Integration of pre-clinical, clinical and post-marketing safety data

Carmen Nitsche

October, 2006

Agenda

- Drug safety - background
- Safety and the drug development process
- Drug safety teams - needs and challenges
- Summary

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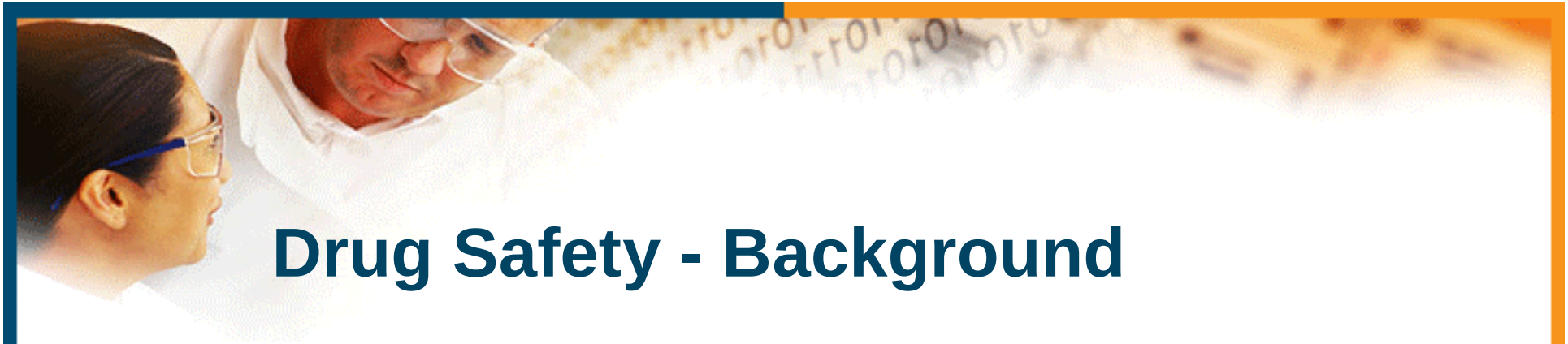

Drug Safety - Background

- Often referred to as pharmacovigilance
- Focuses on gathering, detecting, and analyzing adverse events information to prevent further or future related events in humans.
- Not necessarily limited to medications
  - **Herbal and other supplements/biologicals**
- Can be very complex
  - **Drug–Drug interactions**
  - **Rare effects**

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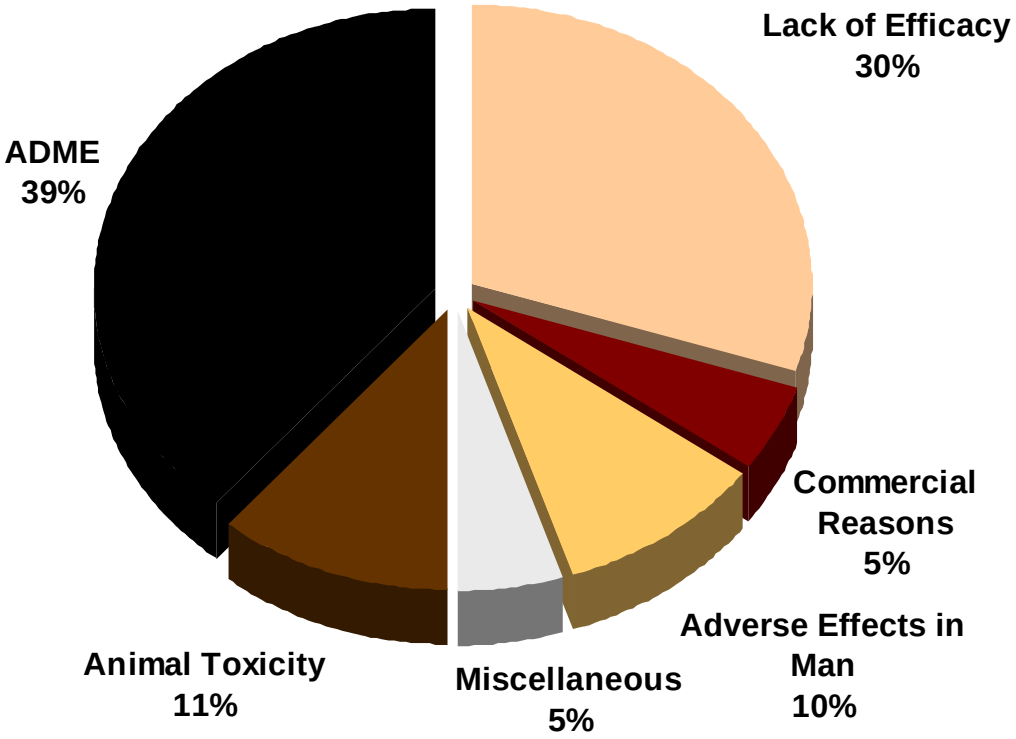
ADME-Tox Liabilities Account for 60% of NCE Failures

