

# **OARSI FDA OA INITIATIVE**

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# **OARSI FDA OA INITIATIVE Safety Working Group**

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(As stand in for the work of the Safety Group)

## Safety Considerations

VOTING	NON-VOTING
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## Safety Related to Exposure

- Safety data is relative to what is being treated
  - Benefit and risk are inherently important to understand the possibility of approval and use
- Prevention, structure modification and improvement in signs and symptoms have different “tolerance” levels for safety.
  - For a preventive therapy which is used BEFORE a disease state is established there is a different acceptance of AE risk than that tolerated in an observed treatment for an established disease state

## Challenges to the Working Group

- What risks are patients and/or society willing to accept?
    - For symptomatic only therapies?
    - For disease modifying therapies?
  - Three grids were formed to evaluate agents offering:
    - Symptomatic relief only
    - Structure-modifying only, and
    - Symptom relieving plus structure-modifying.
- In the context of:
- Systemically administered
  - Topically or Intra-articular injection with minimal to no systemic absorption
  - Autologous cartilage implants
- And for “prevention” / risk reduction?

## Considerations

- Examples:
  - For a symptomatic agent, "overall safety" shouldn't be worse than that observed with NSAIDs.
  - A SMOAD however, may allow more potential adverse events if the ultimate clinical outcome is longer term function without symptoms
    - New agents for RA and DM have now ~ 2500-3000 patient-years exposure requirements for approval.
    - Relevance of two recently released FDA guidance documents

Guidance for Industry, Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention HHS/FDA/CDER DRAFT February 2008

Guidance for Industry, Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes HHS/FDA/CDER December 2008

## Considerations

- A commitment for safety information after approval to narrow the “window” of CI estimates around actual risks (known or unknown) to <1:10,000 - 1:30,000. RCTs and other means (e.g.- claims databases) should be used.
- An outcomes study prior to registration was not felt to be needed prior to approval, if the *a priori* concern is low (no preclinical or clinical **signal**).

## Minimum Requirements: ICH Guidelines

ICH guidelines (E1, 1994) are considered “minimums” to characterize the safety of a new agent predominantly with chronic exposure, but:

- Don't reveal Rare (<1/1000) or long-term AEs nor,
- AEs in at risk, or special populations (for example those with HTN, on low-dose aspirin or other concomitant medications)

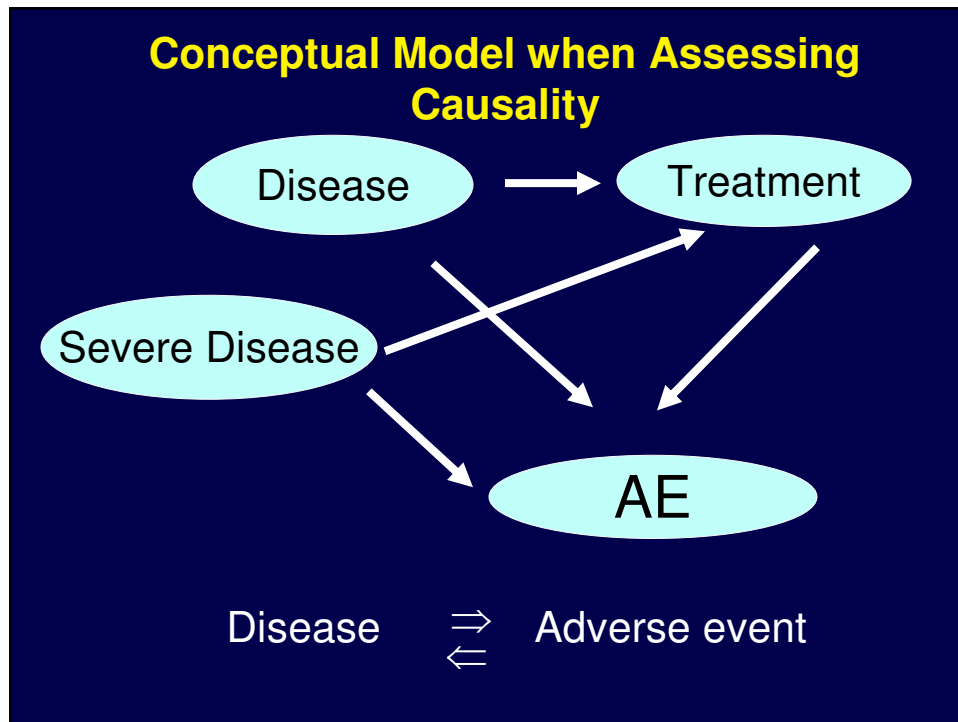
Duration	Time	Exposure (patients)	Incidence Rate Characterized
Short-term	≤3 months	1500	~1%
Mid-term	6 months	300-600	0.5 - 5%
Long-term	1 year	100	3%
not ICH characterized	≥1 year	2500-3000	0.1%

