

1 Stephen P. Swinton (SBN 106398)  
2 LATHAM & WATKINS LLP  
3 12670 High Bluff Drive  
4 San Diego, CA 92130  
5 Telephone: (858) 523-5400  
6 Facsimile: (858) 523-5450  
7 Email: steve.swinton@lw.com

8 Nina M. Gussack  
9 Kenneth J. King  
10 PEPPER HAMILTON LLP  
11 3000 Two Logan Square  
12 Eighteenth & Arch Streets  
13 Philadelphia, PA 19103-2799  
14 Telephone: (215) 981-4000  
15 Facsimile: (215) 981-4750  
16 Email: gussackn@pepperlaw.com  
17 Email: kingk@pepperlaw.com

18 Attorneys for Defendant  
19 Eli Lilly and Company, a corporation

20 **UNITED STATES DISTRICT COURT**  
21 **SOUTHERN DISTRICT OF CALIFORNIA**

22 IN RE INCRETIN-BASED  
23 THERAPIES PRODUCTS  
24 LIABILITY LITIGATION

25 *This Documents Relates to All Cases*

MDL CASE NO. 13-md-2452 AJB (MDD)

**DECLARATION OF MATTHEW J.  
HAMILTON IN SUPPORT OF  
DEFENDANTS AMYLIN  
PHARMACEUTICALS, LLC AND ELI  
LILLY AND COMPANY'S MOTION  
TO STRIKE OR SEAL  
CONFIDENTIAL INFORMATION IN  
CERTAIN DOCUMENTS ATTACHED  
TO PLAINTIFFS' PAPERS RELATED  
TO THE DEFENSE OF PREEMPTION**

Hon. Anthony J. Battaglia

1 I, Matthew J. Hamilton, declare as follows:

2 1. I am an attorney with Pepper Hamilton LLP, counsel for Defendant  
3 Eli Lilly and Company (“Lilly”). I am licensed to practice in the Commonwealth  
4 of Pennsylvania. I have personal knowledge of the facts set forth herein. I submit  
5 this declaration in support of the Motion to Strike or Seal Confidential Information  
6 in Certain Documents Attached to Plaintiffs’ Papers Related to the Defense of  
7 Preemption.

8 2. Amongst the numerous exhibits to their papers, Plaintiffs submitted as  
9 an exhibit to their Memorandum in Support of Their Motion for Summary  
10 Judgment on the Affirmative Defense of Preemption the preemption expert report  
11 of a statistician, Dr. David Madigan; and attached as exhibits to their Response to  
12 Defendants’ Motion for Summary Judgment on Preemption grounds the general  
13 causation expert reports of Dr. Madigan and epidemiologist Dr. Kenneth Carson.  
14 One section in each of Dr. Madigan’s reports discusses Lilly’s confidential and  
15 proprietary information. Two sections of Dr. Carson’s report discuss Lilly’s  
16 confidential and proprietary information. As demonstrated below, compelling  
17 reasons exist to seal this confidential and proprietary information. While this  
18 Declaration, and the Declaration of Amy J. Laurendeau each address specific  
19 sections of the Madigan and Carson reports (and the documents to which they  
20 relate), Amylin Pharmaceuticals, LLC (“Amylin”) and Lilly as alliance partners  
21 share a common interest in the confidential nature of their documents, and each  
22 relies upon and adopts the rationale offered by the other. Documents attached  
23 hereto supporting our Motion are as follows:

24 3. A true and correct copy of the U.S. Food and Drug Administration  
25 Guidance for Industry – E2C Clinical Safety Data Management: Periodic Safety  
26 Update Reports for Marketed Drugs is attached as Exhibit A.

27

28

1           4.       A true and correct copy of the U.S. Food and Drug Administration  
2 Guidance of Industry – Addendum to E2C Clinical Safety Data Management:  
3 Periodic Safety Update Reports for Marketed Drugs is attached as Exhibit B.

4           5.       A true and correct copy of the ADA/EASD/IDF Statement  
5 Concerning the Use of Incretin Therapy and Pancreatic Disease is attached hereto  
6 as Exhibit C.

7           6.       A true and correct copy of the article entitled, “A Lone Voice Raises  
8 Alarms on Lucrative Diabetes Drugs,” which was authored by Andrew Pollack and  
9 appeared in the *New York Times* on May 30, 2013, is attached as Exhibit D.

10          7.       A true and correct copy of the statement entitled, “Pancreatic Safety  
11 of Incretin-Based Drugs – FDA and EMA Assessment,” which was published in  
12 the *New England Journal of Medicine* on February 27, 2014 and was authored by  
13 Amy G. Egan, M.D., M.P.H., Eberhard Blind, M.D., Ph.D., Kristina Dunder, M.D.,  
14 Pieter A. de Graeff, M.D., B. Timothy Hummer, Ph.D., Todd Bourcier, Ph.D., and  
15 Curtis Rosebraugh, M.D., M.P.H. is attached as Exhibit E.

16          8.       A true and correct copy of Judyth Pendell, *The Adverse Side Effects of*  
17 *Pharmaceutical Litigation*, AEI-Brookings Joint Center For Regulatory Studies  
18 (2003) is attached as Exhibit F.

19          9.       **Madigan Preemption report at page 3, ¶ 8; Madigan General**  
20 **Causation report at page 3, ¶ 9:** Lilly seeks to maintain under seal a single  
21 paragraph that appears in both the Madigan Preemption Report, p. 3, ¶ 8, and the  
22 Madigan General Causation Report, p. 3, ¶ 9. In that paragraph, Dr. Madigan  
23 discusses internal pharmacovigilance and safety analyses regarding pancreatic  
24 cancer and cites a document bates labeled LILLY02444252, which contains  
25 confidential e-mail communications between Amylin and Lilly employees between  
26 February 26, 2011 and March 1, 2011 regarding a confidential regulatory response.  
27 Lilly designated LILLY02444252 as Confidential.

28

1           **10.** Paragraph 8 in the Madigan Preemption and Paragraph 9 in the  
2 Madigan General Causation report reflect confidential discussions of preliminary  
3 safety data for pancreatic cancer. The document on which the report sections are  
4 based reflects the results of Lilly’s confidential analysis of a potential pancreatic  
5 cancer signal in Byetta safety data. The potential signal/data were discussed in  
6 confidential regulatory submissions, including a Periodic Safety Update Report.  
7 Periodic Safety Update Reports are proprietary and confidential per the FDA  
8 Guidance for Industry – Addendum to E2C Clinical Safety Data Management:  
9 Periodic Safety Update Reports for Marketed Drugs (Exhibit B hereto) which  
10 states at page 7: “PSURs contain proprietary information. Therefore, the title page  
11 of a PSUR should contain a statement on the confidentiality of the data and  
12 conclusions included in the report.”

13           **11. Carson General Causation report at pages 5-6, § IV.C:** This  
14 section of Dr. Carson’s general causation report discusses Lilly’s clinical trial data  
15 and internal pharmacovigilance and safety analyses regarding pancreatic cancer.  
16 Further this section is based on LILLY01451801, a document produced by Lilly  
17 and designated “Confidential – Attorneys’ Eyes Only” pursuant to the Protective  
18 Order. This document is the final study report for an internally conducted  
19 epidemiology study regarding the increased risk of *de novo* pancreatic and thyroid  
20 cancer in persons with Type 2 Diabetes compared to nondiabetics.

21           **12. Carson General Causation report at pages 32-33, § VII.E.2:** This  
22 section of Dr. Carson’s general causation report discusses Lilly’s clinical trial data  
23 and internal pharmacovigilance and safety analyses regarding pancreatic cancer.  
24 Further this section is based on LILLY01451801, a document produced by Lilly  
25 and designated “Confidential – Attorneys’ Eyes Only” pursuant to the Protective  
26 Order. This document is the final study report for an internally conducted  
27 epidemiology study regarding the increased risk of *de novo* pancreatic and thyroid  
28 cancer in persons with Type 2 Diabetes compared to nondiabetics.

1           13. Exhibits 4, 9, and 11 to the Declaration of Ana C. Reyes in Support of  
2 Merck Sharp & Dohme Corp.'s Motion to Seal the Parties' Summary Judgment  
3 Memoranda on the Affirmative Defense of Preemption and Accompanying  
4 Exhibits are proposed public versions of Plaintiffs' Exhibits which reflect these  
5 limited redactions of Lilly's confidential material, as well as those identified by  
6 defendants Merck and Novo Nordisk in their Motions to Seal.

7 //

8 I declare under penalty of perjury under the laws of the United States that  
9 the foregoing is true and correct.

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11           Executed on August 21, 2015 in the Commonwealth of Pennsylvania.

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15 Matthew J. Hamilton  
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# EXHIBIT A

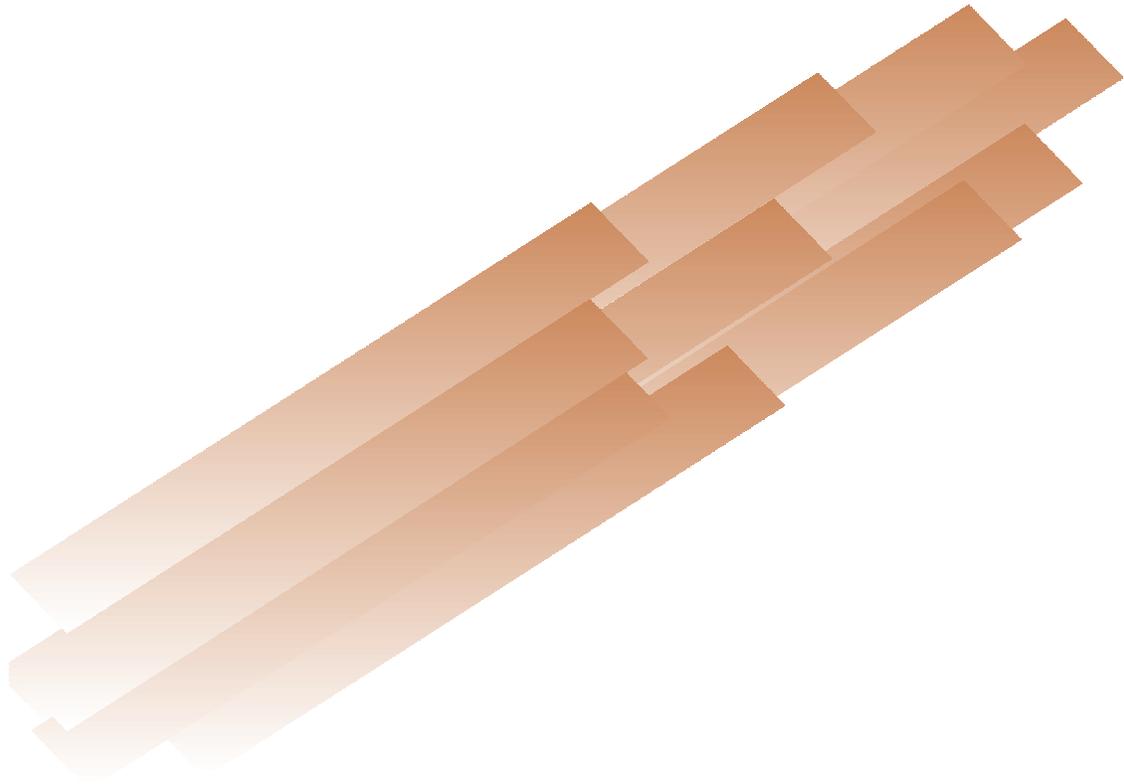
# **Guidance for Industry**

**E2C Clinical Safety Data**

**Management: Periodic Safety**

**Update Reports for Marketed**

**Drugs**



**November 1996**  
**ICH**

# **Guidance for Industry**

## **E2C Clinical Safety Data**

### **Management: Periodic Safety**

### **Update Reports for Marketed**

### **Drugs**

Additional copies are available from:  
the Drug Information Branch (HFD-210),  
Center for Drug Evaluation and Research (CDER),  
5600 Fishers Lane, Rockville, MD 20857 (Tel) 301-827-4573  
<http://www.fda.gov/cder/guidance/index.htm>

or

Office of Communication,  
Training, and Manufacturers Assistance (HFM-40)  
Center for Biologics Evaluation and Research (CBER)  
1401 Rockville Pike, Rockville, MD 20852-1448,  
<http://www.fda.gov/cber/guidelines.htm>  
(Fax) 888-CBERFAX or 301-827-3844  
(Voice Information) 800-835-4709 or 301-827-1800

**U.S. Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research (CDER)**  
**Center for Biologics Evaluation and Research (CBER)**  
**November 1996**  
**ICH**

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# GUIDANCE FOR INDUSTRY<sup>1</sup>

## E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs

### I. INTRODUCTION (1)

#### A. Objectives of the Guidance (1.1)

The main objective of ICH is to make recommendations to harmonize technical requirements for registration or marketing approval. However, because new products are introduced at different times in different markets and the same product may be marketed in one or more countries and still be under development in others, reporting and use of clinical safety information should be regarded as part of a continuum.

