CAPRA Symposium on Diabetes Current Practice, Future Trends Review and Approval of New Drugs for Diabetes in Today's Climate

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Disclaimer

- Opinions expressed are those of the presenter and may not necessarily reflect those of Therapeutic Products Directorate.

Agenda

- The changing climate for the review and approval of “ethical” drugs.
- Recent guidance on risk assessment.
- Emphasis on risk minimization.

Climate Change

Tomorrow's "smart" regulator builds on today's and yesterday's experience.

- What was yesterday's regulatory climate?

Yesterday's Climate

- In the 1960s thalidomide was used by pregnant women in Europe and Canada to treat morning sickness. Women who took the drug in early pregnancy gave birth to children with severe birth defects such as missing or shortened limbs.
- Thalidomide was removed from the market.
- Subsequently, new regulations and drug screening methods were introduced.

Yesterday's Climate

- In 1970 the University Group Diabetes Program (UGDP) study was published.
- It was the first controlled trial to test the benefit of lowering blood glucose on the incidence of complications of diabetes.
- However, it showed no benefit of glycemic control in new-onset type 2 diabetics.
- Moreover, a major concern was the observation that the sulfonylurea agent (tolbutamide) and a biguanide (phenformin) were associated with increased cardiovascular mortality.

What is Today's Climate?

- The U.K. House of Commons, Health Committee, recently issued a report on the *Influence of the Pharmaceutical Industry.*
- This report provides a critical evaluation of today's climate that industry, regulators, doctors and patients now face.

Today's Climate

- "The consequences of lax oversight is that the industry's influence has expanded and a number of practices have developed which act against the public interest."
- "The industry affects every level of healthcare provision, from the drugs that are initially discovered and developed through clinical trials, to the promotion of drugs to the prescriber and the patient groups, to the prescription of medicines and the compilation of clinical guidelines."

Today's Climate

- "Once licensed, medicines are intensely promoted to prescribers. The very high costs of developing a new drug make it vital that a company recoups its costs as quickly as possibly after licensing..."
- "At the heart of the problem may be the trend for the industry to become ever more driven by its marketing force."

Today's Climate

- "Promotion of medicines to patients and links between drug companies and patient organisations may add to this problem, leading patients to demand new drugs from their doctors..."
- "GPs are particular targets; they have more prescribing freedom than hospital specialists."

Today's Climate

- "The most immediately worrying consequence of the problems described above is the unsafe use of drugs. Over-prescription of the COX-2 inhibitors, Vioxx and Celebrex, has been linked to thousands of deaths and many more cases of heart failure. This case illustrate a series of failures... there were inadequacies in the licensing and post-marketing surveillance procedures and excessive promotion of the drugs to doctors."

Today's Climate

- The report concludes:

  "We need an industry which is led by the values of its scientists not those of its marketing force."

Science Based Regulation

- The International Conference on Harmonisation (ICH) brings together scientists and regulators from industry and government to discuss and develop science based guidelines related to drug development and risk management.

