FDA Advisory Committee

December 14-15, 2006

KETEK® (telithromycin)

sanofi-aventis US

Overall Comments on Hepatic Events

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Focusing on the Questions

- **No question** as to some rare risk of hepatic events analogous to other antibiotics…this has been known and examined by sponsor and FDA since before 2001

- **Current question**: Is the risk of hepatic events
  - Significantly different from comparators
  - Acceptable given Ketek's beneft-risk

Question: Re The Risk Of Hepatic Events

Significantly different from comparators?

- Basis for answering the question:
  - Signal has been known since prior to approval,
  - Signal strengthened in
    - Reporting rate analysis..noted limited due to reporting and publicity biases
    - Data mining disproportionality analyses

Question: Is The Risk Of Hepatic Events Significantly Different From Comparators?

But, signal analysis of spontaneous reports are of limited value

- Numbers of spontaneous reports should not be quantified
  - Many reporting biases, notably publicity bias
  - Marked secular trends
  - Never a reliable estimate of incidence[1]
  - Very incomplete data preventing good causality assessment
- NEJM commentary[2] of reporting rates based on Person-Years is misleading…estimates should be on persons exposed; denominator estimates are also crude

1. Miwa, L.J., et al. "Value of Epidemiologic Studies in Determining the True Incidence of Adverse Events: The NSAID Story." Archives of Internal Medicine, 1997; 157:2129-2136.
2. Graham DJ Telithromycin and Acute Liver Failure. NEJM 2006; 355: 2260.

Question: Is The Risk Of Hepatic Events Significantly Different From Comparators?

Only possible basis

- Formal epidemiological* studies with defined
  - Denominator
  - Detectable outcome (numerator)

  that are both measurable in a representative, sufficiently large population.

**Given the rareness of the events, even extremely large randomized trials would not be likely to detect sufficient events*

Features of these Epidemiologic Studies

OUTCOME

- Cases of severe liver injury temporally associated with antibiotic but causality of event not determinable
- No specific ICD9 CM code for ALF
- Could not quantify rate of ALF if ~ 1/million baseline (one reason “severe” Liver Injury used)
- Hospitalization serves as unambiguous indicator of severe liver injury

STUDY POWER

- Both studies powered to rule out the very high risk estimate for telithromycin in signalling analyses
- The PHARMetric study had >90% power to rule out 4x greater risk of severe liver injury

Epidemiological Investigation of Hepatic Injury

1) PHARMetrics Integrated Outcome Database
   - 12 million active enrollees in June 2005

2) Ingenix I3 Proprietary Research Database
   - A separate 12 million enrollees

PHARMetrics Data: Distribution of Severe Hepatic Injury Events

Event →	Telithromycin (N=124,413)	Augmentin (N=93,871)	Clarithromycin (N=202,456)	Moxifloxacin (N=111,336)
Liver necrosis	4	1	11	8
Hepatic coma	1	2	2	4
Hepatitis unspecified	7	4	17	11
Liver transplant	0	0	0	1
Total*	11	6	26	21

* One patient may have >1 event.

PHARMetrics Data: Crude and Adjusted Risk Ratios of Severe Hepatic Injury

	Crude		Adjusted*	
	Risk ratio	95% C.I.	Risk ratio	95% C.I.
Augmentin**	1.00	N/A	1.00	N/A
Clarithromycin	2.00	0.82 – 4.85	1.95	0.80 – 4.73
Moxifloxacin	2.90	1.17 – 7.19	2.58	1.04 – 6.43
Telithromycin	1.37	0.51 – 3.71	1.44	0.53 – 3.89

* Covariates age, sex, prior history of liver disease, and Charlson Index were adjusted in the GEE models