The regulatory requirements, particularly regarding frequency of submission and content of periodic safety updates, are not the same in the three regions (EU, Japan, United States). To avoid duplication of effort and to ensure that important data are submitted with consistency to regulatory authorities, this guidance on the format and content for comprehensive periodic safety updates of marketed medicinal products has been developed.<sup>2</sup>

#### B. Background (1.2)

When a new medicinal product is submitted for marketing approval, except in special situations, the demonstration of its efficacy and the evaluation of its safety are based at most on several thousand patients. The limited number of patients included in clinical trials, the exclusion at least initially of certain patients at-risk, the lack of significant long-term treatment experience, and the limitation of concomitant therapies do not allow a

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<sup>1</sup> This guidance was developed within the Expert Working Group (Efficacy) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 1996. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and the United States. This guidance was published in the *Federal Register* on May 19, 1997 (62 FR 27470), and is applicable to drug and biological products. This guidance represents the Agency's current thinking on periodic safety update reports for marketed drugs. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

<sup>2</sup> Guidances are not legally binding. Some portions of this guidance may not be reflected in existing regulations. To that extent, until the regulations are amended, marketing authorization holders (MAHs) must comply with existing regulations.

thorough evaluation of the safety profile. Under such circumstances, the detection or confirmation of rare adverse reactions is particularly difficult, if not impossible.

In order to develop a comprehensive picture of clinical safety, medicinal products should be closely monitored, especially during the first years of commercialization. Surveillance of marketed drugs is a shared responsibility between regulatory authorities and MAHs. They record information on drug safety from different sources and procedures have been developed to ensure timely detection and mutual exchange of safety data. Because all information cannot be evaluated with the same degree of priority, regulatory authorities have defined the information to be submitted on an expedited basis; in most countries this rapid transmission is usually focused on the expedited reporting of adverse drug reactions (ADRs) that are both serious and unexpected.

Reevaluation of the benefit/risk ratio of a drug is usually not possible for each individual ADR case, even if serious. Therefore, periodic safety update reports (PSURs) present the worldwide safety experience of a medicinal product at defined times postauthorization, in order to:

- Report all the relevant new information from appropriate sources;
- Relate these data to patient exposure;
- Summarize the market authorization status in different countries and any significant variations related to safety;
- Create periodically the opportunity for an overall safety reevaluation;
- Indicate whether changes should be made to product information in order to optimize the use of the product.

However, if PSURs required in the different countries where the product is on the market require a different format, content, period covered, and filing date, MAHs would need to prepare on an excessively frequent basis different reports for the same product. In addition, under such conditions, different regulators could receive different kinds and amounts of information at different times. Thus, efforts are needed to harmonize the requirements for PSURs, which will also improve the efficiency with which they are produced.

The current situation for periodic safety reports on marketed drugs is different among the three ICH regions. For example:

- The U.S. regulations require quarterly reports during the first 3 years, then annual reports. FDA has recently published proposed rules<sup>3</sup> that take into account the Council for International Organizations of Medical Sciences (CIOMS) Working Group II proposals.<sup>4</sup>
- In the EU, Council Directive 93/39/EEC and Council Regulation 2309/93 require reports with a periodicity of 6 months for 2 years, annually for the 3 following years, and then every 5 years, at the time of renewal of registration.
- In Japan, the authorities require a survey on a cohort of a few thousand patients established by a certain number of identified institutions during the 6 years following authorization. Systematic information on this cohort, taking into account a precise denominator, must be reported annually. Regarding other marketing experience, adverse reactions that are nonserious, but both mild in severity and unlabeled, must be reported every 6 months for 3 years and annually thereafter.

Following a discussion of the objectives and general principles for preparing and submitting PSURs, a model for their format and content is presented.

Appended is a glossary of important relevant terms.

### **C. Scope of the Guidance (1.3)**

This guidance on the format and content of PSURs is considered particularly suitable for comprehensive reports covering short periods (e.g., 6 months, 1 year) often prepared during the initial years following approval/authorization.

This guidance might also be applicable for longer term reporting intervals; however, other options may be appropriate.

### **D. General Principles (1.4)**

1. One report for one active substance (1.4.1)

Ordinarily, all dosage forms and formulations as well as indications for a given pharmacologically active substance should be covered in one PSUR. Within the

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<sup>3</sup> Adverse Experience Reporting Requirements for Human Drug and Licensed Biological Products; Proposed Rule, *Federal Register*, October 27, 1994 (59 FR 54046 to 54064).

<sup>4</sup> International Reporting of Periodic Drug-Safety Update Summaries; Final Report of CIOMS, Working Group II, CIOMS, Geneva, 1992.

single PSUR, separate presentations of data for different dosage forms, indications, or populations (e.g., children versus adults) may be appropriate.

For combinations of substances also marketed individually, safety information for the fixed combination may be reported either in a separate PSUR or included as separate presentations in the report for one of the separate components, depending on the circumstances. Cross-referencing all relevant PSURs is considered important.

## 2. General scope of information (1.4.2)

All relevant clinical and nonclinical safety data should cover only the period of the report (interval data) with the exception of regulatory status information on authorization applications and renewals, as well as data on serious, unlisted ADRs (see section I.D.5 (1.4.5)), which should be cumulative.

The main focus of the report should be ADRs. For spontaneous reports, unless indicated otherwise by the reporting health-care professional, all adverse experiences should be assumed to be ADRs; for clinical study and literature cases, only those judged not related to the drug by both the reporter and the manufacturer/sponsor should be excluded.

Reports of lack of efficacy specifically for drugs used in the treatment of life-threatening conditions may represent a significant hazard and, in that sense, be a "safety issue." Although these types of cases should not be included with the usual ADR presentations (i.e., line listings and summary tabulations), such findings should be discussed within the PSUR (see section II.H (2.8)), if deemed medically relevant.

Increase in the frequency of reports for known ADRs has traditionally been considered as relevant new information. Although attention should be given in the PSUR to such increased reporting, no specific quantitative criteria or other rules are recommended. Judgment should be used in such situations to determine whether the data reflect a meaningful change in ADR occurrence or safety profile and whether an explanation can be proposed for such a change (e.g., population exposed, duration of exposure).

## 3. Products manufactured and/or marketed by more than one company (1.4.3)

Each MAH is responsible for submitting PSURs, even if different companies market the same product in the same country. When companies are involved in contractual relationships (e.g., licensor-licensee), arrangements for sharing safety information should be clearly specified. In order to ensure that all relevant data

will be duly reported to appropriate regulatory authorities, respective responsibilities for safety reporting should also be clearly specified.

When data received from a partner company(ies) might contribute meaningfully to the safety analysis and influence any proposed or effected changes in the reporting company's product information, these data should be included and discussed in the PSUR, even if it is known that they are included in another company's PSUR.

#### 4. International birth date and frequency of review and reporting (1.4.4)

Each medicinal product should have as an international birth date (IBD) the date of the first marketing authorization for the product granted to any company in any country in the world. For administrative convenience, if desired by the MAH, the IBD can be designated as the last day of the same month. When a report contains information on different dosage forms, formulations, or uses (indications, routes, populations), the date of the first marketing authorization for any of the various authorizations should be regarded as the IBD and, therefore, determine the data lock point for purposes of the unified PSUR. The data lock point is the date designated as the cutoff for data to be included in a PSUR.

The need for a report and the frequency of report submission to authorities are subject to local regulatory requirements. The age of a drug on the market may influence this process. In addition, during the initial years of marketing, a drug will ordinarily receive authorizations at different times in different countries; it is during this early period that harmonization of reporting is particularly important.

However, independent of the required reporting frequency, regulatory authorities should accept PSURs prepared at 6-month intervals or PSURs based on multiples of 6 months. Therefore, it is recommended that the preparation of PSURs for all regulatory authorities should be based on data sets of 6 months or multiples thereof.

Once a drug has been marketed for several years, the need for a comprehensive PSUR and the frequency of reporting may be reviewed, depending on local regulations or requests, while maintaining one IBD for all regulatory authorities.

In addition, approvals beyond the initial one for the active substance may be granted for new indications, dosage forms, populations, or prescription status (e.g., children versus adults; prescription to nonprescription status). The potential consequences on the safety profile raised by such new types and extent of population exposures should be discussed between regulatory authorities and MAHs since they may influence the requirements for periodic reporting. The MAH should submit a PSUR within 60 days of the data lock point.

5. Reference safety information (1.4.5)

The objective of a PSUR is to establish whether information recorded during the reporting period is in accord with previous knowledge on the drug's safety, and to indicate whether changes should be made to product information. Reference information is needed to perform this comparison. Having one reference source of information in common for the three ICH regions would facilitate a practical, efficient, and consistent approach to the safety evaluation and make the PSUR a unique report accepted in all areas.

It is a common practice for MAHs to prepare their own "Company Core Data Sheet" (CCDS) which covers material relating to safety, indications, dosing, pharmacology, and other information concerning the product. In a practical option for the purpose of periodic reporting is for each MAH to use, as a reference, the safety information contained within its central document (CCDS), which would be referred to as "Company Core Safety Information" (CCSI).

For purposes of periodic safety reporting, CCSI forms the basis for determining whether an ADR is already *Listed* or is still *Unlisted*, terms that are introduced to distinguish them from the usual terminology of "expectedness" or "labeledness" that is used in association with official labeling. Thus, the local approved product information continues to be the reference document upon which labeledness/expectedness is based for the purpose of local *expedited* postmarketing safety reporting.

6. Presentation of data on individual case histories (1.4.6)

**Sources of information**

Generally, data from the four following sources of ADR case information are potentially available to an MAH and could be included in the PSUR:

- a. Direct reports to MAHs (or under MAH control):
- Spontaneous notifications from health care professionals;
  - Spontaneous notifications from nonhealth care professionals or from consumers (nonmedically substantiated);
  - MAH-sponsored clinical studies<sup>5</sup> or named-patient ("compassionate") use.

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<sup>5</sup> What constitutes a clinical study may not always be clear, given the recent use of, for example, stimulated reporting and patient-support programs. In some of these circumstances, the distinction between spontaneous reporting and a clinical study is not well defined. The MAH should specify how relevant data from such sources are included.

- b. Literature.
- c. ADR reporting systems of regulatory authorities.
- d. Other sources of data:
  - Reports on ADRs exchanged between contractual partners (e.g., licensors-licensees);
  - Data in special registries, such as maintained in organ toxicity monitoring centers;
  - Reports created by poison control centers;
  - Epidemiological data bases.

### **Description of the reaction**

Until an internationally agreed coding terminology becomes available and its use broadly implemented, the event terms used in the PSUR will generally be derived from whatever standard terminology ("controlled vocabulary" or "coding dictionary") is used by the reporting company.

Whenever possible, the notifying reporter's event terms should be used to describe the ADR. However, when the notifying reporter's terms are not medically appropriate or meaningful, MAHs should use the best alternative compatible event terms from their ADR dictionaries to ensure the most accurate representation possible of the original terms. Under such circumstances, the following should be borne in mind:

- To make it available on request, the "verbatim" information supplied by the notifying reporter should be kept on file (in the original language and/or as a medically sound English translation, if applicable).
- In the absence of a diagnosis by the reporting health-care professional, a suggested diagnosis for a symptom complex may be made by the MAH and used to describe a case, in addition to presenting the reported individual signs, symptoms, and laboratory data.
- If an MAH disagrees with a diagnosis that is provided by the notifying health-care professional, it may indicate such disagreement within the line listing of cases (see below).
- MAHs should report and try to understand all information provided within a case report. An example is a laboratory abnormality not addressed/evaluated by the notifying reporter.

Therefore, when necessary and relevant, two descriptions of the signs, symptoms, or diagnosis could be presented in the line listing: First, the reaction as originally reported; second, when it differs, the MAHs medical interpretation (identified by asterisk or other means).

### **Line listings and/or summary tabulations**

Depending on their type or source, available ADR cases should be presented as individual case line listings and/or as summary tabulations.

A line listing provides key information but not necessarily all the details customarily collected on individual cases; however, it does serve to help regulatory authorities identify cases that they might wish to examine more completely by requesting full case reports.

MAHs can prepare line listings of consistent structure and content for cases directly reported to them (or under their control) (see section I.D.6(a) (1.4.6(a))) as well as those received from regulatory authorities. They can usually do the same for published cases (ordinarily well documented; if not, followup with the author may be possible). However, inclusion of individual cases from second- or third-hand sources, such as contractual partners and special registries (see section I.D.6(d) (1.4.6(d))) might not be (1) possible without standardization of data elements, or (2) appropriate due to the paucity of information, and might represent unnecessary re-entry/reprocessing of such information by the MAH. Therefore, summary tabulations or possibly a narrative review of these data is considered acceptable under these circumstances.

In addition to individual case line listings, summary tabulations of ADR terms for signs, symptoms, and diagnoses across all patients should usually be presented to provide an overview. Such tabulations should be based on the data in line listings (e.g., all serious ADRs and all nonserious unlisted ADRs), but also on other sources for which line listings are not requested (e.g., nonserious listed ADRs). Details are found in section II.F.4 (2.6.4).

## **II. MODEL FOR A PSUR (2)**

The following sections are organized as a sample PSUR. In each of the sections, guidance is provided on what should be included.

### **Sample Title Page**

- Periodic safety update report for: (product);

- MAH's name and address (corporate headquarters or other company entity responsible for report preparation);
- Period covered by this report: (dates);
- International birth date: date (country of IBD);
- Date of report;
- (Other identifying information at the option of MAH, such as report number).

### **Table of Contents for Model PSUR**

- Introduction;
- Worldwide market authorization status;
- Update of regulatory authority or MAH actions taken for safety reasons;
- Changes to reference safety information;
- Patient exposure;
- Presentation of individual case histories;
- Studies;
- Other information;
- Overall safety evaluation;
- Conclusion;
- Appendix: Company Core Data Sheet.