Failure of New Chemical Entities (n=198)



ADME: Absorption/Distribution/Metabolism/Elimination

DDT Vol 2, No. 10, October 1997

"Managing Toxicology for the Future" An excerpt from D&MD's Market Analysis Report; By Mike Silver, PhD and Brigitta Tadmor, PhD January 2003

"About one third of all drugs fail preclinical or clinical testing because of apparent or suspected drug toxicities. ***According to industry estimates, companies spend about $2 billion annually on toxicity-related drug failures.*** *The inaccuracy of safety screens in place today can also lead to enormous lost opportunity costs. Termination of a single potential blockbuster drug in development or on the market can lead to lost revenue far exceeding the total direct cost of industry failures.* ***Despite the staggering financial losses associated with toxicity-related drug failures, companies typically spend only about 5% of their total R&D budget on drug safety evaluations."*** ***<emphasis added>***

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http://www.drugandmarket.com/default.asp?section=feature&article=011403

Post-market failures

- Vioxx had $2.5B in sales when it was pulled from the market in Fall 2004
  - **Merck Inc. stock fell 33% in less than a month**
- Not an isolated incident
  - **Rezulin**
  - **Seldane**
  - **Baycol**
  - **Fen-Phen**
- Millions spent in litigation, settlements and fines

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Changes in approach

- Drug safety teams becoming more interdisciplinary and horizontal
  - **More interaction and communication with researchers at all stages**
  - **Greater attention paid to safety issues from the beginning of development**
  - **Information from all stages of drug development fed back into the early phases of the research process**

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What do drug safety teams do?

- Conduct toxicity studies and evaluate the results
- Handle regulatory reporting
- Monitor safety issues
  - **Existing drugs and new candidates**
- Compile safety assessments

What kinds of questions do drug safety teams have?

- What do we know about the toxicological mechanism of this compound or compounds like it? What can we predict?
- What side effects are we seeing in humans?
- How does this compare to the preclinical results?
- Do our competitors have any similar compounds in their pipeline or approved? Why was research on competitor drug X terminated?
- Do any of the above have implications on our developing pipeline?

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Where is the needed data?

- In-house data
  - **ADME/tox screening data, etc.**
- Journal articles
- Conferences
- Regulatory submissions (multiple countries)
  - **From new drugs to post-marketing feedback**
  - **Clinical study results**
- Books
- Commercial and Public Databases
- Personal contacts

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Drug safety - The information challenge

- Much of published safety data and precedent is held in disparate sources
  - **inconsistent or non-existent indexing**
  - **information difficult to find quickly**
  - **Sources are in different formats**
  - **No longitudinal view of the data**
  - **Must integrate different data types**
    - Preclinical/clinical/post-market

