Cholesterol Omnibus 2004
Aware of Cholesterol Terms

	1997 N=957 %	2000 N=1912 %	2004 N=1811 %
LDL	48	56	64
HDL	51	61	68
Triglycerides	N/A	N/A	77

Sample: Aware of “cholesterol”.

Cholesterol Omnibus 2004
Knowledge of Own Total Cholesterol

	1997 N=1424 %	2000 N=1912 %	2004 N=1811 %
Know number	27	29	28
Can describe own TC	N/A	94	91
High		10	8
Borderline high		18	17
Normal		66	66

Sample: Aware of “cholesterol”.

Cholesterol Omnibus 2004
Knowledge of Own LDL Cholesterol

	1997 N=459 %	2004 N=1165 %
Know number	7	7
Can describe own LDL	N/A	72
High		5
Borderline high		10
Normal		57

Sample: Aware of LDL “cholesterol”.

Pivotal Label Comprehension Study: Self-Selection Among Men and Women

	Men <45 N=149 %	Men ≥45 N=158 %	Women <55 N=254 %	Women ≥55 N=135 %
Correct + Acceptable	89	87	92	93
Correct	76	52	76	56
Qualify	0	1	0	1
Do not qualify	76	51	76	56
Acceptable	13	35	16	36
Use but volunteered Dr. mention	10	32	15	33
Don't know but volunteered Dr. mention	3	3	1	4
Incorrect	11	13	8	7
Use/no Dr. mention	9	12	7	7
Don't know/no Dr. mention	2	1	1	1