#### **A. Introduction (2.1)**

The MAH should briefly introduce the product so that the report "stands alone" but is also placed in perspective relative to previous reports and circumstances.

Reference should be made not only to product(s) covered by the report but also to those excluded. Exclusions should be explained; for example, they may be covered in a separate report (e.g., for a combination product).

If it is known that a PSUR on the same product(s) will be submitted by another MAH, some of whose data are included in the report (see section I.D.6 (1.4.6)), the possibility of data duplication should be noted.

## **B. Worldwide Market Authorization Status (2.2)**

This section of the report provides cumulative information.

Information should be provided, usually as a table, on all countries in which a regulatory decision about marketing has been made related to the following:

- Dates of market authorization, and subsequent renewal;
- Any qualifications surrounding the authorization, such as limits on indications if relevant to safety;
- Treatment indications and special populations covered by the market authorization, when relevant;
- Lack of approval, including explanation, by regulatory authorities;
- Withdrawal by the company of a license application submission if related to safety or efficacy;
- Dates of launch when known;
- Trade name(s).

Typically, indications for use, populations treated (e.g., children versus adults), and dosage forms will be the same in many or even most countries where the product is authorized. However, when there are important differences, which would reflect different types of patient exposure, such information should be noted. This is especially true if there are meaningful differences in the newly reported safety information that are related to such different exposures. If more convenient and useful, separate regulatory status tables for different product uses or forms would be considered appropriate.

Country entries should be listed in chronological order of regulatory authorizations. For multiple authorizations in the same country (e.g., new dosage forms), the IBD for the active substance and for all PSURs should be the first (initial) authorization date.

Table 1 is an example, with fictitious data for an antibiotic, of how a table might be organized. The drug was initially developed as a solid oral dosage form for outpatient treatment of various infections.

**C. Update of Regulatory Authority or MAH Actions Taken for Safety Reasons (2.3)**

This section should include details on the following types of actions relating to safety that were taken during the period covered by the report and between data lock point and report submission:

- Marketing authorization withdrawal or suspension;
- Failure to obtain a marketing authorization renewal;
- Restrictions on distribution;
- Clinical trial suspension;
- Dosage modification;
- Changes in target population or indications;
- Formulation changes.

The safety related reasons that led to these actions should be described and documentation appended when appropriate; any communication with the health profession (e.g., Dear Doctor letters) as a result of such action should also be described with copies appended.

**D. Changes to Reference Safety Information (2.4)**

The version of the CCDS with its CCSI in effect at the beginning of the period covered by the report should be used as the reference. It should be numbered, dated, and appended to the PSUR and include the date of last revision.

Changes to the CCSI, such as new contraindications, precautions, warnings, ADRs, or interactions, already made during the period covered by the report, should be clearly described, with presentation of the modified sections. The revised CCSI should be used as the reference for the next report and the next period.

With the exception of emergency situations, it may take some time before intended modifications are introduced in the product-information materials provided to prescribers, pharmacists, and consumers. Therefore, during that period the amended reference document (CCDS) may contain more "listed" information than the existing product information in many countries.

When meaningful differences exist between the CCSI and the safety information in the official data sheets/product information documents approved in a country, a brief comment should be prepared by the company, describing the local differences and their consequences on the overall safety evaluation and on the actions proposed or initiated. This commentary may be provided in the cover letter or other addendum accompanying the local submission of the PSUR.

#### **E. Patient Exposure (2.5)**

Where possible, an estimation of accurate patient exposure should cover the same period as the interim safety data. While it is recognized that it is usually difficult to obtain and validate accurate exposure data, an estimate of the number of patients exposed should be provided along with the method used to derive the estimate. An explanation and justification should be presented if the number of patients is impossible to estimate or is a meaningless metric. In its place, other measures of exposure, such as patient-days, number of prescriptions, or number of dosage units are considered appropriate; the method used should be explained. If these or other more precise measures are not available, bulk sales (tonnage) may be used. The concept of a defined daily dose may be used in arriving at patient exposure estimates. When possible and relevant, data broken down by sex and age (especially pediatric versus adult) should be provided.

When a pattern of reports indicates a potential problem, details by country (with locally recommended daily dose) or other segmentation (e.g., indication, dosage form) should be presented if available.

When ADR data from clinical studies are included in the PSUR, the relevant denominator(s) should be provided. For ongoing and/or blinded studies, an estimation of patient exposure may be made.

#### **F. Presentation of Individual Case Histories (2.6)**

1. General considerations (2.6.1)
  - Followup data on individual cases may be obtained subsequent to their inclusion in a PSUR. If such information is relevant to the interpretation of the case (significant impact on the case description or analysis, for example), the new information should be presented in the next PSUR, and the correction or clarification noted relative to the earlier case description.
  - With regard to the literature, MAHs should monitor standard, recognized medical and scientific journals for safety information on their products and/or make use of one or more literature search/summary services for that purpose. Published cases may also have been received as spontaneous

cases, be derived from a sponsored clinical study, or arise from other sources. Care should be taken to include such cases only once. Also, no matter what "primary source" is given a case, if there is a publication, it should be noted and the literature citation given.

- In some countries, there is no requirement to submit medically unconfirmed spontaneous reports that originate with consumers or other nonhealth care professionals. However, such reports are acceptable or requested in other countries. Therefore, medically unconfirmed reports should be submitted as addenda line listings and/or summary tabulations only when required or requested by regulatory authorities. However, it is considered that such reports are not expected to be discussed within the PSUR itself.

## 2. Cases presented as line listings (2.6.2)

The following types of cases should be included in the line listings (Table 2); attempts should be made to avoid duplicate reporting of cases from the literature and regulatory sources:

- All serious reactions, and nonserious unlisted reactions, from spontaneous notifications;
- All serious reactions (attributable to drug by either investigator or sponsor), available from studies or named-patient ("compassionate") use;
- All serious reactions, and nonserious unlisted reactions, from the literature;
- All serious reactions from regulatory authorities.

Collection and reporting of nonserious, listed ADRs may not be required in all ICH countries. Therefore, a line listing of spontaneously reported nonserious listed reactions that have been collected should be submitted as an addendum to the PSUR only when required or requested by a regulatory authority.

## 3. Presentation of the line listing (2.6.3)

The line listing(s) should include each patient only once regardless of how many adverse event/reaction terms are reported for the case. If there is more than one event/reaction, they should all be mentioned but the case should be listed under the most serious ADR (sign, symptom, or diagnosis), as judged by the MAH. It is possible that the same patient may experience different ADRs on different occasions (e.g., weeks apart during a clinical trial). Such experiences would probably be treated as separate reports. Under such circumstances, the same

patient might then be included in a line listing more than once, and the line listings should be cross-referenced when possible. Cases should be organized (tabulated) by body system (standard organ system classification scheme).

The following headings should usually be included in the line listing:

- MAH case reference number;
- Country in which case occurred;
- Source (e.g., clinical trial, literature, spontaneous, regulatory authority);
- Age and sex;
- Daily dose of suspected drug (and, when relevant, dosage form or route);
- Date of onset of the reaction. If not available, best estimate of time to onset from therapy initiation. For an ADR known to occur after cessation of therapy, estimate of time lag if possible (may go in Comments section);
- Dates of treatment. If not available, best estimate of treatment duration;
- Description of reaction as reported, and when necessary as interpreted by the MAH (English translation when necessary). See section I.D.6 (1.4.6) for guidance;
- Patient outcome (at case level) (e.g., resolved, fatal, improved, sequelae, unknown). This field does not refer to the criteria used to define a "serious" ADR. It should indicate the consequences of the reaction(s) for the patient, using the worst of the different outcomes for multiple reactions;
- Comments, if relevant (e.g., causality assessment if the manufacturer disagrees with the reporter; concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect drug(s); dechallenge/rechallenge results if available).

Depending on the product or circumstances, it may be useful or practical to have more than one line listing, such as for different dosage forms or indications, if such differentiation facilitates presentation and interpretation of the data.

#### 4. Summary tabulations (2.6.4)

An aggregate summary for each of the line listings should usually be presented. These tabulations ordinarily contain more terms than patients. It would be useful to have separate tabulations (or columns) for serious reactions and for nonserious reactions, for listed and unlisted reactions; other breakdowns might also be appropriate (e.g., by source of report). See Table 3 for a sample data presentation on serious reactions.

A summary tabulation should be provided for the nonserious, listed, spontaneously reported reactions (see also section II.F.2 (2.6.2)).

The terms used in these tables should ordinarily be those used by the MAH to describe the case (see section I.D.6 (1.4.6)).

Except for cases obtained from regulatory authorities, the data on serious reactions from other sources (see section I.D.6(c) (1.4.6(c))) should normally be presented only as a summary tabulation. If useful, the tabulations may be sorted by source of information or country, for example.

When the number of cases is very small, or the information inadequate for any of the tabulations, a narrative description rather than a formal table is considered suitable.

As previously described, the data in summary tabulations should be interval data, as should the line listings from which they are derived. However, for ADRs that are both serious and unlisted, a cumulative figure (i.e., all cases reported to date) should be provided in the table(s) or as a narrative.

#### 5. MAH's analysis of individual case histories (2.6.5)

This section may be used for brief comments on the data concerning individual cases. For example, discussion can be presented on particular serious or unanticipated findings (e.g., their nature, medical significance, mechanism, reporting frequency, etc.). The focus here should be on individual case discussion and should not be confused with the global assessment in the Overall Safety Evaluation (section II.I. (2.9)).

### **G. Studies (2.7)**

All completed studies (nonclinical, clinical, epidemiological) yielding safety information with potential impact on product information, studies specifically planned or in progress, and published studies that address safety issues, should be discussed.

#### 1. Newly analyzed company-sponsored studies (2.7.1)

All relevant studies containing important safety information and newly analyzed during the reporting period should be described, including those from epidemiological, toxicological, or laboratory investigations. The study design and results should be clearly and concisely presented with attention to the usual standards of data analysis and description that are applied to nonclinical and clinical study reports. Copies of full reports should be appended only if deemed appropriate.

2. Targeted new safety studies planned, initiated, or continuing during the reporting period (2.7.2)

New studies specifically planned or conducted to examine a safety issue (actual or hypothetical) should be described (e.g., objective, starting date, projected completion date, number of subjects, protocol abstract).

When possible and relevant, if an interim analysis was part of the study plan, the interim results of ongoing studies may be presented. When the study is completed and analyzed, the final results should be presented in a subsequent PSUR as described under section II.G.1 (2.7.1).

3. Published safety studies (2.7.3)

Reports in the scientific and medical literature, including relevant published abstracts from meetings, containing important safety findings (positive or negative) should be summarized and publication reference(s) given.

## **H. Other Information (2.8)**

1. Efficacy-related information (2.8.1)

For a product used to treat serious or life-threatening diseases, medically relevant lack of efficacy reporting, which might represent a significant hazard to the treated population, should be described and explained.

2. Late-breaking information (2.8.2)

Any important, new information received after the data base was frozen for review and report preparation may be presented in this section. Examples include significant new cases or important followup data. These new data should be taken into account in the Overall Safety Evaluation (section II.I (2.9)).

## **I. Overall Safety Evaluation (2.9)**

A concise analysis of the data presented, taking into account any late-breaking information (section II.H.2 (2.8.2)), and followed by the MAH assessment of the significance of the data collected during the period and from the perspective of cumulative experience, should highlight any new information on:

- A change in characteristics of listed reactions, e.g., severity, outcome, target population;
- Serious unlisted reactions, placing into perspective the cumulative reports;
- Nonserious unlisted reactions;
- An increased reporting frequency of listed reactions, including comments on whether it is believed the data reflect a meaningful change in ADR occurrence.

The report should also explicitly address any new safety issue on the following (lack of significant new information should be mentioned for each):

- Drug interactions;
- Experience with overdose, deliberate or accidental, and its treatment;
- Drug abuse or misuse;
- Positive or negative experiences during pregnancy or lactation;
- Experience in special patient groups (e.g., children, elderly, organ impaired);
- Effects of long-term treatment.

## **J. Conclusion (2.10)**

The conclusion should:

- Indicate which safety data do not remain in accord with the previous cumulative experience, and with the reference safety information (CCSI);
- Specify and justify any action recommended or initiated.

Appendix: Company Core Data Sheet

The Company Core Data Sheet in effect at the beginning of the period covered should be appended to the PSUR.

### III. GLOSSARY OF SPECIAL TERMS (3)

**Company Core Data Sheet (CCDS):** A document prepared by the MAH containing, in addition to safety information, material relating to indications, dosing, pharmacology, and other information concerning the product.

**Company Core Safety Information (CCSI):** All relevant safety information contained in the CCDS prepared by the MAH and which the MAH requires to be listed in all countries where the company markets the drug, except when the local regulatory authority specifically requires a modification. It is the reference information by which listed and unlisted are determined for the purpose of periodic reporting for marketed products, but not by which expected and unexpected are determined for expedited reporting.

**Data Lock Point (Data Cut-off Date):** The date designated as the cut-off date for data to be included in a PSUR. It is based on the international birth date (IBD) and should usually be in 6-month increments.

**International Birth Date (IBD):** The date of the first marketing authorization for a new medicinal product granted to any company in any country in the world.

**Listed Adverse Drug Reaction (ADR):** An ADR whose nature, severity, specificity, and outcome are consistent with the information in the CCSI.

**Spontaneous Report or Spontaneous Notification:** An unsolicited communication to a company, regulatory authority, or other organization that describes an adverse reaction in a patient given one or more medicinal products and which does not derive from a study or any organized data collection scheme.

