

# **Outline of Presentation**

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- Incidence in clinical trials
- Incidence for marketed drug
  - Overall
  - By labeling change
  - By duration of therapy

## **Worldwide Clinical Trial Data**

| <b>Sponsor</b>       | <b># Pts. Exposed</b> | <b>Jaundice</b> | <b>Hepatic Death</b> |
|----------------------|-----------------------|-----------------|----------------------|
| <b>Parke-Davis</b>   | <b>7,656</b>          | <b>3</b>        | <b>1</b>             |
| <b>NIH</b>           | <b>585</b>            | <b>1</b>        | <b>1</b>             |
| <b>Sankyo</b>        | <b>4,147</b>          | <b>0</b>        | <b>0</b>             |
| <b>GlaxoWellcome</b> | <b>3,203</b>          | <b>0</b>        | <b>0</b>             |
| <b>TOTAL</b>         | <b>15,591</b>         | <b>4</b>        | <b>2*</b>            |

**Incidence Rate of a Fatal Liver Event = 1 in 7,800**

**95% CI: 1 in 2,200 - 1 in 62,900**

**\*These patients were also jaundiced.**

**Overall Post-Marketing  
Reporting Rate**

**March 1997–March 1999**

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**35 in 1.58 million = 1 in 45,098**

## Factors Increasing Reporting Rates for Adverse Events

|                                 | Rezulin |
|---------------------------------|---------|
| Newness <sup>1,2,3,4</sup>      | ✓       |
| Severity <sup>1,5,6,7,2,8</sup> | ✓       |
| Clarity of signal <sup>9</sup>  | ✓       |

1. Milstien JB, et al. *Drug Information J.* 1986;20:157.

2. Lumley CE et al. *Pharmaceut Med.* 1986;1:205.

3. Faich GA, et al. *JAMA.* 1987;257:2068.

4. Sachs RM, Bortnichak EA. *Am J Med.* 1987;81:49.

5. Faich GA, et al. *Arch Intern Med.* 1998;148:758.

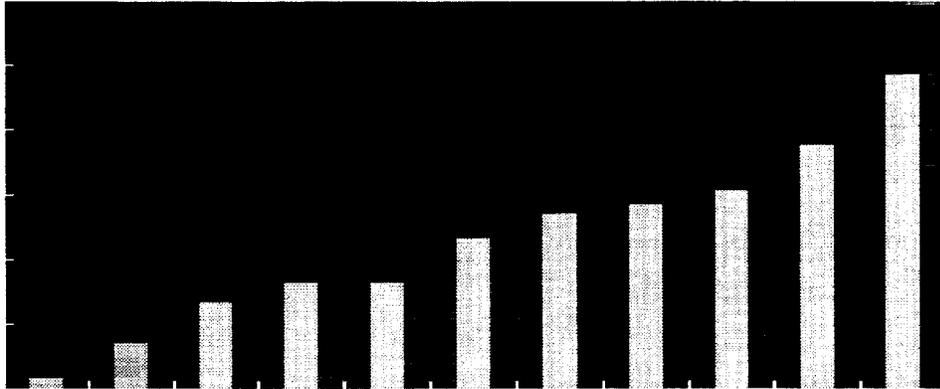
6. Piazza Hepp TD, Kennedy DL. *Am J Health-Syst Pharm.* 1995;52:1436.

7. Bergman U, et al. *Brit Med J.* 1978;2:464.

8. Rogers AM, et al. *Arch Intern Med.* 1988;148:1596.

9. Koch-Weser J. *NEJM.* 1969;280:20.

## Trend in Post-Marketing Reports (All Drugs)



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| Secular trend <sup>5,3,6,10,11</sup> | ✓       |
| Active monitoring                    | ✓       |

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| Sales representative contacts        | ✓       |
| Publicity <sup>1,2,3</sup>           | ✓       |