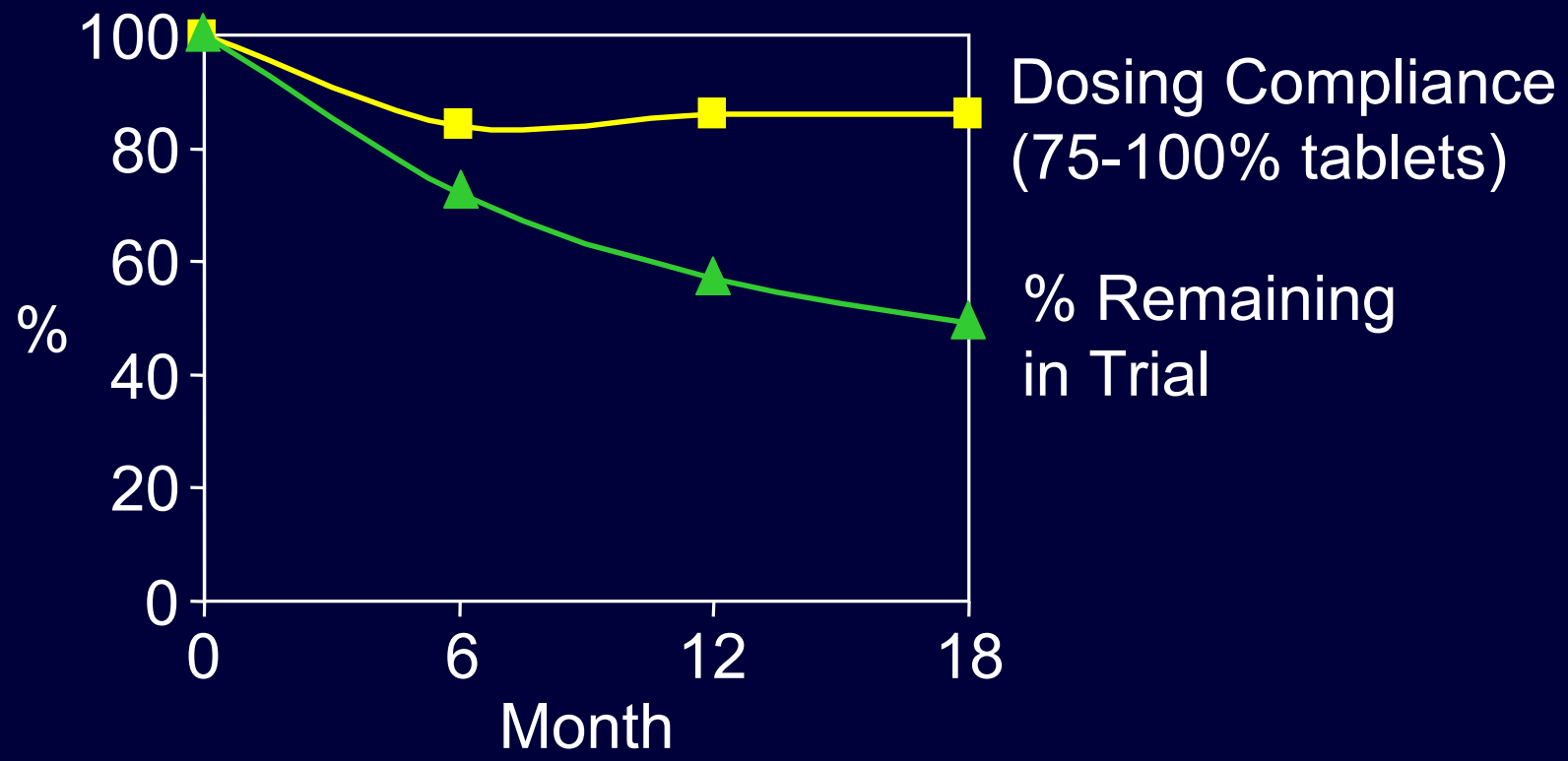
CUSTOM Results

Self-Selection Behavior – Non-Purchasers

- 2111 Non-Purchasers
- 438 final purchase decision of need more information
- 1673 decided not to purchase
  - 98% (1634 of 1673) were found to be ineligible for MOTC by label criteria
  - 1652 provided a reason for not wanting to purchase. Two most common reasons:
    - 64% (1054 of 1652) thought MOTC was not right for them
      - 99% (1040 of 1054) were found to be ineligible by label criteria
    - 19% (315 of 1652) talked to their doctor
      - 97% (304 of 314) were found to be ineligible by label criteria

MEVACOR™ OTC Use Over Time

Study 076 (N=722)



Comparison of Rx and OTC Persistence

Time Interval	Persistence Rate	Source
2 years	25%	Jackevicius, et al. *JAMA* 2002;288(4): 462-7
6 months	43%	Applegate. *JAMA* 2002;288(4):495-7 Benner, et al. *JAMA* 2002;288(4):455-61
12 months	50%	Wirebaugh SR, Whitney EJ. *P&T* 1993;18(6):559-62, 567-71
12 months	64%	Avorn, et al. *JAMA* 1998;279(18):1458-62
6 months	61%	CUSTOM Study 084
6 months	72%	MEVACOR™ OTC Pharmacy Study 076
12 months	57%	MEVACOR™ OTC Pharmacy Study 076

Liver Disease and Lovastatin in Kaiser Permanente Population

Patient Cohorts

- Exposed
  - Patients with evidence of liver abnormalities who took lovastatin
- Controls (Unexposed)
  - Patients with known liver abnormalities who did not take lovastatin
- Lab, inpatient, and outpatient databases were used for both cohorts

Liver Disease and Lovastatin in Kaiser Permanente Population

Disease Inclusions

- Chronic Hepatitis (w/out liver failure or hepatic coma)
  - Viral Hepatitis B
  - Viral Hepatitis C
  - Other specified Hepatitis
- Metabolic disorders
  - Hemochromatosis
  - Wilson's Disease
- Other chronic liver disease
  - Chronic liver disease and cirrhosis
  - Alcoholic fatty liver
  - Alcoholic cirrhosis of liver
- Other chronic liver disease (continued)
  - Alcoholic liver damage
  - Chronic hepatitis (not viral)
  - Chronic hepatitis, NOS
  - Chronic persistent hepatitis
  - Other chronic hepatitis
  - Cirrhosis of liver w/out alcohol
  - Biliary cirrhosis
  - Other chronic nonalcoholic liver disease
  - Unspecified chronic liver disease w/out alcohol

Liver Disease and Lovastatin in Kaiser Permanente Population

Final Study Population and Results

- Exposed
  - n=6,886
  - Hy's Rule
    - 6 Patients
    - Person-days exposed to lovastatin = 2,347,456 (6431 person-years)
    - Incidence rate – 2.6 per 10,000 person-days
- Controls
  - n=37,470
  - Hy's Rule
    - 626 patients
    - Person-days at risk = 56,960,578 (156,056 person-years)
    - Incidence rate = 11.0 per 10,000 person-days
- $P < 0.001$ in favor of exposure to lovastatin

Differences in FDA and MRL Analysis of Fetal Toxicity Data

- FDA method of analysis focuses on differences between individual group mean data and concurrent controls and does not utilize statistics unless $P<0.05$
- MRL method relies on combination of dose response relationships, statistical significance, both concurrent and historical control data, and reproducibility (if multiple studies)
- Examples of differences are shown on the following slides

FDA overview of Study 2

Selected Lovastatin Reprotoxicity Studies	Route	Doses (m/k/d)	Maternal NOAEL (m/k/d)	Exposure Multiple*	Rat Fetal / Neonate Findings				
					Death	Skeletal Malformations	Develop-mental Delays	Decrease Weight	External/ Visceral Malformations
Segment I (Dosing 15 Days prior to mating through Gestation Day 20)									
2.	Oral	2,20,200	20 2	15X 2X	√			√	