**Unlisted Adverse Drug Reaction:** An ADR whose nature, severity, specificity, or outcome are not consistent with the information included in the CCSI.

**Table 1 — Example of Presentation of Worldwide Market Authorization Status**

<b>Country</b>	<b>Action-Date</b>	<b>Launch Date</b>	<b>Trade Name(s)</b>	<b>Comments</b>
Sweden	A <sup>1</sup> - 7/90 AR - 10/95	12/90 -	Bacteroff -	- -
Brazil	A - 10/91 A - 1/93	2/92 3/93	Bactoff Bactoff-IV	- IV dosage form
United Kingdom	AQ - 3/92 A - 4/94	6/92 7/94	Bacgone Bacgone-C (skin infs)	Elderly (> 65) excluded (PK) Topical cream
Japan	LA - 12/92	-	-	To be refiled
France	V - 9/92	-	-	Unrelated to safety
Nigeria	A - 5/93 A - 9/93	7/93 1/94	Bactoff Bactoff	- New indication
Etc...				

<sup>1</sup> Abbreviations for Action: A = authorized; AQ = authorized with qualifications; LA = lack of approval; V = voluntary marketing application withdrawal by company; AR = authorization renewal.

**Table 2 — Presentation of Individual Case Histories**  
(See sections II.F.2 (2.6.2) and II.F.4 (2.6.4) for full explanation)

Source	Type of Case	Only Summary Tabulation	Line Listing and Summary Tabulation
<b>1. Direct Reports to MAH</b> <ul style="list-style-type: none"> <li>● Spontaneous ADR reports<sup>1</sup></li> </ul>	S	-	+
	NS U	-	+
	NS L <sup>2</sup>	+	-
	SA	-	+
<b>2. Literature</b>	S	-	+
	NS U	-	+
<b>3. Other sources</b> <ul style="list-style-type: none"> <li>● Regulatory authorities</li> <li>● Contractual partners</li> <li>● Registries</li> </ul>	S	-	+
	S	+	-
	S	+	-

<sup>1</sup> Medically unconfirmed reports should be provided as a PSUR addendum only if required or requested by regulatory authorities, as a line listing and/or summary tabulation.

<sup>2</sup> Line listing should be provided as PSUR addendum only if required or requested by regulatory authority.

S = serious; L = listed; A = attributable to drug (by investigator or sponsor); NS = nonserious; U = unlisted.

**Table 3 — (Example of summary tabulation)<sup>1</sup>  
 Number of Reports by Term (Signs, Symptoms and Diagnoses)  
 from Spontaneous (Medically Confirmed), Clinical Study  
 and Literature Cases: All Serious Reactions**

(An \* indicates an unlisted term)

Body system/ ADR term	Spontaneous/ Regulatory bodies	Clinical trials	Literature
CNS hallucinations* etc. etc.	2	0	0
_____	_____	_____	_____
Sub-total			
CV etc. etc.			
_____	_____	_____	_____
Sub-total			
Etc.			
TOTAL			

<sup>1</sup> This table is only one example of different possible data presentations which are at the discretion of the MAH (e.g., serious and nonserious in the same table or as separate tables, etc).

In a footnote (or elsewhere), the number of patient-cases that represent the tabulated terms might be given (e.g., x-spontaneous/regulatory, y-clinical trial, and z-literature cases).

## EXHIBIT B

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# Guidance for Industry

## Addendum to E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)

February 2004  
ICH

# Guidance for Industry

## Addendum to E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)**

**February 2004  
ICH**

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**Guidance for Industry<sup>1</sup>**  
**Addendum to E2C Clinical Safety Data Management:**  
**Periodic Safety Update Reports for Marketed Drugs**

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if that approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

## **INTRODUCTION**

This addendum is intended to provide practical guidance for the preparation of periodic safety update reports (PSURs) as recommended in the ICH guidance *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs*, which was endorsed by the ICH in November 1996 and published by the FDA in May 1997. The E2C guidance has been implemented in some but not all ICH countries.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

## **BACKGROUND**

The PSUR is a practical and achievable mechanism for summarizing interval safety data, especially covering short periods (e.g., 6 months or 1 year), and for conducting an overall safety evaluation. It is a tool for marketing authorization holders (MAHs) to conduct systematic analyses of safety data on a regular basis. In addition to covering ongoing safety

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<sup>1</sup> This guidance was developed within the Expert Working Group (Efficacy) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, February 2003. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the USA.

## ***Contains Nonbinding Recommendations***

issues, the PSUR should also include updates on emerging and/or urgent safety issues, and major signal detection and evaluation that are addressed in other documents.

PSURs are of value and importance to all parties in protecting the public health. The ICH E2C guidance was developed to harmonize PSURs submitted to the regulatory authorities in terms of content and format as well to introduce the concept of international birth date (IBD). However, the original E2C guidance has been interpreted in different ways by both MAHs and regulatory authorities. These differing interpretations have resulted in a perception that the guidance was not sufficient to accommodate the broad range of products and diverse circumstances that arise in practice. The Council for International Organizations of Medical Sciences (CIOMS) Working Group V made several recommendations and developed new concepts to harmonize the practice of preparing PSURs that have been taken into account in preparing this addendum.<sup>2</sup>

### **THE ADDENDUM**

This addendum addresses only those E2C provisions considered to need further clarification, guidance, or increased perceived flexibility beyond that provided in the ICH E2C guidance. This document should always be used in conjunction with the E2C guidance. To facilitate the use of this document, the numbering of the sections and paragraphs corresponds to the numbering in the E2C guidance.

This addendum addresses the following concepts not previously addressed by E2C:

- Summary bridging report (see section I.D.4.b (1.4.4.2)<sup>3</sup>)
- Addendum report (see section I.D.4.c (1.4.4.3))
- Proprietary information (see section II (2))
- Executive summary (see section II (2))
- Risk management program (see section II.H.3 (2.8.3))
- Benefit-risk analysis (see section II.H.4 (2.8.4))

#### **D. General Principles (1.4)**

##### ***1. One Report for One Active Substance (1.4.1)***

It is strongly recommended that information on all indications, dosage forms, and regimens for the active substance be included in a single PSUR, with a single data lock point common for all aspects of product use. There is a great advantage to having a consistent, broad-based examination of the safety information for the active substance(s) in a single document. When relevant, data relating to a particular indication, dosage form, or dosing

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<sup>2</sup> Report of CIOMS Working Group V, *Current Challenges in Pharmacovigilance: Pragmatic Approaches*, 2001, Geneva.

<sup>3</sup> Arabic numbers in parentheses reflect the organizational breakdown in the document endorsed by the ICH Steering Committee at Step 4 of the ICH process, February 2003.

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regimen should be presented in a separate section within the body of the PSUR and any safety issues addressed accordingly without preparing a separate PSUR.

There are instances when separate PSURs might be considered appropriate. In these cases, the regulatory authorities should be notified and their agreement obtained at the time of authorization.

Examples include:

- Fixed combinations: Options include either a separate PSUR for the combination with cross-reference to the single agent(s) PSUR(s) or inclusion of the fixed combination data within one of the single agent PSURs.
- When an active substance is used in two or more different formulations (e.g., systemic preparations versus topical administration), two or more PSURs, with the same or different IBDs, can be useful.

#### *4. International Birth Date and Frequency of Review and Reporting (1.4.4)*

Whenever possible, PSURs should be based on the IBD. If, in the transition period to a harmonized birth date for that product, the use of a local approval date is appropriate, the MAH can submit its already prepared IBD-based PSUR plus:

- line-listings and/or summary tabulations covering the additional period (when the additional period is less than 3 months for a 6-month or annual PSUR, or 6 months for a longer duration PSUR) with comment on whether the data reveal a new and important risk

or

- an addendum report when the additional period is greater than 3 months for a 6-month or annual PSUR, or 6 months for a longer duration PSUR (see section 1.4.4.3)

##### *a. Synchronization of national birth dates with the IBD (1.4.4.1)*

For drugs that are on the market in many countries, the MAH can synchronize local or national birth dates with the IBD.

For a drug where the IBD is not known, the MAH can designate an IBD to allow synchronization of reports to all regulatory authorities. Once an IBD is designated, the MAH should notify the regulatory authorities, and the IBD should be adhered to thereafter.

It is recognized that long intervals between approvals could put the drug in a 5-year cycle in one region and a 6-month cycle in another region. For practical purposes, if a single date (month, day, and year) for the IBD is not attainable, the MAH can contact the regulatory authorities to negotiate a mutually acceptable birth month and day. For example,

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where there are different approval dates, it can be useful for reports to be submitted on the same month and day (e.g., every January 18 and July 18), whether every 6 months, annually, or every 5th year.

b. Summary bridging reports (1.4.4.2)

A *summary bridging report* is intended to be a concise document integrating the information presented in two or more PSURs to cover a specified period over which a single report is requested or required by regulatory authorities. The report should not contain any new data but should provide a brief summary bridging two or more PSURs (e.g., 2 consecutive 6-month reports for an annual report or 10 consecutive 6-month reports to make a 5-year report). The summary bridging report is intended to assist regulatory authorities with a helpful overview of the appended PSURs. The PSUR data should not be repeated but should be cross-referenced to individual PSURs. The format of the summary bridging report should be identical to that of the usual PSUR, but the content should consist of summary highlights and an overview of data from the attached PSURs to which it refers (see CIOMS V Report, pp. 154-156). Upon request from the regulatory authority, a summary tabulation of serious, unlisted reactions should be included in the summary bridging report.

Summary bridging reports can be used in situations where the MAH prepares short duration reports (e.g., 6-month or annual reports) indefinitely, especially if new indications or formulations are likely to be introduced over the years. For reports considered out of date relative to a particular regulatory authority's requirement, an addendum report could also be submitted (see section 1.4.4.3). For a PSUR that spans longer time intervals (e.g., 5 years), an addendum report would only be considered appropriate if the time since preparation of the 5-year PSUR and the locally-required report is greater than 6 months.

The summary bridging report ordinarily should not include line listings. If summary tables covering the period of the appended PSURs are considered appropriate, there should be a clear understanding that the tables will be generated from live databases, which change over time as cases are updated. These tables will then reflect the most up-to-date data available at the time they are generated. It is recognized that the case counts in these summary tables can differ somewhat from the contents of the individual tables in the appended PSURs. A general statement describing the differences should be provided.

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### c. Addendum reports (1.4.4.3)

MAHs should set IBDs for all their products and can synchronize their local renewals. However, when a requested or required report covers data that fall outside the defined period, use of an addendum report is recommended.

An *addendum report* is an update to the most recently completed PSUR when a regulatory authority requests or requires a safety update outside the usual IBD reporting cycle. An addendum report should be used when more than 3 months for a 6-month or an annual report, and more than 6 months for a longer-interval report, have elapsed since the data lock point of the most recent PSUR. It might also be appropriate to provide an addendum to the summary bridging report.

The addendum report should summarize the safety data received between the data lock point of the most recent PSUR and the regulatory authority's requested cut-off date. It is not intended that the addendum report provide an in-depth analysis of the additional cases, as these can be included in the next regularly scheduled PSUR. Depending on circumstances and the volume of additional data since the last scheduled report, an addendum report can follow the ICH E2C format or a simplified presentation. The proposed minimal report should include the following sections containing any new information or changes beyond the most recent PSUR to which the addendum report refers:

- Introduction (purpose; cross reference to most recent PSUR)
- Changes to the Company Core Safety Information (CCSI) (including a copy of the most recent CCSI document if it differs from the one in the PSUR)
- Significant regulatory actions bearing on safety
- Line listing(s) and/or summary tabulations
- Conclusions (brief overview of new information and any impact on the known safety profile)

### d. Restarting the clock (1.4.4.4)

For products in a long-term PSUR cycle, the return to 6-month or annual reporting could apply after important additions or changes in clinical use are first approved in an ICH region, such as:

- A new, clinically dissimilar indication
- A previously unapproved use in a special patient population, such as children, pregnant women, or the elderly
- A new formulation or new route of administration

The decision on whether to restart the clock should be discussed with the regulatory authority no later than the time of granting the relevant marketing authorization. Even if the clock "restarts," the analyses in the PSUR should focus on the newly indicated population by identifying and characterizing any differences from the established safety profile in the previously indicated populations.

### ***Contains Nonbinding Recommendations***

- e. Time interval between the data lock point and the submission (1.4.4.5)

In regions where they are required, PSURs are to be submitted within 60 days of the data lock point. To facilitate the preparation of both current and future PSURs, as well as safety reports outside of the PSUR, the regulatory authority will attempt to send comments to the MAH:

- as rapidly as possible, if any issues of noncompliance with the ICH format and content of a PSUR are identified (particularly those that preclude review)
- as rapidly as possible, if additional safety issues are identified that could prompt further evaluation by the MAH that should either be included in the next PSUR or provided as a separate stand-alone report
- before the next data lock point, if any additional analyses or issues of content are identified that should be included in the next PSUR.

#### **Additional Time for Submissions**

In rare circumstances, an MAH can make a special request to the regulatory authority for 30 additional calendar days to submit a PSUR. Ideally, this request should be made before the data lock point. The regulatory authority will attempt to send response to MAH as rapidly as possible.