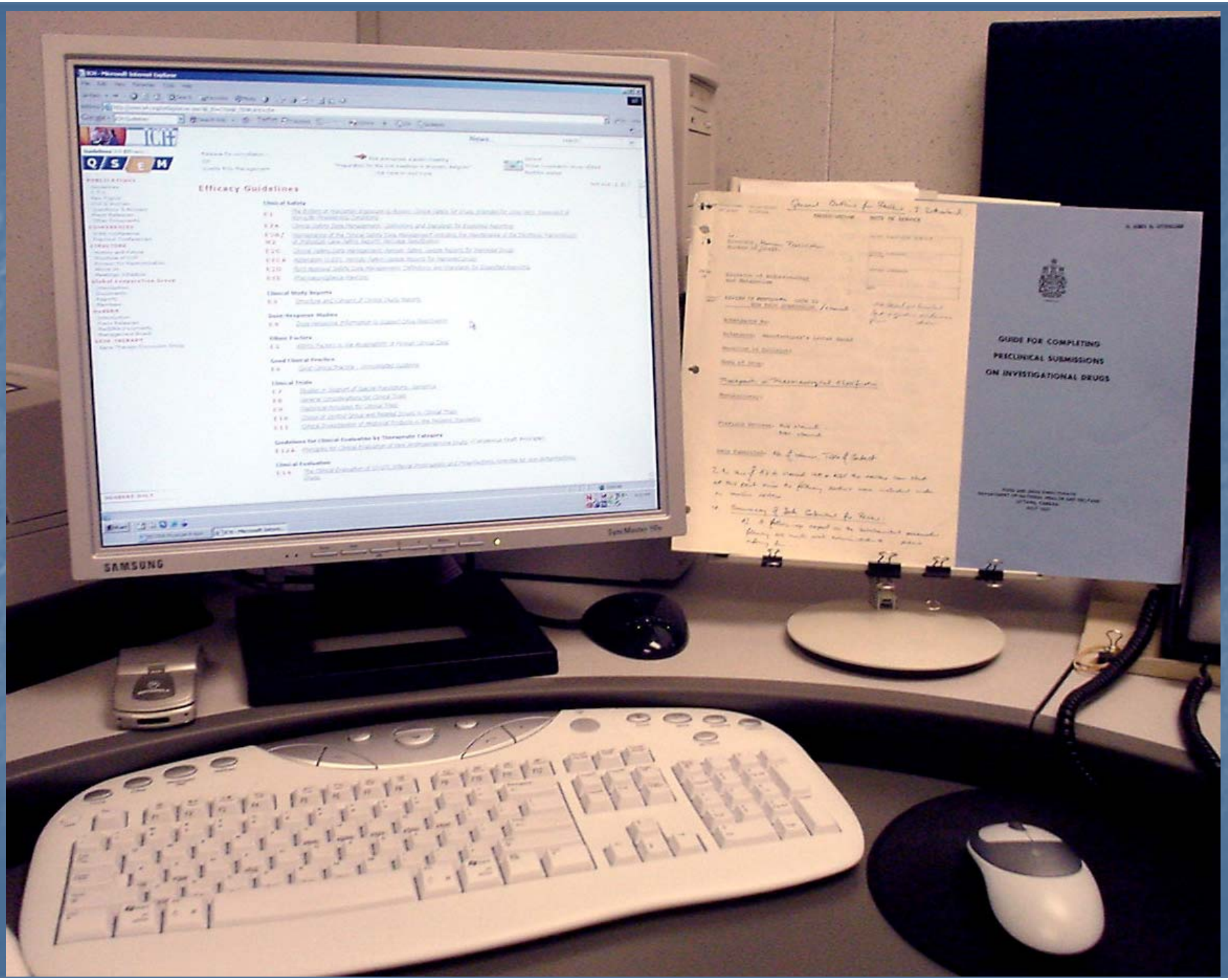
D. JAMES B. SUTHERLAND

GUIDE FOR COMPLETING PRECLINICAL SUBMISSIONS ON INVESTIGATIONAL DRUGS

FOOD AND DRUG DIRECTORATE
DEPARTMENT OF NATIONAL HEALTH AND WELFARE
OTTAWA, CANADA.
JULY 1965.

Sources of Guidance Documents

- Today there are hundreds of guidelines:
- International and Regional
  - ICH – Scientific & technical guidelines ~ 80
  - WHO, EMEA
- National
  - FDA, HC – Scientific & Regulatory
  - Associations - Clinical Practice guidelines


Efficacy Guidelines
GUIDE FOR COMPLETING
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ON INVESTIGATIONAL DRUGS
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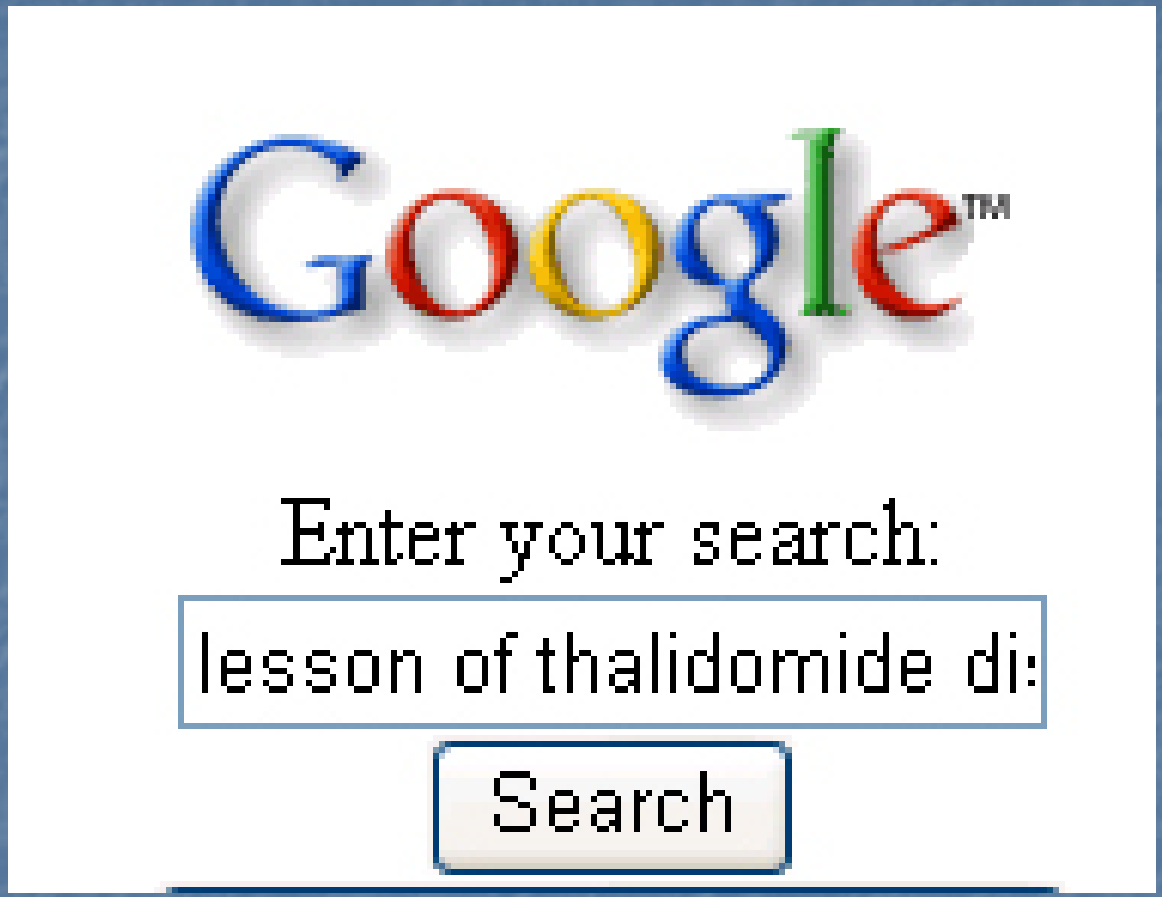
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Therapeutic Guidelines