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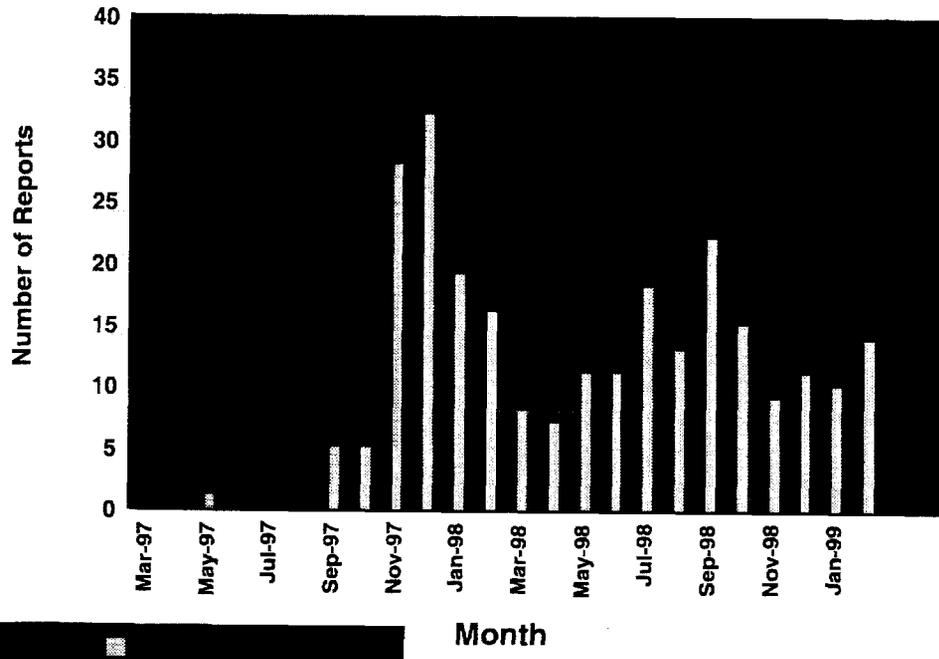
11. Burke LB, et al. Chapter 9. In: *Pharmacoepidemiology An Introduction*, 3<sup>rd</sup> Edition, AG Harzema, et al. ed. Cincinnati: Whitney Books Company, 1998.

12. Meinzinger MM, Barry WS. *Drug Information J.* 1990;24:575.

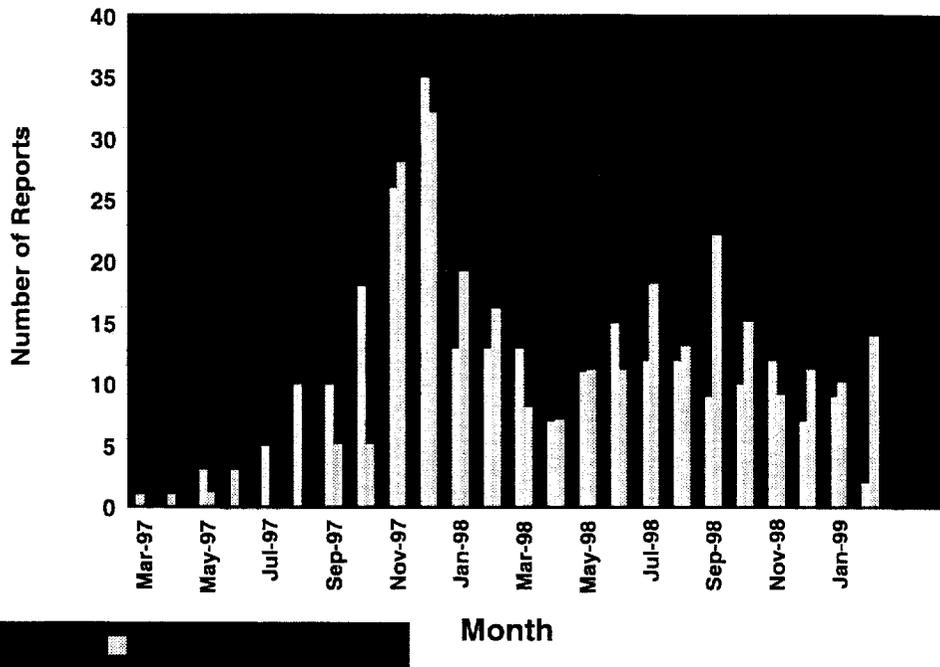
13. Rawlins MD. *Brit J Clin Pharmac.* 1988;26:1.