- Never sure of comprehensiveness

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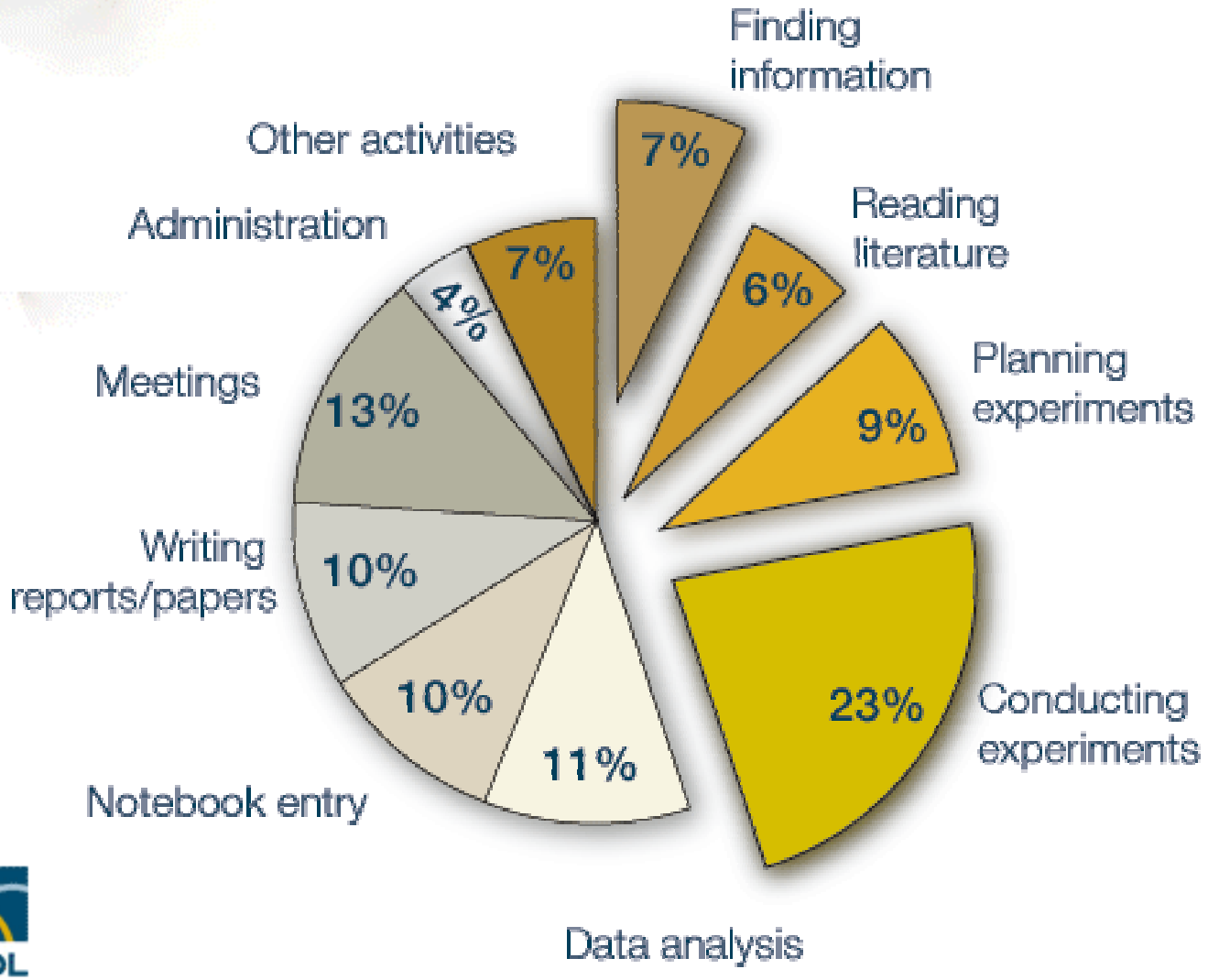
How scientists spend their time?



Outsell 2005

The Need - Drug Safety

- "…….. people in our toxicology department spend 40% of their time searching for safety information…and usually have no confidence that they have found all of what is available…"
  - ***A Global VP, Preclinical Dev***

What do drug safety teams need?

- Better safety data
- Integrated preclinical, clinical and post-marketing data
- Better data organization and context

…….. and make it easy to use

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Better Safety Data

- FDA Approval Packages
  - **Extremely rich source of information available via the Freedom of Information Act**
  - **Generally Untapped**
    - Not well indexed or searchable
    - Formats: paper, microfiche, bitmap
    - Tedious to find specific facts (side effects or adverse events)
    - Finding class/target/effect/dose relationships can be impossible

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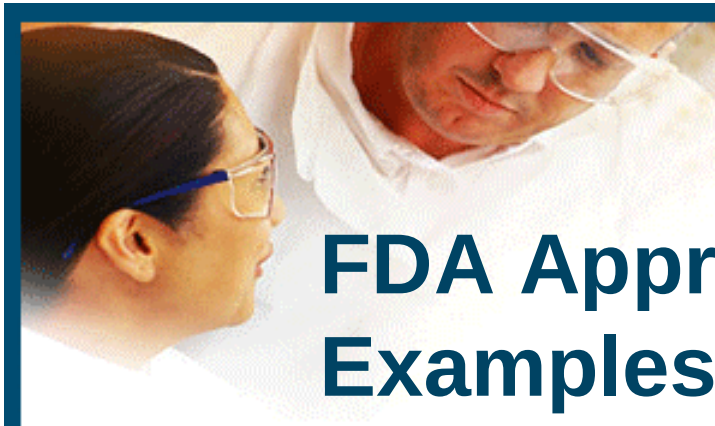


FDA Approval Packages - Examples of Original Documents

REVIEW AND EVALUATION OF CLINICAL DATA

NDA: 19-839/S-035
20-990/S-003*

SPONSOR: Pfizer Pharmaceuticals Group

DRUG: Zoloft (Sertraline HCl) Tablets and Oral Concentrate

DATE OF DOCUMENT: 5/25/2001

DATE RECEIVED: 5/29/2001

I. REVIEW:

These supplemental new drug applications listed above provide for the use of Zoloft (sertraline HCl) ta
Zoloft (sertraline HCl) oral concentrate for the long-term treatment of post-traumatic stress disorder (P

In response to our approvable letter, the sponsor has submitted the updated version of the proposed pac
insert taking into account the comments received from us. All of the suggestions received from the Ag
were incorporated into the labeling with the exception of the following few items:

1. Under INDICATIONS AND USAGE, PTSD, in the fourth and final paragraph of this subsect
term [redacted] was deleted in the first sentence of this paragraph because the patients that enter
open label 24-week treatment had already completed a 12-week placebo-controlled trial prior
entering the open label treatment.

