patrick O'Malley, *Senior Director, International Regulatory Affairs, Eli Lilly & Co, USA*

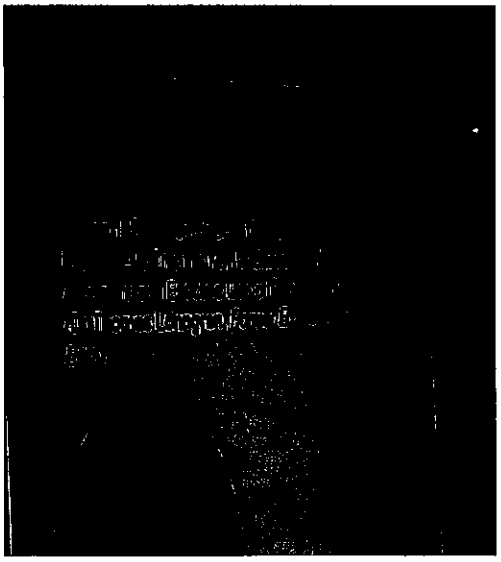
A complete Workshop Report including full presentation summaries and syndicate recommendations will be available shortly.

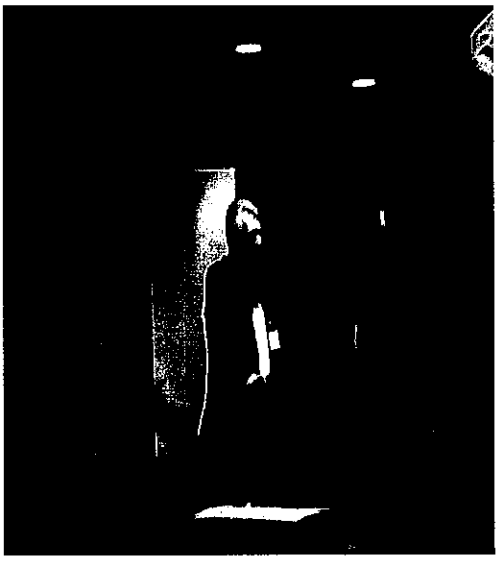
CMR International Institute for Regulatory Science
The Johnson Building, 77 Hatton Garden, London, EC1N8JS, UK
Email: institute@cmr.org Website: www.cmr.org

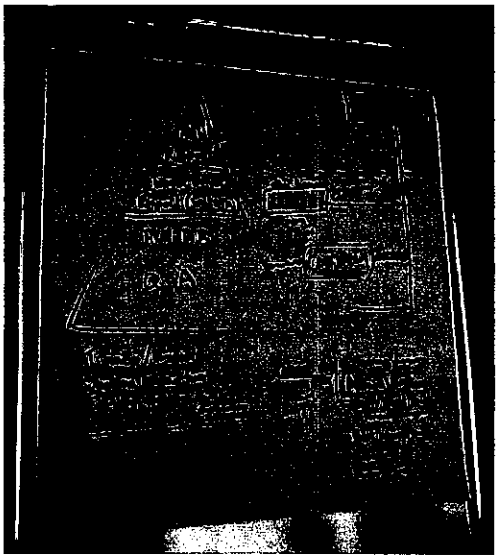
CMR International Institute for Regulatory Science 活動相片