14. Rossi AC, et al. *JAMA.* 1988;259:1203.

### Effect of Publicity on Reports of Jaundice/Hyperbilirubinemia



### Effect of Publicity on Reports of Jaundice/Hyperbilirubinemia



# **Reporting of Liver Transplants**

1998

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## **United Network for Organ Sharing**

- 4,394 transplants
- 4 transplants involved patients taking Rezulin
- Each transplant was reported to Parke-Davis and the FDA

## **Conclusion**

- No evidence of unreported transplants

# **Survey of Physicians Treating Patients with Type 2 Diabetes**

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## **Methods**

- AE reporting and safety monitoring of patients with Type 2 diabetes receiving oral hypoglycemic drugs
- 600 physicians surveyed
  - Randomly selected
  - Proportion in each specialty matched prescriber mix
- Anonymity

# **Survey of Physicians Treating Patients with Type 2 Diabetes**

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| <b>Adverse Event</b>                                | <b>% Likelihood of Report</b> |
|-----------------------------------------------------|-------------------------------|
| <b>Liver failure leading to death or transplant</b> | <b>92</b>                     |
| <b>Lactic acidosis leading to death</b>             | <b>90</b>                     |
| <b>Jaundice</b>                                     | <b>61</b>                     |
| <b>Lactic acidosis with full recovery</b>           | <b>58</b>                     |
| <b>Reversible Liver Dysfunction</b>                 | <b>49</b>                     |
| <b>Hypoglycemia</b>                                 | <b>17</b>                     |

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# **Survey of Physicians Treating Patients with Type 2 Diabetes**

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## **LFT monitoring awareness**

- 96% of physicians were aware of the need for LFT monitoring

## **LFT monitoring compliance**

- 97% of patients receive baseline LFTs
- 82% of patients receive monthly X 8 LFTs

## **Issues With Claims Data**

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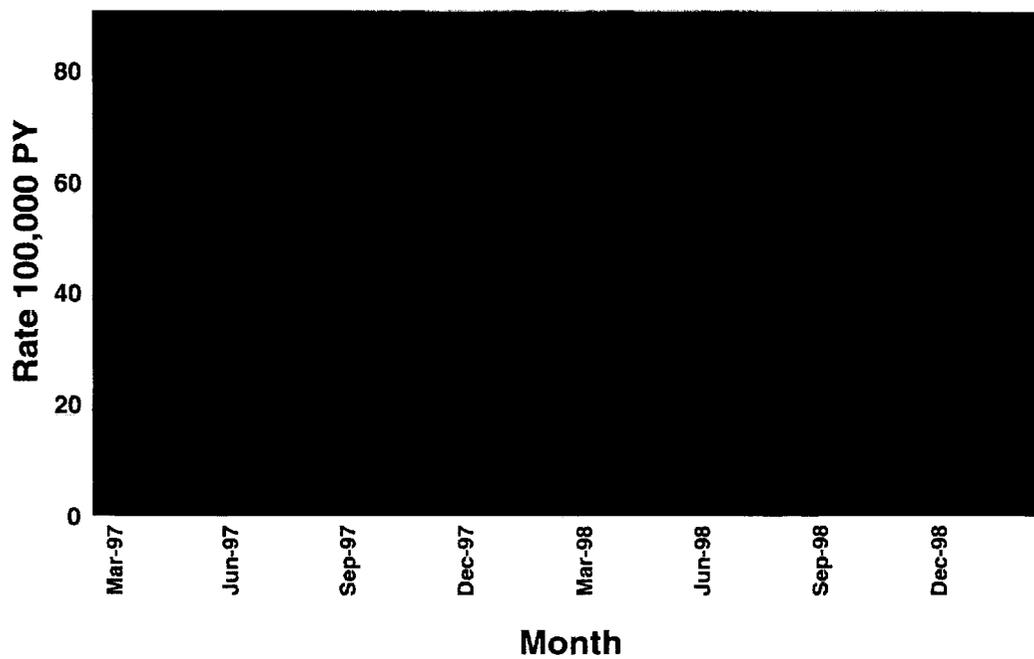
### **UHC Study**