** Augmentin was used as a reference group in the GEE models

Table 1 – I3 Demographic Characteristics

Demographics	Telithromycin (N=102,660) N	%	Clarithromycin (N=102,660) N	%
Age				
0 - 9	40	0.0	43	0.0
10 - 19	4,637	4.5	4,424	4.3
20 - 29	12,136	11.8	12,132	11.8
30 - 39	24,235	23.6	24,356	23.7
40 - 49	28,309	27.6	28,460	27.7
50 - 59	21,822	21.3	21,710	21.1
60 - 64	6,135	6.0	6,166	6.0
65 +	5,346	5.2	5,369	5.2
Gender				
Female	62,138	60.5	61,871	60.3
Male	40,522	39.5	40,789	39.7
Region				
Northeast	10,656	10.4	10,752	10.5
Midwest	26,238	25.6	26,121	25.4
South	56,635	55.2	56,758	55.3
West	9,131	8.9	9,029	8.8

Hepatic Injury Occurred Within 60 Days of an Antibiotic Use, Ingenix Database Study

	Telithromycin	Clarithromycin	Teli + Clari
Acute liver failure	0	2	0
Hy's law*	1	0	1
Liver enzyme elevation	2	0	2
Other	1	0	0

* Hy's law: hepatocellular jaundice, ALT ≥ 3 ULN, direct bilirubin > 3 mg/dl, and absence of alkaline phosphatase elevation

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LFT elevation =/= severe liver injury

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Hepatic Injury C
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Analysis of >1 antibiotic describes higher risk group

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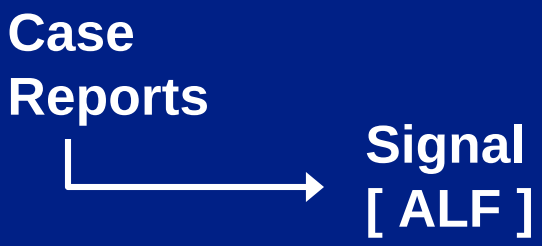
Summary

- Severe hepatic injury was signaled in clinical development and spontaneous reports and required further investigation by epidemiological studies.
- Data from two independent retrospective cohort studies using PHARMetrics and Ingenix, the largest two health insurance databases, demonstrates that:
  - In >200,000 telithromycin exposed, very small number of severe liver events
  - Severe hepatic injury is a rare event among telithromycin users
  - The risk of severe hepatic injury following telithromycin use does not exceed the risk demonstrated by other oral antibiotics

From Signal to Risk Quantification



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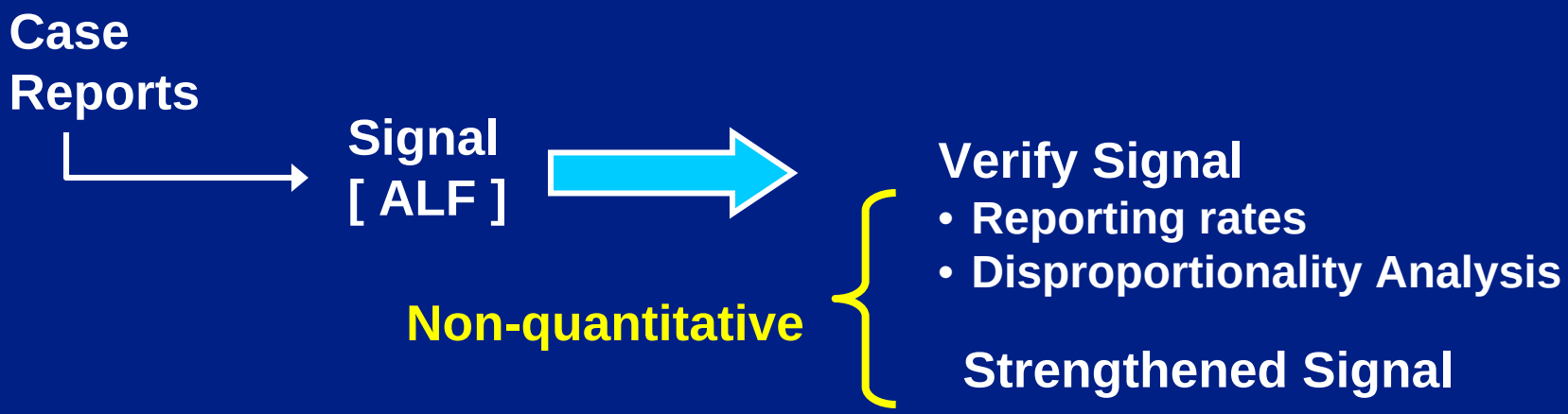