The basis of such a request should be justified and could include:

- A large number of case reports for the reporting period, provided that there is no new significant safety concern
- Issues raised by regulatory authorities in the previous PSUR for which the MAH is preparing additional or further analysis in the next PSUR
- Issues identified by the MAH for additional or further analysis

The MAH should make such a request only for the single PSUR in question and not for subsequent PSURs. The regulatory authority will generally expect subsequent PSURs to be submitted on the appropriate date and to retain their original periodicity.

## ***Contains Nonbinding Recommendations***

### **5. Reference Safety Information (1.4.5)**

It is important to highlight the differences between the CCSI and the local product information/local labeling in the cover letter accompanying the local submission of the PSUR, as described in E2C section 2.4.

#### **PSUR covering a period of 6 months or 1 year**

For 6-month and annual reports, the version of the CCSI in effect at the beginning of the period covered by the report should be used as the reference.

#### **PSUR covering a period of over 1 year**

When producing a longer duration PSUR or a summary bridging report, it is often impractical to base the analysis of listedness on the CCSI that was in effect at the beginning of the period. There can be considerable variation in listedness over the reporting period, depending on when the assessment of listedness is made (e.g., on an ongoing basis, such as at adverse event/adverse drug reaction (AE/ADR) case entry, or when a PSUR is compiled). The latest CCSI in effect at the end of the period can be used. The MAH should ensure that all changes to the CCSI made over the period are described in section 4 of the PSUR (Changes to the Reference Safety Information).

When listedness is assessed at the time of PSUR preparation after the data lock point, it is generally considered appropriate to use the current version of the CCSI as the reference document, as long as that choice is made clear in the PSUR text. MAHs assessing listedness at case entry or on an ongoing basis throughout the reporting period should include the current version of the CCSI and comment on the reasons for any changes in listedness assessment over time. In both cases, changes made to the CCSI since the previous PSUR should be explained in sections 4 (Changes to Reference Safety Information) and/or 9 (Overall Safety Evaluation).

## **II. MODEL FOR A PERIODIC SAFETY UPDATE REPORT (PSUR) (2)**

PSURs contain proprietary information. Therefore, the title page of a PSUR should contain a statement on the confidentiality of the data and conclusions included in the report.

MAHs should prepare a brief overview, or *executive summary*, of each PSUR to provide the reader with a description of the most important information. This executive summary should be placed at the beginning of the PSUR immediately after the title page. An example of an executive summary can be found in the CIOMS V report, p. 333.

## *Contains Nonbinding Recommendations*

### **E. Patient Exposure (2.5)**

Estimations of patient exposure for marketed drugs often rely on gross approximations of in-house or purchased sales data or volume. This information is not always reliable or available for all products. For example, hospital-based (inpatient exposure) statistics from the major use-monitoring sources are frequently unavailable. It is also difficult to obtain accurate data for generics, nonprescription drugs, or multiple drug regimens. Background information, detailed explanation, and examples of patient exposure estimations are given in the CIOMS V report, pp. 167-181.

When exposure data are based on information from a period that does not fully cover the period of the PSUR, the MAH can make extrapolations using the available data. When this is done it should be clearly indicated what data were used and why it is valid to extrapolate for the PSUR period in question (e.g., stable sales over a long period of time, seasonal use of the product).

The MAH should use a consistent method of calculation across PSURs for the same product. If a change in the method is appropriate, both previous and current methods and calculations should be shown in the PSUR introducing the change.

In summary bridging reports, recalculation of patient exposure data to cover the entire reporting period can be appropriate if the exposure periods used in the individual PSURs overlap.

As described in E2C, when the pattern of reports indicate a potential safety problem, detailed presentation by clinical indication, approved or unapproved, should be provided when available.

### **F. Presentation of Individual Case Histories (2.6)**

There is no specific guidance in E2C on the presentation of individual case report narratives. As it is impractical to present all case reports for the reporting period in this section of the PSUR, a brief description of the criteria used to select cases for presentation should be given.

This section should contain a description and analysis of selected cases, including fatalities, presenting new and relevant safety information and grouped by medically relevant headings or system organ classes (SOCs).

## ***Contains Nonbinding Recommendations***

### *1. General Considerations (2.6.1)*

#### **Consumer and Other Nonhealthcare Professional Reports**

MAHs should prepare standard line listings and tabulations that are considered acceptable by all regulatory authorities, as described in E2C. To achieve this goal, MAHs should follow a consistent practice across all PSURs for all products by presenting consumer and other nonhealthcare professional reports in separate line listings. When included in the analysis of safety issues in section 6 or 9, consumer reports should clearly be identified as such.

### *3. Presentation of the Line Listing (2.6.3)*

#### **“Comments” field**

E2C indicates that the “Comments” field should be used only for information that helps to clarify individual cases.

### **G. Studies (2.7)**

Only those company-sponsored studies and published safety studies, including epidemiology studies, that produce findings with potential impact on product safety information should be included with a discussion of any final or interim results. The MAH should not routinely catalogue or describe all the studies.

### **H. Other Information (2.8)**

#### *3. Risk Management Programs (2.8.3)*

When an MAH has specific risk management programs in place, they can be discussed in this section.

#### *4. Benefit-risk Analysis Report (2.8.4)*

When a more comprehensive safety or benefit-risk analysis (e.g., all indications reviewed) has been conducted separately, a summary of the analysis should be included in this section.

### **J. Overall Safety Evaluation (2.9)**

Discussion and analysis for the overall safety evaluation should be organized by SOC rather than by listedness or seriousness. Although related terms might be found in different SOCs, they should be reviewed together for clinical relevance.

# EXHIBIT C

# ADA/EASD/IDF Statement Concerning the Use of Incretin Therapy and Pancreatic Disease

Alexandria,  
June 28, 2013



Incretin therapy refers to medications such as GLP-1 receptor agonists and DPP-4 inhibitors, which are used to improve diabetes control and increase weight loss, either alone or in conjunction with other medications such as metformin or insulin. Extensive regulatory and clinical trials have examined the efficacy and effectiveness of these agents compared to both placebo and active therapies, including other members of this class of drugs.

These studies have shown universal superiority in glucose control and weight loss as compared to placebo, and at least equivalence, if not superiority, to active therapies such as sulphonylureas, TZDs, and long acting insulins. Over 80,000 subjects are currently enrolled in ongoing CVD outcome trials mandated by the U.S. Food and Drug Administration (FDA). These studies all have Data Safety Monitoring Boards reviewing patient level data for safety. One study, Savor, has completed and publically announced its primary findings without any suggestion of adverse outcomes. No studies have been terminated for safety concerns.

Recent epidemiologic studies, rodent studies, and a recent human autopsy study raised concerns that these agents (predominantly sitagliptin and exenatide, by virtue of their time on the market and thus longer patient exposure), may be associated with pancreatic changes ranging from pancreatitis to premalignant lesions. A June 2013 National Institutes of Health workshop reviewed the epidemiologic associations between diabetes and pancreatic carcinoma, showing an approximate 82 percent increased risk of malignancy associated with disease, independent of therapy. The FDA presented a thorough review of the pre-clinical pathology from submissions of all products on the market and under development, and three additional submissions requested, finding no concerns for pancreatic disease. Discussions of the human autopsy study identified significant study limitations and suggested alternative explanations for the findings reported by the investigators.

The American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation are committed to improving the lives of all people with diabetes, ensuring that a broad spectrum of safe and effective therapies is available to meet the needs of the diverse population affected by this disease. The three organizations firmly believe that people taking these medications, or those who may consider taking them, should be informed of all that is currently known about their potential risks and advantages in order to make the best possible decisions about their treatment and care, in consultation with their health care providers. At this time, there is insufficient information to modify current treatment recommendations. No patient should discontinue medication without first consulting with their health care provider. Their health care provider should take into account the patient's therapeutic responses and adverse events when considering whether to maintain or alter established therapy.

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The American Diabetes Association is leading the fight to Stop Diabetes and its deadly consequences and fighting for those affected by diabetes. The Association funds research to prevent, cure and manage diabetes; delivers services to hundreds of communities; provides objective and credible information; and gives voice to those denied their rights because of diabetes. Founded in 1940, our mission is to prevent and cure diabetes and to improve the lives of all people affected by diabetes.

For more information please call the American Diabetes Association at 1-800-DIABETES (1-800-342-2383) or visit [www.diabetes.org](http://www.diabetes.org) (<http://www.diabetes.org?loc=pressrelease>) . Information from both these sources is available in English and Spanish.



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# EXHIBIT D

May 30, 2013

# A Lone Voice Raises Alarms on Lucrative Diabetes Drugs

By **ANDREW POLLACK**

LOS ANGELES — Dr. Peter C. Butler initially declined a request by the drug maker Merck to test whether its new diabetes drug, Januvia, could help stave off the disease in rats.

“I said, I’m not interested in your money, go away,” Dr. Butler recalled.

Merck no doubt now wishes it had. When Dr. Butler finally agreed to do the study, he found worrisome changes in the pancreases of the rats that could lead to pancreatic cancer. The discovery, in early 2008, turned Dr. Butler into a crusader whose follow-up studies now threaten the future of not only Januvia but all the drugs in its class, which have sales of more than \$9 billion annually and are used by hundreds of thousands of people with Type 2 diabetes.

“I knew some stuff that I thought was a worry and I was obliged to pursue it,” said Dr. Butler, chief of the division of endocrinology at the University of California, Los Angeles.

Based on his latest study, both the [Food and Drug Administration](#) and the [European Medicines Agency](#) have begun investigations that could lead to new warnings on the drugs, or even to their removal from the market.

Or they could result in no action at all.

Dr. Butler faces powerful opponents in the makers of the drugs and many diabetes specialists, who say his studies are contradicted by other evidence.

“The data are inconclusive,” said Dr. Robert Ratner, chief scientific and medical officer of the American Diabetes Association. He said even if there were some excess risk, it would be “exceptionally low.”

Nancy Thornberry, who heads diabetes drug development at Merck, said that clinical trials, the gold standard of medical evidence, had found no increased risk of pancreatic disease from Januvia, even when results of [trials were pooled](#) to achieve greater numbers. “In fact, my mother takes sitagliptin,” she added, referring to Januvia by its generic name.

Questions about whether the drugs raise the risk of pancreatitis, a painful and possibly lethal inflammation of the pancreas, arose soon after the first one, Byetta, now sold by Bristol-Myers Squibb and AstraZeneca, was approved in 2005. The drugs’ labels already contain warnings about

that. What is new and potentially more serious is a possible risk of pancreatic cancer, which is virtually untreatable and kills most victims within a year.

Many people in the field compare Dr. Butler to Dr. Steven Nissen, the well-known Cleveland Clinic cardiologist whose warnings about Avandia, a different type of diabetes drug, led to its being banned in Europe and highly restricted in the United States.

Both men have faced criticism from those who call them zealots. The F.D.A. is about to examine data suggesting that Avandia might not be so dangerous after all. Some critics say Dr. Butler overstates his conclusions and that his findings have not been replicated by others.

“Basically, no one in the entire world over the last 10 years, with thousands of animals,” has found what Dr. Butler found, said Dr. Daniel J. Drucker, a professor of medicine at the University of Toronto and a consultant to many drug companies.

Still, Dr. Butler is not easy to write off. He is a former editor of *Diabetes*, the flagship journal of the American Diabetes Association. And he has some defenders.

“He should be an American hero, actually, a rugged individualist who is not going to be browbeaten,” said Dr. Edwin Gale, professor emeritus at the University of Bristol in Britain, who recently wrote [a commentary](#) with Dr. Butler on the drugs.

Dr. Butler was born in Kenya to British parents, though he has worked in the United States since 1987 and is an American citizen. His wife, Dr. Alexandra E. Butler, a pathologist who occupies the office next to his, has also worked on some of the studies.

In the last month, lawyers defending drug companies against a lawsuit claiming that Byetta had caused a patient's pancreatitis, subpoenaed virtually all of Dr. Butler's records.

“I think the message here is they want him out of business,” said Brian Depew, a lawyer representing the plaintiff, Ross Hubert of New Hampshire, who claims that Byetta caused him to get pancreatitis. Dr. Butler said U.C.L.A. told him not to comment on the subpoena.

More than 100 lawsuits representing 575 plaintiffs around the country are claiming injury from Byetta, mostly pancreatitis, according to the latest quarterly regulatory filing from Bristol-Myers. Forty-three suits claim that Januvia caused pancreatic cancer, according to Merck.

Other drugs in the class, called incretin mimetics, are Bydureon and Onglyza, which are also sold by Bristol-Myers Squibb and AstraZeneca; Victoza from Novo Nordisk; Tradjenta from Eli Lilly and Boehringer Ingelheim; and Nesina from Takeda. By far the biggest, though, is Merck's Januvia and the related Janumet, which had global sales of \$5.7 billion last year.

Dr. Butler said that after his group presented its rat findings to Merck, “I never heard from them

again,” except from company lawyers asking when the study would be published.

He said that studies done by the drug companies that led to the drugs’ approval by the F.D.A. tended to use young healthy animals that would not be expected to get pancreatic cancer.

The concern, he said, was that the drugs work essentially by increasing levels of a hormone called glucagonlike peptide-1. That hormone might accelerate precancerous conditions already present in middle-aged people, much as the hormone estrogen might promote growth of nascent breast tumors.

Three other pieces of evidence raise possible concerns.

One is the side effects reported to the F.D.A., typically by doctors or companies, after a drug is on the market. Dr. Butler and colleagues found far more cases of pancreatitis and pancreatic cancer reported for the incretin drugs than for Avandia.