## Limitations of Safety Data Assessed in Randomized Controlled Trials [RCTs]

- TNF $\alpha$  inhibitors and other biologic agents initially approved for use in CD and RA with limited databases – FDA thought use would be restricted to patients with severe, refractory disease
  - Subsequently have required 2500 patient years exposure for approval of Adalimumab, Abatacept, Golimumab, Certilizomab Pegol
  - **Natalizumab is an important example**

## Natalizumab and PML

At Risk	Cases	Persons	Incidence
General population	1	200,000	0.0005%
ALL Natalizumab Treated	3	8,000	0.0375%
Post Marketing	0	5,000	0
In RCTs	3	3,000	0.1 %
Natalizumab+IFN $\beta$	2	589	0.34%
Natalizumab >2 years	2	1,000	0.2%
Natalizumab >3 years	1	<100	>1.0%



## OA: Multiple Co-Morbidities

Recent RCTs indicate as many as 40-50% have HTN

- Twice as likely to develop Myocardial infarction (MI)
- 70% more likely to suffer CVA

Risk of Type II Diabetes

- With its own associated CV Risks

COPD and other Respiratory Diseases

Peptic Ulcer and other GI Diseases

Obesity / Metabolic syndrome

Incidence of co-morbid CV disease

- Increasing age
- Renal impairment contribute

## New Requirements: CV Risk in Type II DM

Clear Guidance for approval:

Risk Ratio (95% two-sided ) must be <1.8 and  
 Absolute Risk Ratio <1.5 (“nominally significant increase”)

– Guidance for Industry, Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes HHS/FDA/CDER DRAFT December 2008

Risk Ratio Upper limit: (95% CI)	Other aspects	Impact
≥1.8	Absolute ≥1.5	No approval
>1.8 – 1.3	Overall risk-benefit analysis positive; supports approval	May receive approval  Will require a postmarketing safety trial
<1.3		May not require a postmarketing safety trial

## Lessons from “COX-2s”: CV Risk Estimates

- Celecoxib:
  - RCTs: 1.10 [0.70 – 1.60]
  - 1.30 [0.60 – 2.60]
  - 2.30 [0.90 – 5.50]
  - Cohort Studies: 1.32 [0.69 – 2.16]
  - Case Control: 1.01 [0.90 – 1.13]
- Naproxen:
  - RCTs: HR: 1.57 [0.87 – 2.61]
  - Cohort Studies: 0.94 [0.85 – 1.04]
  - Case Control: 0.96 [0.84 – 1.10]
- Ibuprofen:
  - RCTs: 1.18 [0.93 – 1.19]
  - Cohort Studies: 1.12 [0.90 – 1.38]
  - Case Control: 1.06 [0.95 – 1.18]
- Diclofenac:
  - RCTs: 1.05 [0.93 – 1.19]
  - Cohort Studies: 1.36 [0.51 – 3.65]
  - Case Control: 1.36 [1.21 – 1.54]

McGettigan et al, Solomon et al, Reviewed in Strand Lancet 2007

## Challenges

- Annual CV event rates in RCTs generally  $\leq 1\%$ ;  
higher in CV outcomes trials  $\sim 2\%$  - in homogeneous high risk populations
  - Event rates are lower in subjects with newly diagnosed or earlier disease, eg DM, RA, OA and in subjects with fewer comorbidities
  - BUT is difficult to include high risk patients early in clinical development
- New requirements are designed to provide an incremental increase in the knowledge of CV risk associated with new therapeutic agents
  - effective implementation of this guidance will be challenging.
  - Potential to increase clinical development times by 1-3 years and costs by \$150-300M
  - Potential time and cost implications limit incentives
  - Fewer therapies may be developed; fewer sponsors may be able to develop such therapies; thus limiting access to new treatments.

## Alternatives?

- It is possible to develop a statistical estimate of the number of SAEs of interest considered “tolerable” for a given number of patient years, for an “acceptable” SAE rate per 1,000 patient years
  - As an example: for an unique SAE rate of 1 /1,000 patient years, one can determine that after 3,000 years of patient follow-up, there should be no more than 6 SAE’s – or the 95% confidence intervals will have been violated. In the context of background rates, and arbitrary in nature .
- This “tolerable” SAE number can be calculated repeatedly as patient years are accumulated throughout a trial, or in a clinical development program
- Hence, one could propose that after every incremental 500 patient years are accrued, the number of observed SAEs of interest would be compared to the “tolerable” number, to decide if the SAE rate is in danger of violating the 1/1000 patient years “acceptable” rate.