2. Under DOSAGE AND ADMINISTRATION, Maintenance Treatment, the three paragraphs su
by the Agency were incorporated with a few minor revisions.

In the third sentence of the first paragraph of this section under the sub-heading of Depression
term [redacted] was deleted. It is Pfizer's position that this term is unnece
the data to which it refers is well described in the previous sentence. The phrase "[redacted]
[redacted]" was deleted from the fourth sentence of the first paragraph of this sec
because the statement is repetitive and repeats what was previously been said about the dosing
the same paragraph.

Toxicokinetics:

Table 4.5-1. Summary of toxicokinetic data for CGP 57148B

	3 mg/kg/day		15 mg/kg/day		75 mg/kg/day	
	$AUC_{0\text{-}24h}$ (ng·h/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)	C_{max} (ng/mL)
MALES:						
Days 1/2	214 ± 156	37.2 ± 34.5	1650 ± 1240	216 ± 170	16000 ± 5390	1210 ± 325
Days 91/92	230 ± 107	32.4 ± 18	1460 ± 1710	178 ± 236	16800 ± 6730	1080 ± 384
FEMALES:						
Days 1/2	218 ± 83.0	40.9 ± 20.6	2340 ± 1340	310 ± 152	18000 ± 4500	1230 ± 287
Days 91/92	286 ± 61.1	44.6 ± 13.2	1960 ± 291	208 ± 69.0	15600 ± 4610	1280 ± 143

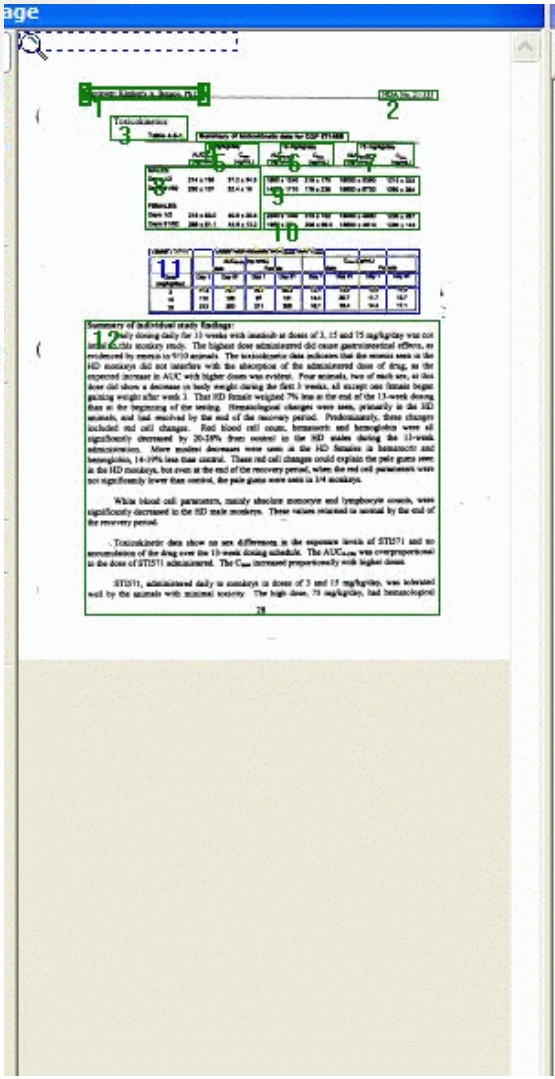
Table 7.1-11 Dose Normalized $AUC_{0\text{-}24}$ and C_{max}

Dose (mg/kg/day)	$AUC_{0\text{-}24}$ (ng h/mL) Male Day 1	$AUC_{0\text{-}24}$ (ng h/mL) Male Day 91	$AUC_{0\text{-}24}$ (ng h/mL) Female Day 1	$AUC_{0\text{-}24}$ (ng h/mL) Female Day 91	C_{max} (ng/mL) Male Day 1	C_{max} (ng/mL) Male Day 91	C_{max} (ng/mL) Female Day 1	C_{max} (ng/mL) Female Day 91
3	71.3	72.7	76.7	96.3	12.4	13.8	10.8	14.9
15	110	188	97	131	14.4	20.7	11.7	13.7
75	213	200	211	208	16.1	16.4	14.4	17.1

Summary of individual study findings:

Daily dosing daily for 13 weeks with imatinib at doses of 3, 15 and 75 mg/kg/day was not lethal in this monkey study. The highest dose administered did cause gastrointestinal effects, as evidenced by emesis in 9/10 animals. The toxicokinetic data indicates that the emesis seen in the HD monkeys did not interfere with the absorption of the administered dose of drug, as the expected increase in AUC with higher doses was evident. Four animals, two of each sex, at this dose did show a decrease in body weight during the first 3 weeks, all except one female began gaining weight after week 3. That HD female weighed 7% less at the end of the 13-week dosing than at the beginning of the testing. Hematological changes were seen, primarily in the HD

OCR Results



Text

Reviewer Kimberly A. Benson. Pn.D.