Public Citizen and the Institute for Safe Medication Practices, two watchdog groups, have since separately found the same thing. Public Citizen has already asked the F.D.A. to remove Victoza from the market.

But these reports are voluntary and can be unreliable. Also, when there is publicity about a safety risk, reports of that side effect can spike.

Several groups have looked at medical records of thousands of patients held by insurance companies. At least three of these studies have found no increased incidence of pancreatitis or pancreatic cancer. But a [recent study](#) found roughly a doubling of the risk of acute pancreatitis among users of the drugs.

But what has prompted the reviews by regulatory agencies has been Dr. [Butler’s study of human pancreases](#) obtained from 34 organ donors who had died for reasons unrelated to pancreatic disease. Seven of the donors happened to have taken Januvia and one had taken Byetta.

The pancreases of those eight people tended to have more precancerous lesions than the organs of the diabetics who had not taken those drugs, or those of the nondiabetics. There was also one case of a neuroendocrine tumor, a type of pancreatic cancer.

Also, the pancreases of the incretin drug users were heavier, with faster growth of certain cells. “There were strange growths” that “you’d never see in a normal human pancreas,” Dr. Alexandra Butler said.

Critics point out that the incretin users were much older than the other diabetics and had been sick longer than other diabetics. That, not the drugs, could have accounted for the findings, they say.

“There are enormous problems with this paper,” said Dr. Ratner of the diabetes association.

Dr. Fred Gorelick, professor of medicine and cell biology at Yale, said the precancerous lesions found were early-stage ones. Many middle-age people have these and they often do not lead to cancer. Still, he said, the study “raised several red flags.”

More information could come out in June when the National Institutes of Health will hold a two-day meeting on possible links between diabetes, diabetes drugs and pancreatic cancer. Dr. Butler will be one of the speakers.

And starting this summer, results will be coming from large randomized clinical trials meant to assess whether the drugs raise the risk of heart attacks. Those trials should also be able to pick up an increased risk of pancreatic cancer that might have been missed by the smaller trials used to win approval of the drugs.

So far the safety concerns have not substantially reduced use of the drugs, though there are signs of “possible softness” recently, said Mark Schoenebaum, a pharmaceutical analyst at ISI Group. He said the evidence of a risk was weak and that the F.D.A. would probably take no action.

Dr. Butler said he was not calling for the drugs to be removed from the market, though he does not prescribe them to his own patients. Rather, he said, studies should be done using M.R.I. scans to see if use of the drugs is enlarging the pancreases of patients.

“We have all these people out there taking these drugs,” Dr. Butler said, “and the problem is: What is happening to their pancreases?”

*This article has been revised to reflect the following correction:*

***Correction: June 3, 2013***

*An article on Friday about the concerns Dr. Peter C. Butler has raised about some diabetes drugs referred imprecisely to Dr. Butler’s position of at the University of California, Los Angeles. He is the chief of the division of endocrinology at the university — not chairman, which the school uses for the head of the department of medicine.*

# EXHIBIT E

likely that such efficacy will be shown until the vaccines are licensed and postmarketing surveillance commences.

Recent evidence suggests that EV71 vaccines do not provide cross-protection against all circulating genetic lineages of EV71 or against coxsackievirus A16.<sup>5</sup> Thus, the Chinese C4A-based vaccines may not generate protective immunity against EV71 in regions where other extant or newly emerged lineages circulate. Consequently, it may be necessary to develop multivalent vaccines to ensure that protection is provided against all EV71 strains.

Nevertheless, this is an exciting development in the global response to the emergence of EV71 as a cause of severe neurologic disease. It is also worth noting

that in the past 17 years, EV71 research and vaccine development have been primarily centered in Asia — a fact that not only reflects the predominance of EV71 epidemics in this region but also underscores the increasing importance of Asia as a center of medical research. Finally, if these vaccines prove to be effective in preventing EV71-associated neurologic disease, an important tool for controlling, or even eradicating, EV71 infection in regions where it is endemic may have been developed. If its promise is realized, a priceless gift will have been given to the children of the Asia–Pacific region and to the rest of the world.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Infectious Diseases and Immunology Department, Sydney Medical School, the University of Sydney, Sydney.

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## Pancreatic Safety of Incretin-Based Drugs — FDA and EMA Assessment

Amy G. Egan, M.D., M.P.H., Eberhard Blind, M.D., Ph.D., Kristina Dunder, M.D., Pieter A. de Graeff, M.D., B. Timothy Hummer, Ph.D., Todd Bourcier, Ph.D., and Curtis Rosebraugh, M.D., M.P.H.

With approximately 25.8 million diabetic patients in the United States and 33 million in the European Union alone, the growing prevalence of diabetes worldwide poses a major public health challenge. Both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are committed to ensuring the safety of drug products marketed for the treatment of diabetes, and post-marketing reports of pancreatitis and pancreatic cancer in patients taking certain antidiabetic

medications have been of concern to both agencies. Working in parallel, the agencies have reviewed nonclinical toxicology studies, clinical trial data, and epidemiologic data pertaining to blood glucose-lowering drug products (e.g., exenatide and sitagliptin) that stimulate postprandial insulin release by potentiating the incretin hormone pathways.

In keeping with the pathophysiological complexity of diabetes, several classes of blood glucose-lowering drugs, encompassing diverse mechanisms of

action, have been developed to treat the disease. The incretins (i.e., glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide) are intestinal hormones that stimulate the postprandial production of insulin and glucagon by the pancreas. In the past decade, drugs that act as incretin receptor agonists (e.g., exenatide) or that inhibit the proteolytic degradation of incretins (e.g., sitagliptin) have been approved by both the FDA and the EMA (see table), in part on the basis of clinical data establishing

Incretin-Based Drugs Approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA).*			
Drug	Incretin-Based Mechanism	Approval Date	
		FDA	EMA
Exenatide	GLP1 agonist	April 28, 2005	November 20, 2006
Sitagliptin	DPP4 inhibitor	October 16, 2006	March 21, 2007
Vildagliptin	DPP4 inhibitor	(Not approved by the FDA)	September 26, 2007
Saxagliptin	DPP4 inhibitor	July 31, 2009	October 1, 2009
Liraglutide	GLP1 agonist	January 25, 2010	June 30, 2009
Linagliptin	DPP4 inhibitor	May 2, 2011	August 24, 2011
Exenatide extended-release	GLP1 agonist	January 27, 2012	June 17, 2011
Alogliptin	DPP4 inhibitor	January 25, 2013	September 19, 2013
Lixisenatide	GLP1 agonist	(Not approved by the FDA)	February 1, 2013

\* GLP1 denotes glucagon-like peptide 1, an incretin; DPP4 denotes dipeptidyl peptidase 4, an exopeptidase that inactivates the incretins.

efficacy in improving glycemic control. The benefit–risk assessment also considered clinical advantages such as reduced risk for drug-related hypoglycemia and possible improvement in body-weight maintenance.

Within the past year, the FDA and the EMA independently undertook comprehensive evaluations of a safety signal arising from postmarketing reports of pancreatitis and pancreatic cancer in patients using incretin-based drugs. These investigations, now complete, included examination of data from a 2013 research report revealing a possible pancreatic safety signal.<sup>1,2</sup> Both agencies committed themselves to assessing the evidence pertinent to reported adverse events, as well as any factors that might confound safety analysis in the context of antidiabetic drugs. Although the disproportionate spontaneous reporting of adverse events is commonly interpreted as a safety signal, there are inherent limitations to the ability to establish causal relationships, including the eval-

uation of events with high background rates, long latency periods, or a possible contribution by the disease itself.

Using the extensive nonclinical assessments completed as part of all marketing applications for incretin-based drugs, the FDA re-evaluated more than 250 toxicology studies conducted in nearly 18,000 healthy animals (15,480 rodents and 2475 nonrodents). Microscopic examinations from these toxicology studies yielded no findings of overt pancreatic toxic effects or pancreatitis. The EMA conducted a similar review of the studies for the incretin-based drugs currently authorized for use in the European Union (see table). In addition, drug-induced pancreatic tumors were absent in rats and mice that had been treated for up to 2 years (their life span) with incretin-based drugs, even at doses that greatly exceed the level of human clinical exposure.

A potential limitation of these toxicology data lies in the use of only healthy animals. To address

this concern, the FDA required sponsors of marketed incretin-based drugs to conduct 3-month pancreatic toxicity studies in a rodent model of diabetes. These studies included extensive histopathological evaluation of the endocrine and exocrine pancreas, including analysis of ductal morphology and histochemical staining capable of disclosing pathological proliferation and apoptosis. Three of these studies have been completed and submitted for review by the FDA, and no treatment-related adverse effects on the pancreas were reported. In addition, approximately 120 pancreatic histopathology slides from one of the three sponsor-conducted studies were subjected to independent and blinded examination by three FDA pathologists. The FDA experts' conclusions regarding these slides were generally concordant with the sponsor's report.

As part of its evaluation of the postmarketing reports of pancreatic adverse events, the FDA also performed its own pancreatic

toxicology studies with exenatide. Rodent models of disease, each accompanied by a nondiseased control, included a mouse model with chemically induced pancreatitis, the Zucker diabetic fatty rat, and C57BL/6 mice fed a high-fat diet. Data from the studies of the pancreatitis mouse and diabetic rat models did not identify exenatide-related pancreatic injury. In the high-fat-diet mouse model, minimal-to-moderate exacerbation of background findings (e.g., acinar-cell hyperplasia, atrophy, and periductal inflammation or fibrosis) were detected after 12 weeks of treatment with exenatide; that mouse model has not been definitively qualified as a model of drug-induced pancreatic responses, but it merits further investigation.

Clinical safety databases reviewed by the FDA included data from more than 200 trials, involving approximately 41,000 participants, more than 28,000 of whom were exposed to an incretin-based drug; 15,000 were exposed to drug for 24 weeks or more, and 8500 were exposed for 52 weeks or more. A similar review was conducted by the EMA, including all studies performed with the incretin-based drugs authorized in the European Union. Small imbalances in the incidence of pancreatitis were reported in premarketing trials, although the overall number of events was small. A pooled analysis of data from 14,611 patients with type 2 diabetes from 25 clinical trials in the sitagliptin database provided no compelling evidence of an increased risk of pancreatitis or pancreatic cancer.<sup>3</sup> Clinical trials in which amylase and lipase levels had been

monitored in a systematic manner showed that incretin-based drugs may increase enzyme levels, but the mean levels were in the normal range. Furthermore, changes in enzyme levels were not associated with gastrointestinal adverse events (i.e., abdominal pain, nausea, and vomiting).

Two cardiovascular outcome trials in patients with type 2 diabetes who were treated with incretin-based drugs have been completed: the Saxagliptin Assessment of Vascular Outcomes Recorded (SAVOR) trial and the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial. The SAVOR trial was a randomized, double-blind, placebo-controlled trial involving 16,492 patients. The EXAMINE trial was a randomized, double-blind, placebo-controlled trial involving 5380 patients. Reported rates of acute pancreatitis in the SAVOR and EXAMINE trials were low, with similar rates of events in the drug and placebo groups (22 and 16, respectively, in SAVOR; 12 and 8, respectively, in EXAMINE).<sup>4,5</sup> The reported incidence of pancreatic cancer was 5 and 12 cases, respectively, in the drug and placebo groups in the SAVOR trial, with no incidence of pancreatic cancer in either group in the EXAMINE trial.

The FDA and the EMA have also independently reviewed a number of observational studies to explore a possible association between incretin-based drugs and acute pancreatitis. Cohort and nested case-control studies, using a variety of large administrative claims databases, have yielded inconsistent results. These studies suffered, to different degrees,

from methodologic shortcomings, including limited power, inadequate outcome validation, incomplete covariate ascertainment, and inadequate confounding control.

Thus, the FDA and the EMA have explored multiple streams of data pertaining to a pancreatic safety signal associated with incretin-based drugs. Both agencies agree that assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data. The FDA and the EMA have not reached a final conclusion at this time regarding such a causal relationship. Although the totality of the data that have been reviewed provides reassurance, pancreatitis will continue to be considered a risk associated with these drugs until more data are available; both agencies continue to investigate this safety signal. The FDA and the EMA believe that the current knowledge is adequately reflected in the product information or labeling, and further harmonization among products is planned in Europe. Ongoing strategies include systematic capture of data on pancreatitis and pancreatic cancer from cardiovascular outcome trials and ongoing clinical trials, which should facilitate meta-analyses, and accumulation of further knowledge regarding these signals in the future.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD (A.G.E., B.T.H., T.B., C.R.); the European Medicines Agency, London (E.B.); Läke-medelsverket, Uppsala, Sweden (K.D.); and

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# EXHIBIT F



**J O I N T   C E N T E R**  
AEI-BROOKINGS JOINT CENTER FOR REGULATORY STUDIES

## **The Adverse Side Effects of Pharmaceutical Litigation**

**Judyth Pendell**

**Related Publication 03-22  
September 2003**

Judyth Pendell is a senior fellow at the AEI-Brookings Joint Center for Regulatory Studies. She thanks Robert Hahn and Adam Sloane for their helpful comments, and the U.S. Chamber of Commerce for its support. The views expressed in this paper reflect those of the author and do not necessarily reflect those of the AEI-Brookings Joint Center for Regulatory Studies or the U.S. Chamber of Commerce.