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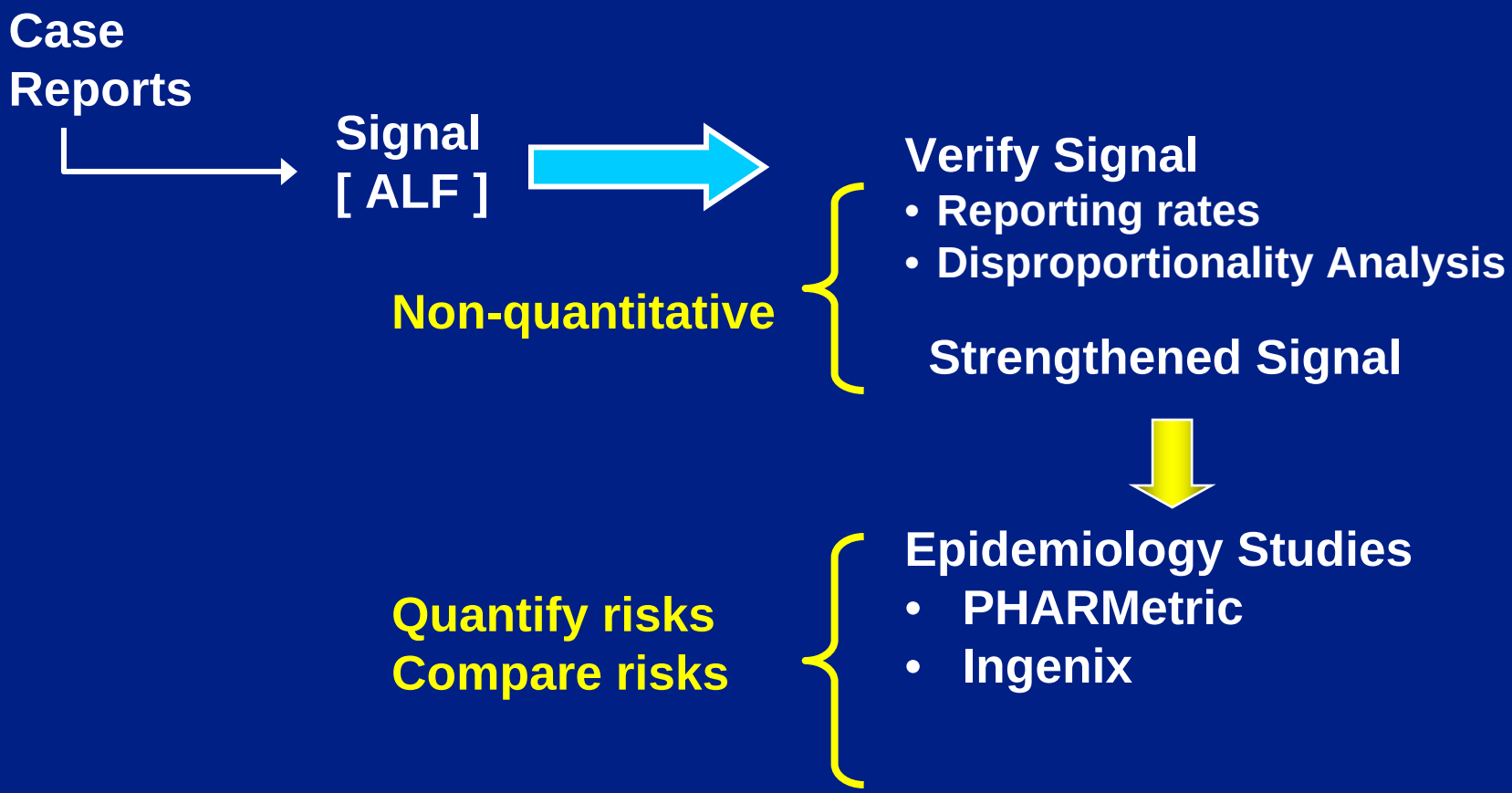