Toxicokinetics:

Tab * 44H. Summary of toxScoUnatic data for CC

	Smg/kaMay		15mefcg/da	
	(nqh/M.)	(ng/mL)	(ng VmL)	(n
MALE S:				
Day* 1/2	214 ±156	37.2 ±34.5	1660 ±1240	21
Oays91/92	230 ±107	32.4 ±18	1460 ±1710	17
FBIALE S:				
Days1/2	216 ±83.0	40.9 ±20.6	2340 ±1340	31
Days 91/92	266 ±61.1	44.6 ±13 J	1960 ±291	20

TaMa 7.1-11 Doa* Normataad AUC, Mk ami

Dm (mattfMay)	oiyi	AUCjMi CngMnL) Day 91	Fanato Dayi	Day 91	0
3	71.3	72.7	76.7	984	
16	110	166	97	131	
76	213	200	211	206	

Summary of individual study findings:

Daily dosing daily for 13 weeks with imatinib at doses
lethal in this monkey study. The highest dose administered di

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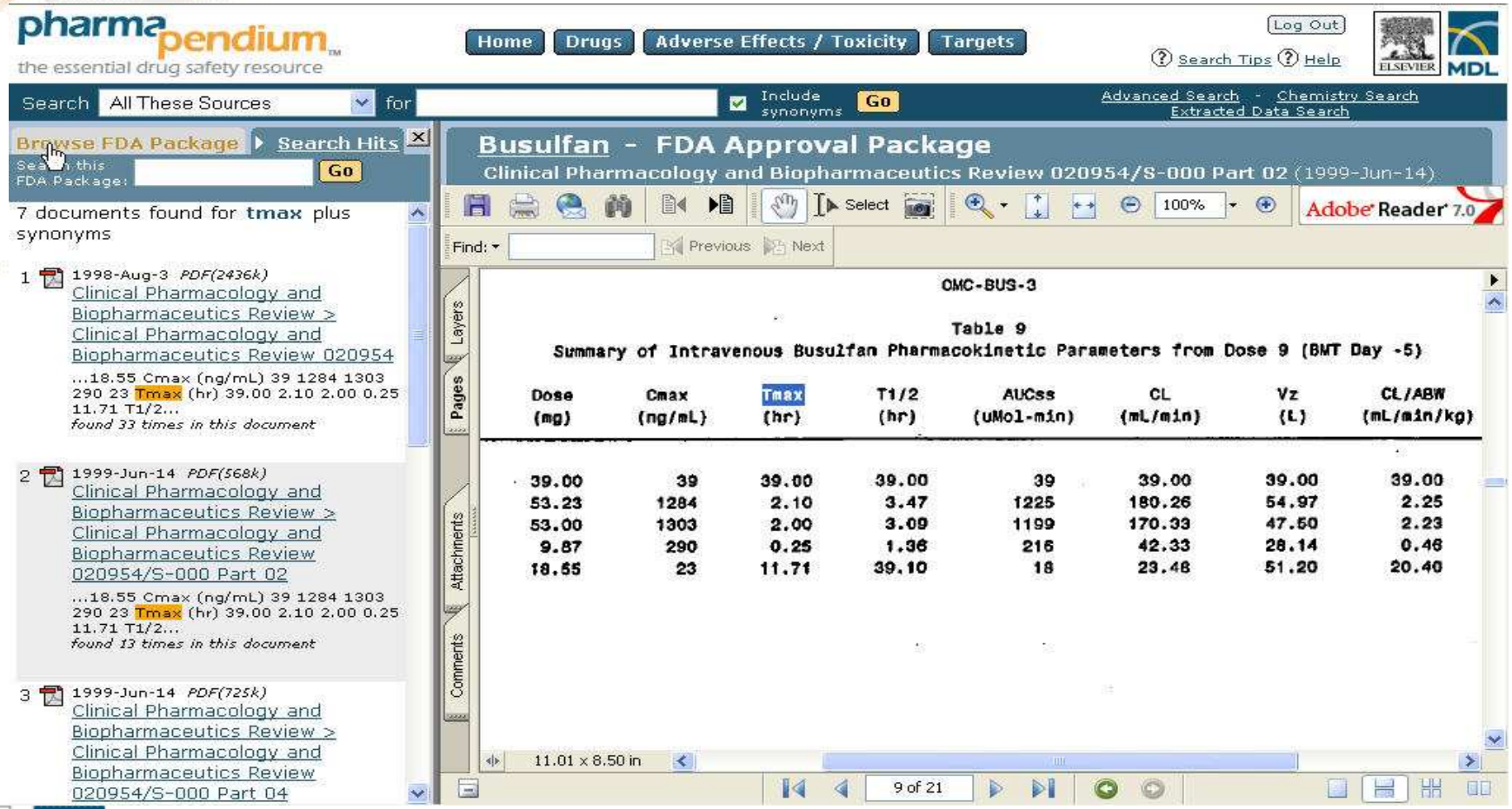
FDA Approval Packages - Busulfan