## **Executive Summary**

Prior research has demonstrated that a fear of unwarranted medical malpractice liability causes doctors and other healthcare practitioners to engage in self-protective activities, such as ordering unnecessary tests or treatments. This paper examines the impact that the liability system could have on prescription drug use. It reports on a Harris poll of doctors, pharmacists and patients. Situations where patients fail to receive appropriate medications as a direct result of the liability system are revealed. It recommends reforms that allow healthcare professionals to know with greater certainty which actions are likely to result in liability.



## The Adverse Side Effects of Pharmaceutical Litigation

Judyth Pendell

### Introduction

Healthcare is a public policy issue in which everyone has a very personal stake. Individual concerns about whether or not quality care will be available when it is needed commonly focus on whether good doctors and hospitals, and the best technology, will be accessible and affordable. It probably rarely occurs to anyone that even when the best care is within reach it might not be forthcoming because doctors or nurses or pharmacists may have concerns about themselves that trump their concerns about their patients.

Fear of unwarranted malpractice liability claims can create just such a conflict. In 2002, Common Good, an organization headed by lawyer and author Philip Howard, produced new, compelling evidence that doctors and other healthcare professionals are so concerned about unfounded lawsuits that they order unnecessary tests and procedures, and sometimes feel constrained from providing the candor and openness that would serve the patient's best interest.

Building on that work, this paper provides a window into how fear of liability could be getting in the way of patients not receiving medications they should have. The paper discusses first the dominance of non-meritorious suits and how the liability system creates undesirable incentives in the delivery of healthcare generally. It then discusses the findings of a Harris poll in which doctors, pharmacists, and patients are interviewed about how liability over pharmaceuticals is affecting their behaviors relative to prescribing, warning, and compliance with prescriptions.<sup>1</sup> It concludes that the randomness and uncertainty of the liability system is creating perverse incentives, including deterring pharmaceutical companies from research and development in some areas.

Healthcare professionals and pharmaceutical companies should be able to anticipate with some reliability which actions will result in liability being imposed, and which actions will provide protection from liability. Healthcare liability should be

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<sup>1</sup> The U.S. Chamber Institute for Legal Reform commissioned Harris Interactive to conduct a study on the issue of pharmaceutical product liability litigation. The study was conducted among three target populations: physicians, pharmacists, and patients. A PowerPoint presentation on "Pharmaceutical Liability Study Report on Findings" prepared for the U.S. Chamber Institute for Legal Reform can be viewed at <http://www.aei-brookings.org/admin/pdffiles/phpgm.pdf>.

reformed to allow for that predictability. Freedom from fear of liability will restore patient well-being as the dominant priority.

### **Background**

The tort system was always meant to affect the conduct of professionals, businesses, and organizations. The rationale has been that if those who provide goods and services are required to pay for the harm they cause they will be deterred from causing harm. The deterrence theory of tort litigation has recently come under intense scrutiny and criticism, however, among legal scholars. Priest<sup>2</sup> and Viscusi<sup>3</sup> have conducted research that concludes that the tort system does not appear to be making products or the environment safer. Sunstein, Schkade, and Kahneman<sup>4</sup> have questioned whether people really want optimal deterrence. Garber,<sup>5</sup> Schwartz,<sup>6</sup> Green,<sup>7</sup> and Burk<sup>8</sup> have focused on whether the tort system over-deters, whether efforts to protect against liability actually create socially undesirable behavior. For example, Garber's research shows how the tort system may be encouraging undesirable behaviors such as avoidance of R&D in product areas at risk of attracting litigation.<sup>9</sup>

Nowhere is this debate more focused than in the healthcare area. According to Alex Azar, the general counsel of the U.S. Department of Health and Human Services, defensive medicine, or the practice of ordering tests or other procedures solely as a protection against litigation, raises healthcare costs by as much as 70 to 126 billion

<sup>2</sup> See George L. Priest, "Understanding the Liability Crisis," *Liability: Perspective and Policy* (1988).

<sup>3</sup> See W. Kip Viscusi, "The Social Costs of Punitive Damages Against Corporations in Environmental and Safety Torts," *Geo. L. J.* 285 (1998). P. 87.

<sup>4</sup> See Cass R. Sunstein, David a. Schkade, Daniel Kahneman, "Do People Want Optimal Deterrence?" *Punitive Damages: How Juries Decide* (2002) The concept of optimal deterrence applied here is that which is accepted in the field of law and economics. "People appear to reject the view, widespread within economic analysis, that punishment should be increased beyond compensation where the probability of detection is low, and that compensation is adequate where the probability of detection is 100%."

<sup>5</sup> See Steven Garber, "Product Liability, Punitive Damages, Business Decisions and Economic Outcomes," *Wis. L. Rev.* (1998). P 237.

<sup>6</sup> See Victor E. Schwartz, Mark A. Behrens, Joseph P. Mastro Simone, "Reining in Punitive Damages "Run Wild": Proposals for Reform by Courts and Legislatures," *Brook L. Rev.* 1003 (1999). P 65.

<sup>7</sup> See Michael D. Green, William B. Schultz, "Tort Law Deference to FDA Regulation of Medical Devices," *Geo. L. J.* 2119 (2000). P 88

<sup>8</sup> See Dan L. Burk, Barbara A. Boczar, "Biotechnology and Tort Liability: A Strategic Industry at Risk," *U. Pitt. L. Rev.* (1994). P. 55.

<sup>9</sup> See Steven Garber, "Liability and Patient Health," Transcript of Conference Sponsored by AEI-Brookings Joint Center and Common Good, March 4, 2003.

dollars a year.<sup>10</sup> Unfortunately, the financial costs are not the entire story. Unnecessary interventions can be invasive, risky, and sometimes painful.

To explore further the importance of the problem of defensive medicine, a recent Harris poll commissioned by Common Good (a healthcare poll hereafter referred to as Harris HC) interviewed physicians, nurses, and hospital administrators to explore how the fear of litigation affects the practice of medicine and the delivery of medical care. It revealed that nearly all physicians and hospital administrators feel that unnecessary or excessive care is very often or sometimes provided because of fear about litigation. Physicians indicated in the poll that fear of malpractice claims causes them (or other physicians) to:

- Order more tests than they would based only on professional judgment of what is medically needed. (91% have noticed other physicians, and 79% report they themselves do this due to concerns about malpractice liability.)
- Refer patients to specialists more often than they would, based only on their professional judgment of what is medically needed. (85% have noticed other physicians, and 74% report they themselves do this due to concerns about malpractice liability).
- Suggest invasive procedures such as biopsies to confirm diagnoses more often than they would, based only on their professional judgment of what is medically needed. (73% have noticed other physicians, and 51% report they themselves do this due to concerns about malpractice liability.)
- Avoid candid discussions of medical mistakes when they are made. (Fear of liability is cited by physicians and hospital administrators as the leading factor that discourages medical professionals from openly discussing and thinking of ways to reduce medical errors.)<sup>11</sup>

Most of the literature on the impact of the liability system on healthcare has focused on defensive medicine in the context of the delivery of care, particularly in relation to diagnostic and treatment procedures. There has been little attention paid to the impact on pharmaceuticals--prescribing, the warnings about side effects, and patient compliance with recommended medications. The Harris HC poll did ask about doctors prescribing more medications than necessary, and it found that doctors prescribe more medications, such as antibiotics, than they would based only on their professional

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<sup>10</sup> See Alex Azar, *id.* at 4.

<sup>11</sup> See *Fear of Litigation*, Harris Interactive, April 2002.

judgment of what is medically needed. (Some 73% have noticed other physicians, and 41% report they themselves do this due to concerns about malpractice liability.) However, the poll did not ask whether doctors sometimes avoid prescribing certain medications that they deem appropriate for their patients because the medications have or could become targets of litigation. Similarly, although the literature on defensive medicine has focused primarily on the delivery of healthcare in doctors' offices and in hospitals, little is known about the impact of liability on pharmacies and pharmacists' practices.<sup>12</sup>

To fill this void and expand what is known about the impact of liability on healthcare, and on patient well being, the U.S. Chamber of Commerce commissioned a Harris poll of physicians, pharmacists, and patients with the objective of better understanding how the behaviors of individuals within these groups are affected by litigation involving pharmaceuticals (hereafter referred to as Harris PHRM).<sup>13</sup> The survey is based upon 250 interviews with physicians, 251 interviews with pharmacists, and 301 interviews with patients. (The sampling error for this poll is +- 6.9% for physicians, +- 6.2% for pharmacists and +-5.6% for patients.) To target patients who are likely to be currently taking medications (or needing to take medications in the future) patients qualified for the poll if they had been diagnosed with at least one of eight specified medical conditions: high cholesterol, hypertension, arthritis, depression, obesity, diabetes, heart disease, or stomach ulcers. The findings of that poll are discussed in this paper, and the entire poll, including detail about the methodology, appears as an attachment.<sup>14</sup>

### **The Impact of the Fear of Pharmaceutical Litigation on Physician Practices**

In most jurisdictions doctors have a duty to warn patients of side effects associated with a drug, and the pharmaceutical companies are relieved of this duty, when

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<sup>12</sup> The Harris poll commissioned by Common Good expanded the prior, almost exclusive, focus of the impact of fear of liability on physician practices to include hospital administrators and nurses. For example, nearly half or 43% of all nurses also feel prohibited or discouraged from doing what they think is right for the patient because of rules or protocols set up for liability protection.

<sup>13</sup> See *Pharmaceutical Liability Study Report on Findings*, Harris Interactive, July 2003.

<sup>14</sup> See <http://www.aci-brookings.org/admin/pdf/files/phpgm.pdf>.

the pharmaceutical company has provided an adequate warning to the doctor<sup>15</sup>. This “learned intermediary doctrine” first emerged in the 1960s, and is premised on several assumptions:

- physicians can evaluate best an individual patient’s medical needs and possible drug sensitivities,
- patients may wish to participate in the decision as to whether or not to take on the risks of a particular drug,
- a physician can provide ongoing supervision of the patient’s use of the drug, and
- physicians are best positioned to manage any possible side effects that do occur.

The learned intermediary doctrine does not relieve the manufacturer of the duty to provide adequate warnings of risks associated with specific drugs it merely requires that an adequate warning be given to physicians who might prescribe the drug. The assumption is that physicians will pass on an appropriate warning to their patients.<sup>16</sup>

The communication of warnings, however, has been distorted and complicated by fears of tort liability. According to FDA Commissioner Dr. Mark McClellan, “So long as the product developers we work with are facing an environment in which any adverse outcome can result in a major lawsuit, we may get labels written for lawyers, not doctors and patients. Because risk management often means reducing liability risks not reducing patient risks, there’s pressure to make labels read like liability avoidance tools. Instead they should be efficient documents for conveying risk--tools for helping doctors help patients. To protect the health of the public product labels should be written with the patient in mind, not a jury.”<sup>17</sup> Three in four (74%) doctors interviewed for the Harris PHRM poll feel that the information contained in the patient packet insert is more complicated than it needs to be--and that product liability litigation plays a critical role in making it complicated. In fact, nine in ten (91%) physicians who think the information is too complicated believe that product liability is the problem.

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<sup>15</sup> See Bernard J. Garbutt III, Melinda e. Hofmann, “Recent Developments in Pharmaceutical Products Liability Law: Failure to Warn, the Learned Intermediary Defense, and Other Issues in the New Millennium,” *Food & Drug L.J.* 269 (2003). P. 58 (Pharmaceutical companies can be sued under negligence or strict liability theories for product defects.)

<sup>16</sup> See Laurie K. Marshall, “Keeping the Duty to Warn Patients of the Risks and Side Effects of Mass-Marketed Prescription Drugs Where it Belongs: With Their Physicians,” *U. Dayton L. Rev.* 95 (2000). P. 26

<sup>17</sup> Mark B McClellan, MD, PhD, Commissioner, Food and Drug Administration. Speech before the Physician Insurers Association of America, May 24, 2003, Chicago, IL.

Since many patients want to participate in making critical medical decisions it is imperative that patients receive accurate and understandable information about the risks and benefits of medical options. This is particularly true for medications where it is almost always true that there are potential adverse side effects. The specter of liability practically assures that warnings will not be clearly worded in a patient-friendly way.

Unfortunately, the malpractice litigation environment in which doctors take on potential liability for the drugs they prescribe and the warnings they issue is far from rational and predictable. The Harris PHRM poll reveals that doctors unanimously (100%) agree that groundless malpractice litigation, or the threat of it, is a major concern to doctors. Nearly all physicians (99%) are personally concerned that they may be the target of groundless litigation or threat of litigation. Two-thirds of doctors (67%) say that they are personally *very* concerned about groundless litigation. Empirical research gives legitimacy to this fear. A study of general medical malpractice claims in the state of New York conducted by Harvard University revealed that for every claim that is filed by a meritorious plaintiff there are five or six other claims that don't involve either a negligence or an injury or both.<sup>18</sup>

Doctors believe that malpractice lawsuits against them that result from prescriptions they have made occur with some frequency. Two in five (40%) doctors are aware of other physicians who have been sued by patients who have experienced side effects from a prescribed drug, even though the drug was indicated and properly prescribed, leading them to think this type of litigation is common practice. In fact, most (57%) doctors are concerned that they may be sued by a patient who experiences side-effects from a drug they properly prescribe.