Jan. 26-27, 2011
Tokyo, Japan

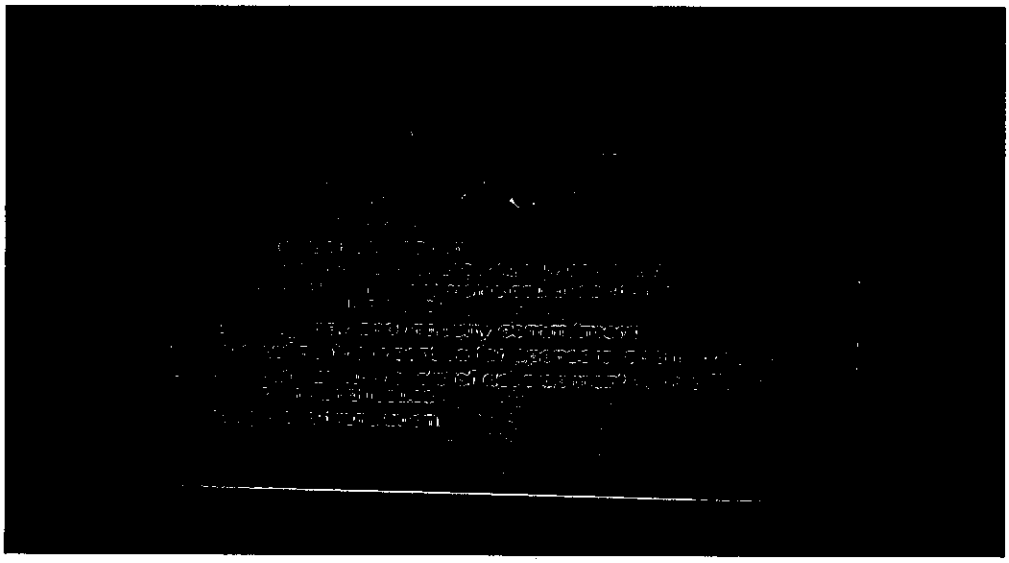
Dr. Thomas Lönngren



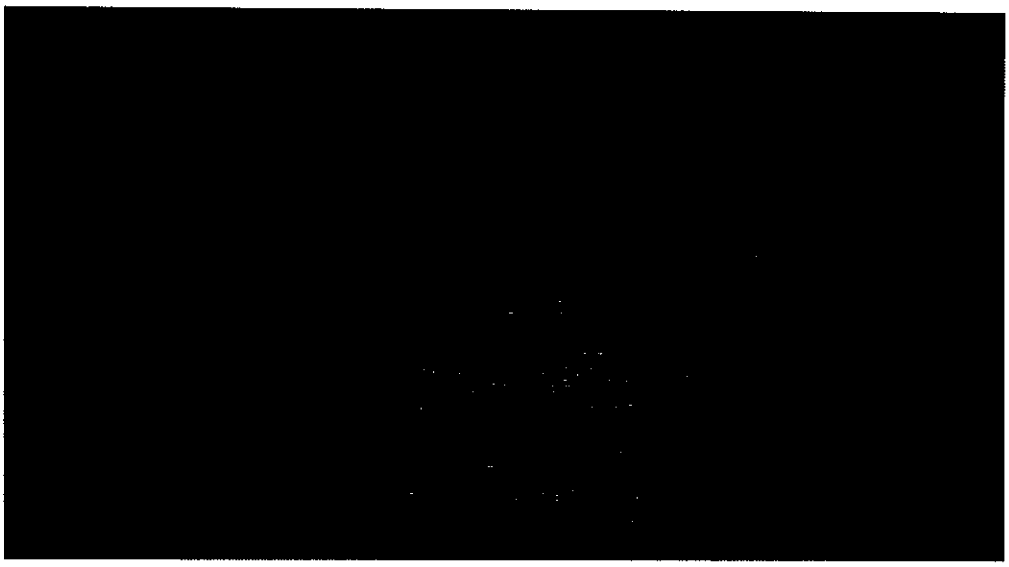




CMR Tokyo Session Summary

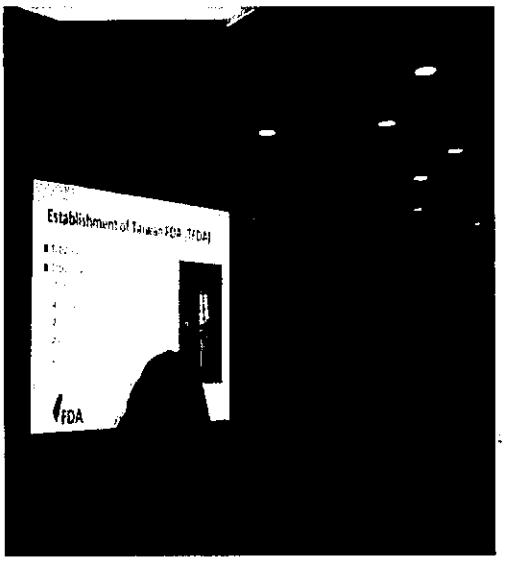


CMR Tokyo Session Summary



Taiwan's Presentation

- APEC week (2+1+2) in Sept. endorsed
- GRP case study of Eli Lilly: showed CDE NDA assessment report
- Cross strait agreement



Post Meeting Discussion-
CMR write a 2-page APEC PER Scheme Pilot Proposal for Comment