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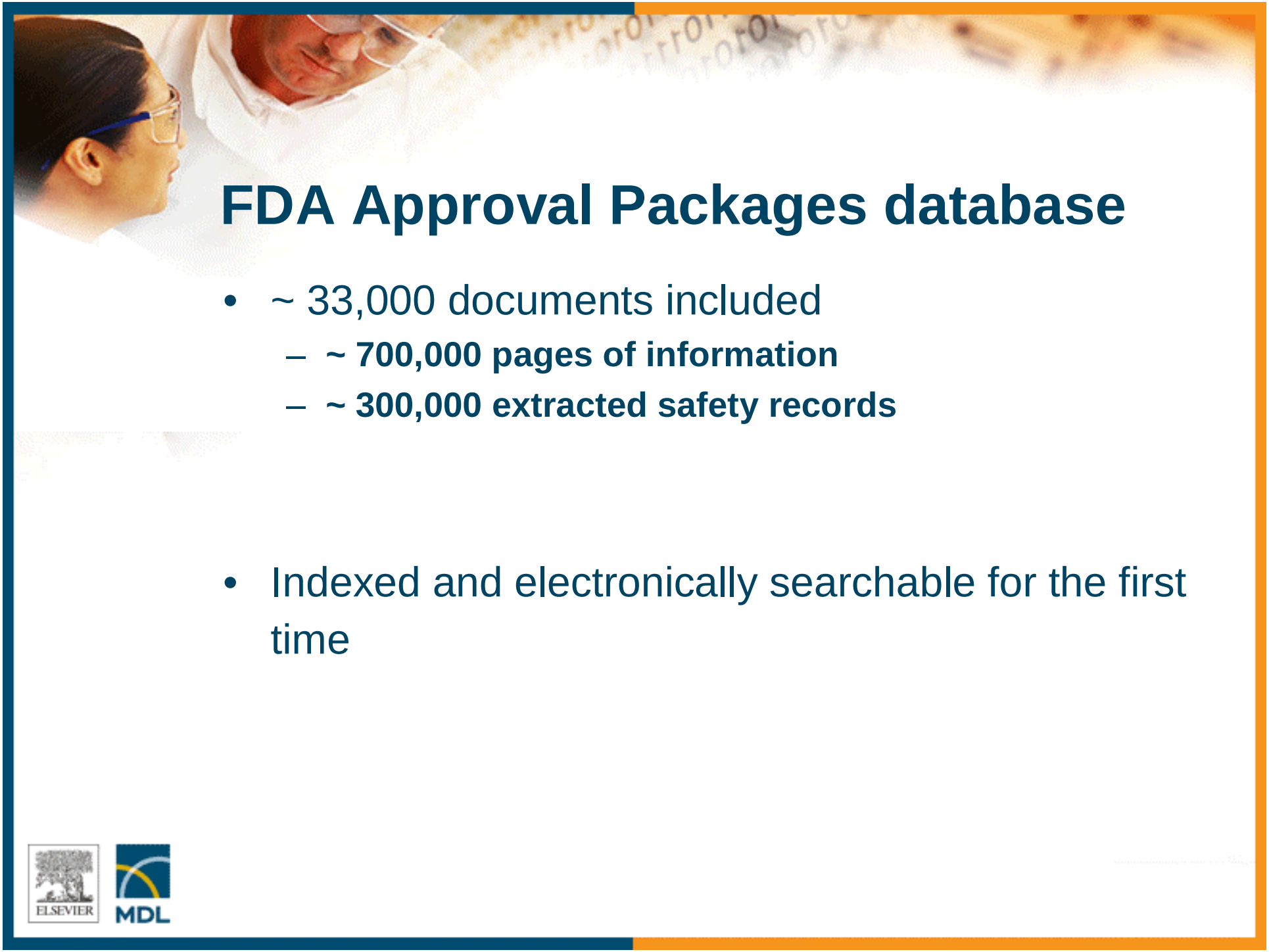
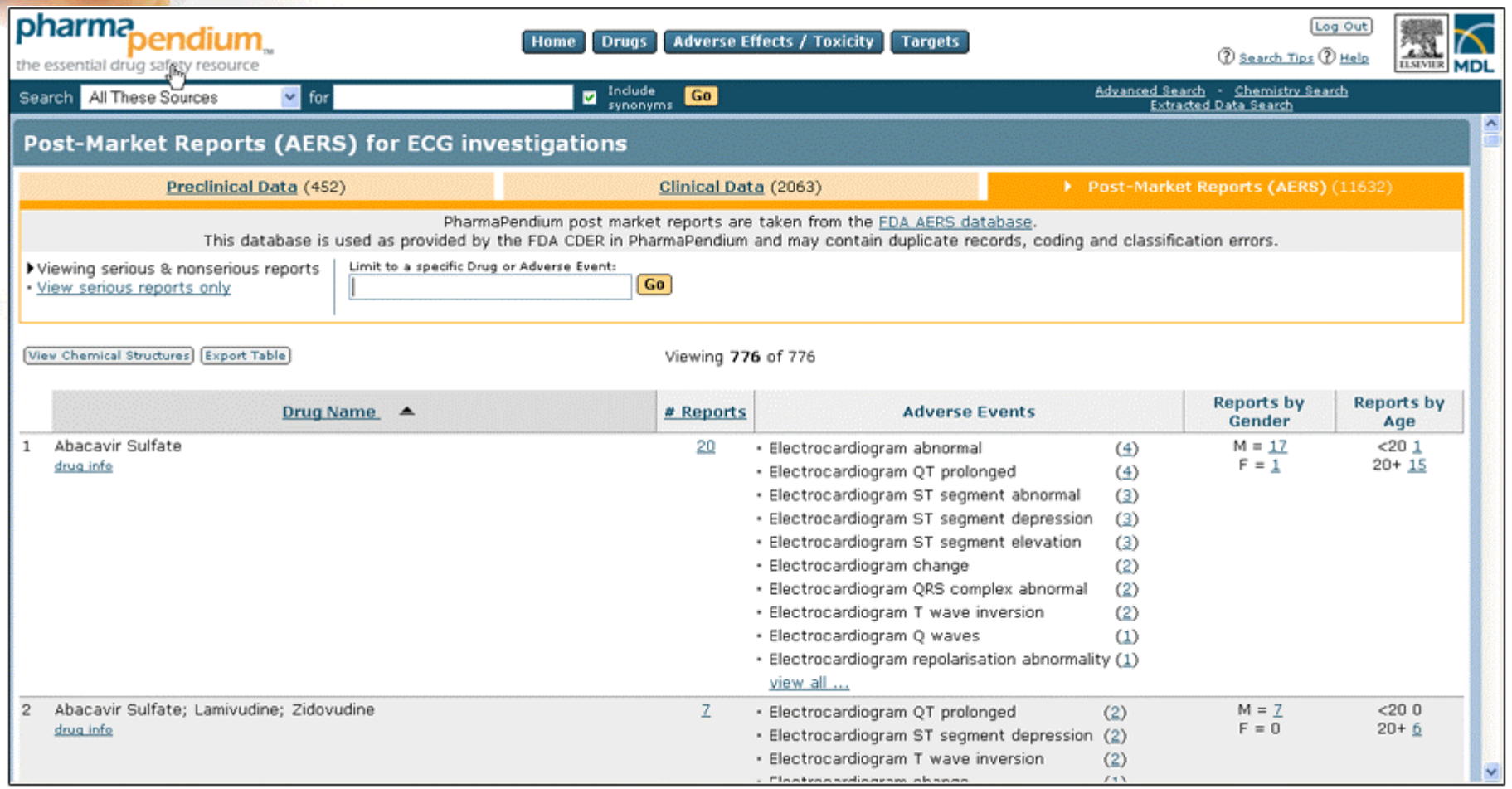