– Dan Bloch, statistical consultant to OMERACT OARSI effort

## Alternatives?

- More specifically, we assume the number of SAEs observed for a given number of patient years is distributed as a Poisson random variable, with the mean equal to the theoretical SAE rate we establish (e.g., 1/1000 pt yrs) and variance equal to this mean multiplied by the total number of patient-years observed.
- These assumptions permit us to establish confidence intervals for actual SAE rates, to decide if it violates the “tolerable rate” we have established.
- For example, 3000 patient-years should have mean of 3 SAEs – but could have as many as 6 before exceeding the confidence intervals – and thereby statistically violating the “tolerable rate”.

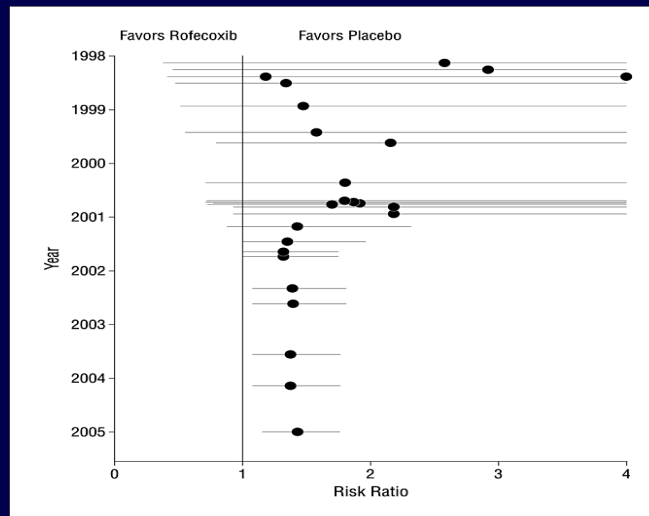
## Alternatives?

- Statistically, this same metric can be applied to patient populations in post-marketing situations
  - Practically, this requires an agreement regarding an estimate of patient years, and confidence that all SAEs are reported and adjudicated
  - More realistically, this metric for RCTs can be applied to longitudinal follow up studies, to monitor SAEs after significantly larger patient years of follow-up are accrued
  - Similar to current registries for RA and other health provider databases – but NOT post marketing surveillance
- A critical consideration is the definition of an “acceptable” SAE rate per 1000 patient years.

## What to Recommend?

- Does what applies to systemically administered symptomatic relief products apply to all?
  - Do the comorbidities in OA require consideration as if a type II DM product?
  - Can we consider an alternative, such as ongoing estimates of adjudicated CV events during the clinical development program?
- What do we apply to non-systemically absorbed topical and/or IA administered products?
- What about potentially structure modifying and/or “preventative” agents?
- How do we strike a “reasonable balance” between potential risk and promising benefit?

Cumulative pooled analysis of investigator-reported cardiovascular thrombotic events and all-cause deaths among all randomized, placebo-controlled rofecoxib trials of 4 weeks' duration or longer conducted by Merck Co Inc (Whitehouse Station, New Jersey)



Ross, J. S. et al. Arch Intern Med 2009;169:1976-1985.

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## Post-marketing Surveillance Data

- Cannot calculate true incidence

$$\text{Incidence} = \frac{\text{Number of events}}{\text{Number of exposed subjects}}$$

- Voluntary; therefore reporting bias
  - Under-reporting
  - Potential over-reporting, eg facilitated reports.....
  - Incomplete data
- Confounding by indication; often not known
- Reflects clinical practice; large and diverse populations and comorbidities
- Identifies 'signals' for study in large cohorts

## Conclusions

- Difficult problem with little understanding of "tolerable"
  - Differences in what is tolerable depending on what the therapy is to do: prevent, alter structural outcomes, or improve symptoms and what about seriously impact symptoms or only modestly impact symptoms
- Overall difficulty in determining causality in a patient population with co morbities and the potential for polypharmacy

## Research Agenda

- Tolerability and how to define it
  - Patients who provide a balance between improvement in suffering vs risk of a specific or general group of SAE's
  - The caregiver's assessment of the same issue
  - What about differences in patients' perspectives in similar approach to understand risk and benefit of prevention and structural modification

## Research Agenda

- Will accrued pt years of exposure assessed within a clinical development program reflect accumulated experience with new therapy in post marketing experience
- Is a year long exposure in this population more informative than accrued patient years of exposure?
- How to weigh the risk of CV events or other SAE's