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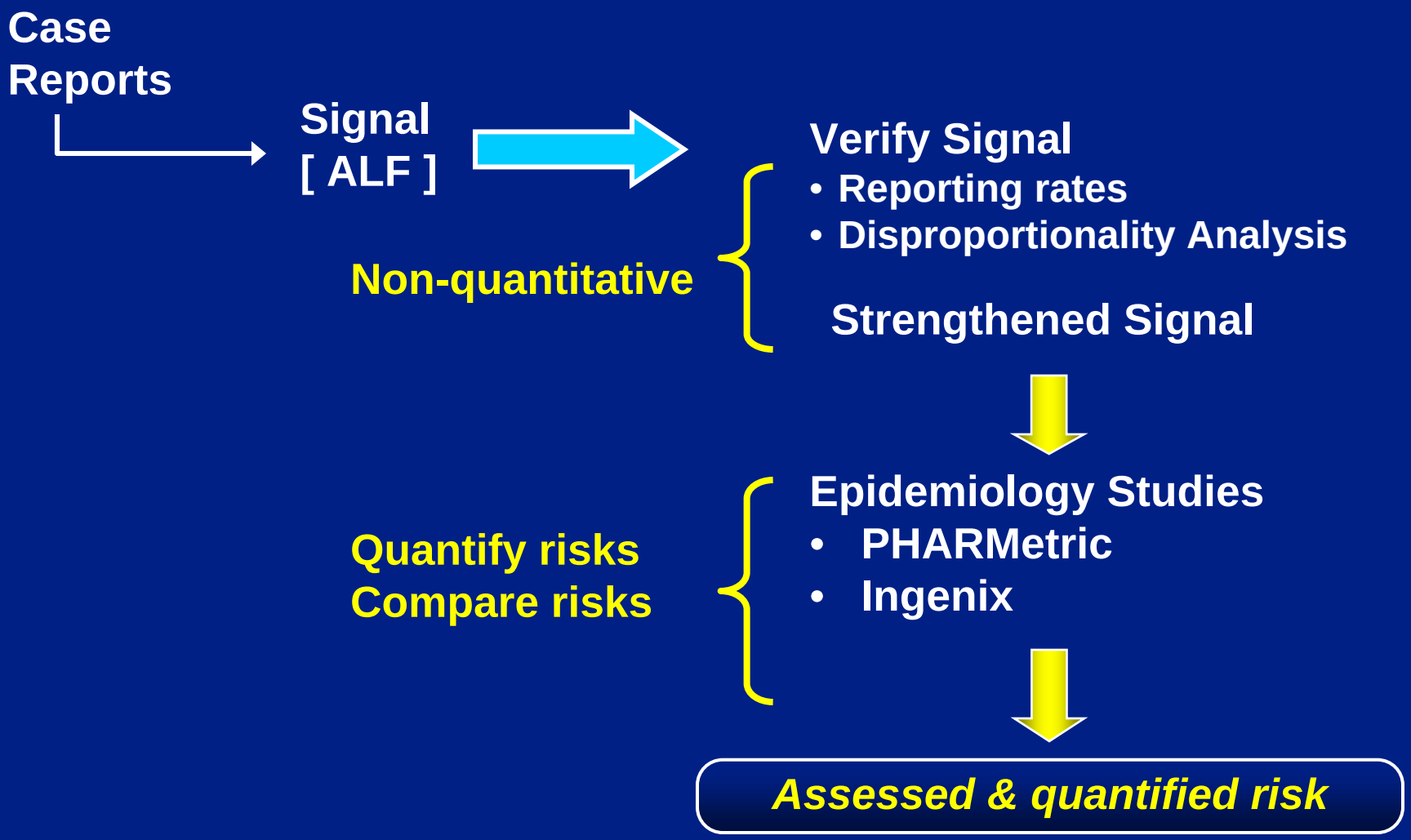

Summary

- **Question**: Is the risk of hepatic events
  - Significantly different from comparators? **NO**
    - Two formal epidemiological studies suggest not
  - Acceptable given Ketek's beneft-risk? **YES**
    - Given
      - Effectiveness data and additional profile re resistant organism

      Plus
      - Relative safety and rareness of severe hepatic events…