FDA Approval Packages database

- ~ 33,000 documents included
  - **~ 700,000 pages of information**
  - **~ 300,000 extracted safety records**

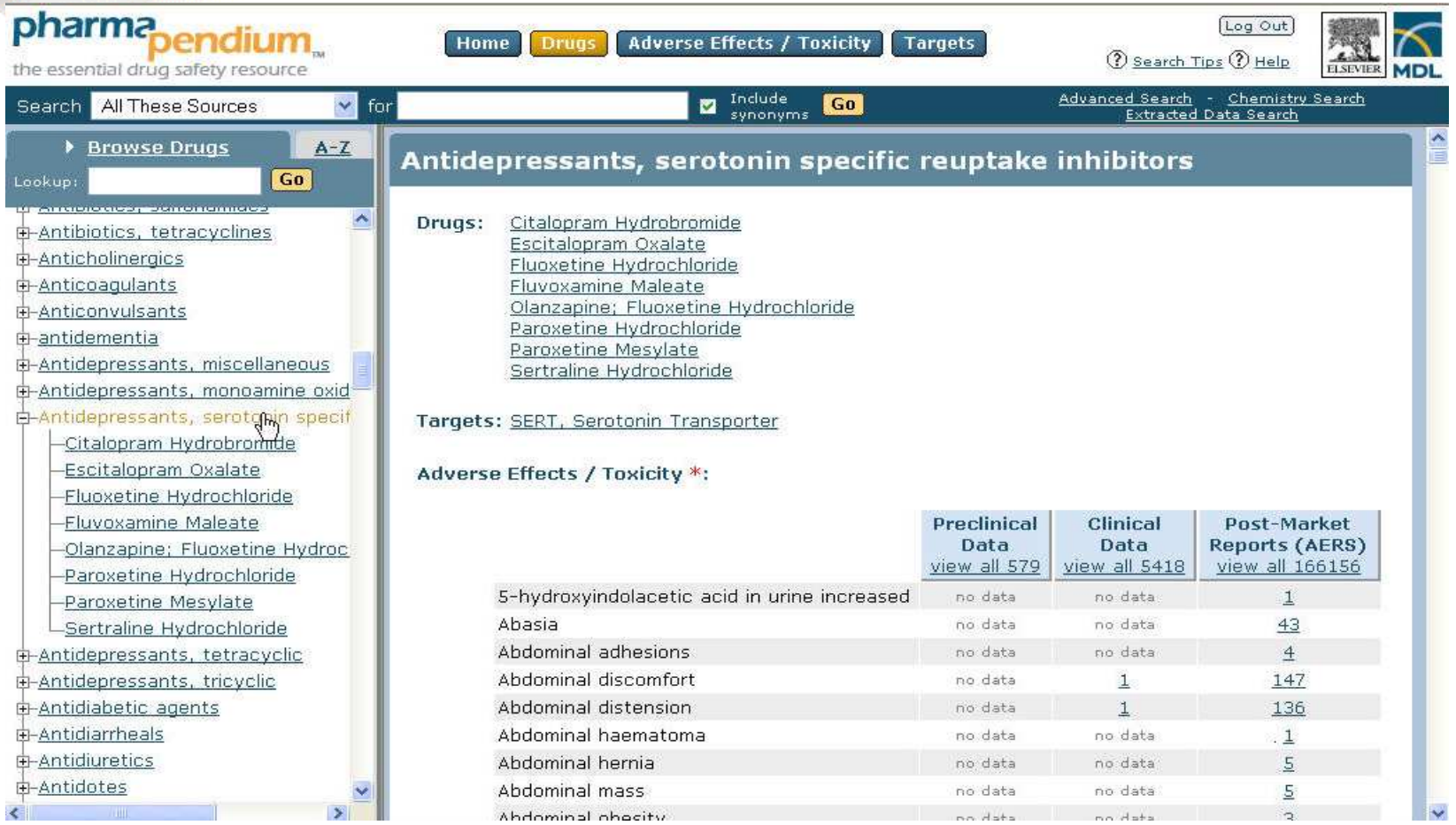
- Indexed and electronically searchable for the first time

Integration - preclin/clin/post-mktg



	Drug Name	# Reports	Adverse Events	Reports by Gender	Reports by Age
1	Abacavir Sulfate drug info	20	• Electrocardiogram abnormal (4) • Electrocardiogram QT prolonged (4) • Electrocardiogram ST segment abnormal (3) • Electrocardiogram ST segment depression (3) • Electrocardiogram ST segment elevation (3) • Electrocardiogram change (2) • Electrocardiogram QRS complex abnormal (2) • Electrocardiogram T wave inversion (2) • Electrocardiogram Q waves (1) • Electrocardiogram repolarisation abnormality (1) view all ...	M = 17 F = 1	<20 1 20+ 15
2	Abacavir Sulfate; Lamivudine; Zidovudine drug info	7	• Electrocardiogram QT prolonged (2) • Electrocardiogram ST segment depression (2) • Electrocardiogram T wave inversion (2)	M = 7 F = 0	<20 0 20+ 6

Better data organization and context



…..and make it easy to use

- Applied user-centered design approach
- Not just “usefulness” but “ease of use” is key
- Know your user and their tasks
- Take into account
  - **Perception**
  - **Language**
  - **Thinking**
  - **Memory**
  - **Motor function**
- Iterative process

Summary

- Drug Safety is a critical business issue
- Safety data is examined throughout the research and development process
- New safety teams are becoming more interdisciplinary and horizontal
- New information resources must address the needs of this new drug safety paradigm

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pharmapendium™

the essential drug safety resource

Unique online resource developed to meet the needs of drug safety teams

- Information delivered in a longitudinal view for better scientific insight
- Best-in-class sources, including FDA Drug Approval Packages
- Usability that simplifies research efforts

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Acknowledgements

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Luming Niu

Thank you