- Howerver, to date, ICH has developed only one therapeutic category guideline – for antihypertensive drugs.
- In the area of diabetes, the latest guideline that has been developed was by the EMEA in 2002.
- *Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus*

Therapeutic Guidelines

- However, one may ask is the EMEA Diabetes Guidance equally applicable to the Canadian setting?
- Do we need additional bridging studies either due to differences in the practice of medicine or the needs of special populations (i.e, aboriginal peoples)?
- See ICH E5 Ethnic Factors Guideline

EMEA NfG - Diabetes Mellitus

- Therapeutic guidelines, while reflecting the state of scientific thinking at time of development, need to be considered together with more recent guidelines.
- Delays can occur in the review process when current issues have not been adequately addressed in the submission.

New Guidance

- So what are some of these newer guidances that need to be considered?

ICH Guidelines – S7B

The Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization...

This draft document addresses nonclinical testing strategies and integrated risk assessment for predicting the potential of pharmaceuticals for delayed ventricular repolarization (QT interval prolongation) associated with ventricular tachycardia and torsade de pointes.

ICH Guidelines – E14

The Clinical Evaluation Of QT/QTc Interval Prolongation And Proarrhythmic Potential

- QT/QTc studies are needed where nonclinical data is not able to preclude this risk. (see S7B)
- Applicable to approved drugs when new doses and rout of administration are being developed.
- Overall discussion of risk assessment should note how this potential concern has been evaluated.

ICH Guidelines – S8

Immunotoxicology Studies for Human Pharmaceuticals

Status: Step 3 released for consultation

- Recommendations on nonclinical testing for immunosuppression induced by low molecular weight drugs (non-biologicals).
- It applies to new pharmaceuticals, as well as to marketed drug products proposed for product label changes.
- Also applies to market drugs that show signs of immunosuppression (increased susceptibility to infections or to the development of tumors).

ICH E2E Pharmacovigilance Planning

- The planning of pharmacovigilance activities in preparation for the early postmarketing period.
- To be provided at time of filing or when a major safety concern has arisen.
- The two main parts are:
  1) *Safety Specification* and
  2) *Pharmacovigilance Plan*

1) Safety Specification

- The Safety Specification is a summary of:
  1) important identified risks of a drug,
  2) important potential risks, and
  3) important missing information.
- It considers the populations potentially at-risk.
- Also, any outstanding safety questions which warrant further investigation during the post-approval period.

Elements of Safety Specification

Populations to be considered should include:

- Children and the elderly
- Pregnant or lactating women
- Co-morbidity such as hepatic or renal disorders
- Differences in disease severity from that studied
- Sub-populations carrying genetic polymorphism
- Patients of different racial and/or ethnic origins

Elements of Safety Specification

- Limitations of the safety database
- Such as:
  - size of the study population
  - study inclusion and exclusion criteria

2) Pharmacovigilance Plan

Structure of the Pharmacovigilance Plan:

- Summary of Ongoing Safety Issues
- Routine Pharmacovigilance Practices
- Action Plan for Safety Issues
- Summary of Actions to be Completed
- Pharmacovigilance Methods
- Design and Conduct of Observational Studies

FDA Approach to Risk Management

The FDA approach to risk management is divided into three parts:

1) Premarketing Risk Assessment
2) Development and Use of Risk Minimization Action Plans (RiskMAP)
3) Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

1) Premarketing Risk Assessment

- Premarketing Risk Assessment guidance was issued in March 2005.
- It discusses the generation, acquisition, analysis, and presentation of premarketing safety data.
- It represents FDA's current thinking and interpretation of related ICH documents.