Doctors are handicapped in their efforts to provide adequate warnings to patients by the failure of the courts to defer appropriately to the expertise of the Food and Drug Administration (FDA). Doctors are dependent upon the patient package inserts provided by the pharmaceutical companies and approved by the FDA. The FDA provides an expert and careful review of all drug labeling, and requires that all warnings must be supported by solid scientific evidence. As Daniel E. Troy, general counsel of the Food and Drug Administration, has noted: "The agency [FDA] demands scientific substantiation not only

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<sup>18</sup> See Michele Mello, "Liability and Patient Health," conference sponsored by AEI-Brookings Joint Center, March 4, 2003. The study focused on medical malpractice claims generally, not just on claims involving pharmaceuticals.

for statements concerning the drug's clinical utility, but also for statements of precaution, contraindication, and warning. A statement in the labeling of a prescription drug has been found by FDA to represent the most current and complete scientific information. If a statement has been omitted, it is generally because FDA has not found it scientifically substantiated or necessary to assure safe use of the drug."<sup>19</sup> Yet, taken together, doctors don't get clear and consistent messages from the FDA and from the courts.

The dominance of lawsuits without negligence creates a situation of great uncertainty for doctors. They realize the liability system does not have clearly defined rules, where violating the rules means liability is incurred and compliance with the rules means protection from liability will be granted. Professor George Priest of Yale Law School has often referred to this as the "gotcha" system of liability.

How does this fear affect physicians' choices regarding prescribing medications? A sizable number of physicians (43%) have avoided prescribing a particular drug that was appropriate for a patient because they were aware that it might be involved in product liability litigation. Although most physicians do not observe this as a common occurrence, 28% of surveyed physicians did indicate it happened frequently or very frequently. This is less than one third, but the results occur in a situation where the number of physicians responding affirmatively should be zero. Clearly, all patients want their doctors to base their care on medical considerations, not legal considerations.

Doctors also are aware that patient behavior may be influenced more by information coming from the liability system than by information about risks coming from their own doctors. Two in five (38%) doctors reported in the survey that they know of patients who have stopped taking a medication that was properly prescribed for them because the patient discovered the drug was involved in product liability litigation. About three in ten (29%) doctors have had patients refuse to take a drug properly prescribed for them because they were aware that the drug was involved in product liability litigation. Despite the fact that the liability system does a poor job of keeping out unfounded lawsuits, some patients seem to treat the mere existence of a lawsuit as an indication that a drug is harmful.

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<sup>19</sup> See Dan Troy, *FDLI Update*, Jan/Feb 2003.

### **The Impact of the Fear of Pharmaceutical Liability on Pharmacists' Behaviors**

Historically, pharmacists have been on the liability hook almost solely through errors made in filling prescriptions: mistakes involving failure to provide the correct medication, the proper dose, or accurate directions for use.<sup>20</sup> Three theories have generally been relied on to relieve pharmacists of a duty to warn:

- 1) it would interfere with the doctor-patient relationship,
- 2) it would violate the learned intermediary doctrine, and/or
- 3) it would contradict public policy.<sup>21</sup>

Recently pharmacists as a professional group have been expanding their role well beyond that of prescription fulfillment to play a more active role in the healthcare delivery system. This new vision of "pharmaceutical care" transforms the pharmacist into a caregiver who provides patient education, monitoring, and adverse event reporting<sup>22</sup>. Through these changes in the professional paradigm, pharmacists are creating a new standard of care, one that incorporates a responsibility to warn patients. As noted by Myhra, of Texas Tech University School of Law:

Today's pharmacy education, in contrast, is patient oriented. Pharmacists receive five or more years of education and training, during which they learn, among other things, how to interact with patients and physicians and how to provide information and warnings to patients. In short, pharmacy schools emphasize the necessity for pharmacists to take active roles in the provision of patient health care and, importantly, in the counseling of patients about prescription medications and potential problems such as adverse interactions and side effects.<sup>23</sup>

Most courts addressing the pharmacists' potential duty to warn have not addressed this shift in the profession. However, courts in several jurisdictions have noted this change and in so doing have found a duty to warn. These courts have acknowledged the expertise of the pharmacist and the potential for improved therapeutic outcomes if

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<sup>20</sup> See R. Paul Asbury, "Pharmacist Liability: The Doors of Litigation Are Opening," *Santa Clara L. Rev.* 907 (2000). P. 40

<sup>21</sup> See Jennifer L. Smith, "Between a Rock and a Hard Place: The Propriety and Consequence of Pharmacists' Expanding Liability and Duty to Warn," *Hous. J. Health L. & Pol'y* 187 (2002). P. 2

<sup>22</sup> See Alison G. Myhra, "The Pharmacist's Duty to Warn in Texas," *Rev. litig.* 27 (1999). P. 18

<sup>23</sup> See *id.* at 60.

this duty is imposed.<sup>24</sup> To some extent the courts may also be reacting to Congressional requirements that pharmacists expand their role and deliver more direct care.<sup>25</sup>

When patients face the task of deciding whether or not to take a medication that has been prescribed for them, they need to balance the potential benefits of the drug against the risk of side effects and the seriousness of the side effects. To do this they need information that does not exaggerate either side of that equation. One would expect that this environment of expanding liability would inhibit candor by pharmacists in that it likely would cause them to overemphasize the risks and seriousness of the side effects. In fact, two in five (39%) pharmacists surveyed in the Harris PHRM poll indicated that they often over-emphasize the possible side effects of prescription drugs to patients. One in ten (10%) does this very often. Half of pharmacists (51%) believe the information given to patients in the patient packet insert is too complicated and that product liability is central to making it complex. So, patients appear to be getting overly complicated information in the package inserts, and then too often they get information from pharmacists who overemphasize the risks.

As is the case with physicians, pharmacists reported instances when patients have stopped taking medication or refused medication that was properly prescribed because of awareness the medication was the subject of litigation. Over two in five (44%) pharmacists report that some of their patients have stopped taking medication that was properly prescribed for them because they found out the drug might be involved in product liability litigation. Two in five (40%) pharmacists also report that patients have refused to take a properly prescribed drug because the patient knew the medication was involved in product liability litigation.

### **The Impact of Pharmaceutical Liability on Patients**

It has already been noted that the fear of liability may have an adverse effect on patients in several respects:

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<sup>24</sup> See *id.* at 71.

<sup>25</sup> The Omnibus Budget Reconciliation Act of 1990 (OBRA) requires states to implement "drug use review" programs to ensure that prescriptions are appropriate, medically necessary, and not likely to result in adverse events. It requires, among other things, that pharmacists offer to discuss with patients, in detail,

- The financial costs of defensive medicine are high and passed through to patients.
- Unnecessary tests or procedures that are not medically necessary but are ordered as a protection against liability impose risks and discomfort on patients.
- Doctors prescribe more medications than are needed, putting patients unnecessarily at risk of side effects.<sup>26</sup>
- Patient packet inserts are more complicated than they need to be due to the influence of liability, interfering with the ability of patients to get meaningful information about risks and possible side effects.
- Physicians sometimes avoid prescribing appropriate medications because of litigation fears.
- Pharmacists sometimes over-emphasize the risks and seriousness of side effects because of liability fears.
- Both physicians and pharmacists report that they are aware of patients who refused to take a medication, or discontinued taking a medication, because of litigation involving the drug.

Harris also went to the patients themselves to supplement this information. In the interest of interviewing people who were currently under medical care, the interviewees were randomly selected from lists of patients with at least one of eight medical problems: high cholesterol, hypertension, arthritis, depression, obesity, diabetes, heart disease, or stomach ulcers. The patients were asked about their awareness of product liability litigation involving specific drugs. As testament to the ubiquity of trial lawyer advertising to solicit clients for pharmaceutical product liability actions, most patients (86%) are aware of advertisements run by law firms about product liability suits over a specific drug. One in five (21%) have seen an advertisement for litigation over a drug they were taking.

Patients react to such advertisements with concern. Nearly nine in ten (86%) of the patients would be concerned if they saw an advertisement regarding litigation over a drug they were taking. Half (50%) would be very concerned. The patients were asked what actions they would take as a result of seeing such litigation ads. The results were as follows:

- Would call their doctor: 90% yes, 6% no, 4% not sure;
- Would stop taking the drug immediately: 25% yes, 44% no, 31% not sure;
- Would call the law firm mentioned in the ad: 19% yes, 47% no, 34% not sure.

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facts about the use of medications, including "side effects, adverse effects, adverse interactions, or contraindications."

<sup>26</sup> In addition, the excessive prescribing of antibiotics has contributed to a reduction in their efficacy.

Less than one in ten (8%) have ever had to do any of these. This is inconsistent with the findings discussed above: one in five has seen a litigation-related ad for a drug he/she was actually taking, nine in ten would react to such an ad with concern, and nine in ten would call their doctors. Since the people who were interviewed were in the continuing care of their doctors, it is possible that the need to call their doctors was obviated by regular visits at which time the medication could be discussed.

The majority of patients (69%) also express concern if a packet insert warns of possible serious side effects, with one in five (20%) patients not taking a drug prescribed by his/her doctor as a result of reading information about possible serious side effects provided by the patient packet insert. This information about patient noncompliance underscores the need to have packet inserts communicate side effects and risks in a way that is clear and meaningful to patients, not in complicated legalese as is often the case.

Although patients would be alarmed by news that a drug they were taking was the object of litigation, patient responses to questions about whether or not such litigation is likely to be meritorious reveal a cynicism about the litigation. Most patients (72%) believe that it is common for law firms to file product liability lawsuits against drug companies when only a small number of people have experienced side effects from a drug. Two in five (41%) think it is *very* common for law firms to do this. Although few patients (27%) say they would join a lawsuit over a drug if they had not experienced side effects, the majority (86%) thinks that it is common for other people to join these lawsuits. Two in five (43%) believe it is very common for people to join a lawsuit over a drug they were taking, even if they had not experienced any side effects from the drug.

Patients have a striking awareness of the possible overdeterrence effect of product liability litigation. The majority of patients (71%) feel that product liability litigation, or the fear of litigation, has likely caused pharmaceutical companies to avoid research in certain product areas. Over a third (35%) say it is very likely that companies have avoided research because they fear groundless product liability litigation. Four in five (80%) patients are concerned that groundless product liability litigation prevents pharmaceutical companies from developing new and beneficial drugs. Nearly half (44%) say they are very concerned this may be occurring.

There is independent evidence that their concerns are founded in fact. Below are some examples:

A Conference Board survey of corporate CEOs, across many industries including pharmaceuticals, revealed that 36% had been prompted to discontinue products because of litigation, and 30% had decided against introducing a new product because of litigation concerns.<sup>27</sup>

In the early 1990s liability against vaccine manufacturers drove many from the market. For some vaccines, only a single supplier existed in 1994. For one manufacturer a single punitive damage claim totaled more than 200 times the annual revenue generated by the vaccine.<sup>28</sup>

Steven Garber of RAND has developed a simulation model based on how R&D decisions get made in pharmaceutical companies. It's based on an investment model that looks at future profit flows and discounts them to present value, factoring in product liability risks above and beyond typical risks for a typical product. Garber uses the model to illustrate how incremental increases in the discount rate caused by projected increases in product liability risks can significantly affect a company's R&D decisions such as whether to initiate clinical trials. He notes that "product liability risks can have a very real, a very very large effect on incentives to innovate."<sup>29</sup>

Finally, the likely impact of significant tort liability in the biotechnology industry is particularly poignant, in light of the role that industry plays in pharmaceutical innovation. To quote Burk, George Mason Law School, and Boczar, McCutchen, Doyle, Brown, and Enersen:

The possibility of overdeterrence in the biotechnology industry is heightened by additional factors related to the structure of the industry. Dedicated biotechnology companies tend to be small, entrepreneurial, and focused on a single product. Any shadow on a small company's single product is likely to portend the end of that company. This is what occurred, for example, in the case of Cetus Corporation. Although Cetus was considered a large and relatively strong DBC, postponement of FDA approval for its flagship product,

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<sup>27</sup> See Schwartz, *supra* note 5, at 1010.

<sup>28</sup> See Gregory C. Jackson, M.D. "Pharmaceutical Product Liability May Be Hazardous to Your Health: A No-Fault Alternative to Concurrent Regulation," *Am. U. L. Rev.* 199 (1992). P. 42. In response to this crisis the Congress passed into law a federally administered compensation system for vaccine claimants.

<sup>29</sup> See Garber *supra* note 8 at 14.

Interleukin-2, contributed to the company's dissolution. A court injunction or major damage award could lead to the same result for many biotech companies, and even a single such incident could well discourage the capital investments that have been required either to start new DBCs or to sustain those already in existence.<sup>30</sup>

## Conclusion

Using a Harris poll of doctors, pharmacists, and patients to inquire about the impact of liability on pharmaceutical prescribing, warning, and compliance adds force to the existing evidence that the tort liability system creates overdeterrent effects. The impact on patients may be significant: doctors may avoid the best prescription because of liability fears; pharmacists may overemphasize the risks and frighten patients into not taking it; patients may learn of litigation involving the drug and not begin the medication or stop taking medication they are currently on; and pharmaceutical companies may fail to develop or to bring to market new medications out of fear that they will become targets of unfounded litigation. More research is needed to clarify how frequently this occurs and to what effect. It is likely that much of this overdeterrence is fueled by the unpredictability of the tort system, which fails to set up clear rules or standards *ex ante* so that doctors and pharmacists can assess which behaviors will expose them to liability and which will protect them from liability. Personal injury litigation involving a specific drug also frequently sends inaccurate signals to patients that a drug may have risks that go beyond what they were told by their physician or pharmacist. Reforms that reduce the unpredictability in the pharmaceutical liability system would go a long way toward protecting the well being of patients.

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<sup>30</sup> See Burk and Goczar *supra* note 7 at 830.