- Claims data often missing
- Claims sometimes not submitted
- Long delays in claim receipt

### **Conclusions**

- Claims data are unreliable
- Data do not reflect absolute level of monitoring
- Data do show 2-3 X increase in monitoring frequency

### Incidence Rates of Serious Liver Events Since Launch

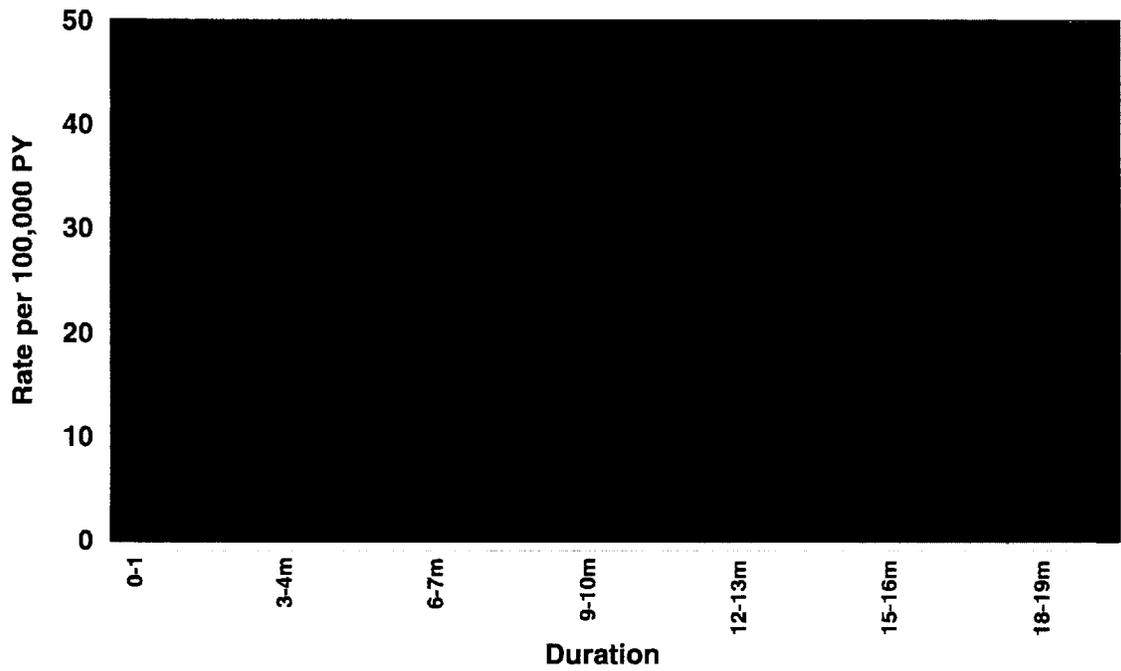


## **Effect of Labeling Changes**

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| <b>Year</b>    | <b>Cases</b> | <b>New Users</b> | <b>Rate</b>        |
|----------------|--------------|------------------|--------------------|
| <b>1997</b>    | <b>20</b>    | <b>726,570</b>   | <b>1 in 36,329</b> |
| <b>1998-99</b> | <b>15</b>    | <b>851,883</b>   | <b>1 in 56,792</b> |

### Reports of Serious Liver Events by Duration on Drug



## **Conclusions Regarding Incidence**

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- The incidence of liver-related death and transplant is low
- The risk of jaundice and death due to liver failure or transplant substantially declines after 6-8 months of therapy
- The reported rate of adverse liver events has decreased following labeling changes