2) Risk Minimization Action Plans

Provides guidance on:

1) Designing *Risk Minimization Action Plans* or *RiskMAPs* to minimize identified product risks.
2) The selecting and developing tools to minimize risks.

Example of FDA Premarketing Risk Minimization Plan

- Let us now look at an example of a new diabetic drug recently approved in the US.

Symlin® (pramlintide acetate)

- The FDA approved Symlin in March 2005
- SYMLIN is a synthetic analog of human amylin, a naturally occurring hormone that is made in the beta cells of the pancreas.
- It is an injectable medicine to control blood sugar for adults with type 1 and type 2 diabetes.
- It is to be used in addition to insulin therapy in patients who cannot achieve adequate control of their blood sugars on intensive insulin therapy alone.

Symlin RiskMAP

Symlin Minimization Action Plan (RiskMAP) is needed to ensure that a sound plan is in place with applicable tools to minimize risks as part of the approval conditions.

1) Risk of hypoglycemia
2) Potential for medication errors
3) Potential for off-label use

Symlin - Medication Guide

- The Medication Guide informs patients that Symlin should only be used if they are already using their insulin as prescribed, but still need better blood sugar control; will follow their doctor's instructions exactly; will follow-up with their doctor often; will test their blood sugar levels before and after every meal, and at bedtime; and understand how to adjust Symlin and insulin doses.

Postmarketing Study Commitment

- Deferred pediatric study is a required postmarketing study commitment.
- A study in adolescents ages 12 - 17 years with type 1 and type 2 diabetes to evaluate the pharmacokinetics and pharmacodynamic effects of different subcutaneous doses of the drug.

Postmarketing Study Commitment

Commitment to conduct:

- multicenter, open-label, observational study to prospectively collect data that characterize drug use following introduction into the marketplace.
- Conduct of a postmarketing observational study to assess the potential hypoglycemic risk.
- Provide Protocol Submission Date, Study Start Date, and Final Report Submission Date.

Risk Management Agreements

- Agreement on risk management procedures designed to encourage safe and effective use of drug:
- No direct-to-consumer advertisement.
- No journal advertising for one year.

Risk Management Agreements

- Promotion limited to physicians who specialize in diabetes management and are supported by certified diabetes educators.
- Gradual introduction into the marketplace, with evaluation of patterns of use by “targeted” and “non-targeted” health care providers.

Risk Management continued

- Assess databases for information regarding prescription practices and submit the results of these assessments on a semi-annual basis.
- Education and outreach programs for health care providers and patients.

Risk Management continued

- Surveillance Plan: reporting of severe hypoglycemic events in an expedited manner for two years or as long as the study is ongoing.
- A 24/7 call center to assist patients and physicians with the use of drug
- Submit copies of promotional materials

Tomorrow's Regulatory Climate

- Therapeutic Products Directorate, by aligning itself with regulators from the United States, Europe and Japan through ICH, is committed to applying the best available scientific guidance and risk management tools to both the pre-market and post-approval of drug products.
- Drugs will be approved in a timely manner based on a satisfactory balance of benefits and risks within conditions specified in the product label and related risk minimization plans.

Concluding Statement

- One thing is crystal clear. The health benefits of ethical drugs contribute enormously to the quality of life of Canadians and have saved many lives.
- The Canadian Pharmaceutical Industry and its associations such as CAPRA play a vital role in ensuring that drugs are used both safely and effectively in Canada.

- Thank you -

Yesterday's Climate

- In the case of Accutane, the manufacturer developed in consultation with regulators, a Strengthened Risk Management Program called S.M.A.R.T., *the System to Manage Accutane-Related Teratogenicity*.
- Black Box Contraindications and Warnings along with use of prescriptions with yellow stickers.
- Patient Package with Patient Medication Guide along with Informed Consent/Patient Agreement forms to be signed before being dispensed.

Yesterday's Climate

- In 1998 the US FDA approved thalidomide to treat leprosy. In order to avoid tragic birth defects, several restrictions were established. Doctors prescribing and pharmacists dispensing thalidomide are required to participate in a program sponsored by the drug's manufacturer.
- Patients had to be educated about the drug's effects.