MRL Data from Study 2 (TT #85-708-0)

	Control	2	20	200 mg/kg/day
"Death"				
Total Pups born	244	268	275	216
# Dead on PND 0	3	4	4	5
# Dead PND 1-7	2	1	7	0
# Dead PND 8-14	0	0	7	0
# Dead PND 15-21	0	1	0	0
# Dead PND 1-21	2	2	14*	0
			* 8/14 from 1 litter	
"Decrease Weight" Female Pups				
PND 0 mean pup weight (g)	6.1	5.9 NS	5.9 NS	5.9 NS
PND 7 mean pup weight (g)	15.6	15.5 NS	14.6 NS	15.1 NS
PND 14 mean pup weight (g)	32.4	32.4 NS	33.0 NS	32.1 NS
PND 21 mean pup weight (g)	51.1	49.2 NS	50.7 NS	49.6 NS

Conclusions: No drug-related deaths or effects on weights in 20 mg/kg/day group.

Maternal Safety Margins for Class C Drugs

Drug	Effect	Effect Level mg/kg	Animal/ Human Dose Ratio
Cimetidine (OTC)	Anogenital distance	194	9.2
Fenofibrate	Embryocidal, terata	-	7 - 18
Epinephrine	Fetal asphyxia	0.001	0.78
Ibuprofen	Fetal ductal constriction	6 - 22	0.16 – 0.49
Lovastatin	Fetal weight, skeletal anomalies	10	23 - 36

Pregnancy Categories

- Pregnancy Category X – Contraindicated in pregnancy. Studies in animals or humans, or investigational or post-marketing reports, have shown fetal risk which clearly outweighs any possible benefit to the patient.

- Pregnancy Category C – Risk cannot be ruled out. Human studies are lacking, and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify the potential risk.

Teratology 49: 446-447, 1994.

Statin Use in Females of Childbearing Age

	1999 N* (%)	2001 N* (%)	2004 N* (%)
Total # Rx	10,269 (44.7)	12,783 (44.6)	18,915 (44.3)
21-30 yrs	48 (0.5)	65 (0.5)	103 (0.5)
31-40 yrs	276 (2.7)	362 (2.8)	480 (2.5)
41-50 yrs	965 (9.4)	1,349 (10.5)	2,057 (10.9)

% of total Rx is of total # prescriptions written. % of each sub-group is % of total # prescriptions written for females.
Source: IMS.
* in thousands.

Exposure to Lovastatin During Human Pregnancy

- Over 27 million patient years of exposure to marketed lovastatin
- 105 reports of pregnancy to WAES (vast majority in 1st trimester)
  - 67 spontaneous prospective reports have no reported congenital abnormalities
  - 38 spontaneous retrospective reports have 7 congenital abnormalities
    - Greater reporting rates occur after congenital defects diagnosed
    - No specific pattern of defects

Human Data Conclusions

- Reported experience with lovastatin exposure during pregnancy is limited
- No evidence that exposure during early pregnancy is associated with increased risk of any specific pattern of congenital abnormalities
- FDA/ODS Review: *"A causal association between in utero statin exposure and identified birth defects cannot be made based on the current information"*

Evaluations of Teratogenic Potential Using Computer-Based Systems

- Human teratogenic risk of 468 FDA approved drugs was assessed using the Teratogen Information System (TERIS), a computer-based teratology resource
- TERIS risk classifications are determined by a consensus of opinion among clinical teratologists
- Risk classifications were grouped into 3 broad categories:
  - No risk, minimal risk, or unlikely to produce an increased risk
  - Associated with a small, moderate, or high risk
  - Risk undetermined

Lo & Friedman, *Obstet Gynecol.* 100, 465-473, 2002.

TERIS Report: Findings on Lovastatin

- Lovastatin is listed among only 6.4% of drugs considered unlikely to pose teratogenic risk in human pregnancy
- Report equated the TERIS risk ratings system category of “none, minimal, or unlikely” to the FDA Use-In-Pregnancy Category of A or B

Lo & Friedman, *Obstet Gynecol.* 100, 465-473, 2002.

Pregnancy Data Summary

- Lovastatin is labeled Category X due to lack of clinical benefit and potential risk from animal studies
- Rat fetal abnormalities are consistent with a Category C
- Limited WAES data provide no evidence that exposure during early pregnancy is associated with increased risk of any specific congenital abnormalities
- TERIS database lists lovastatin as “unlikely” to pose teratogenic risk in human pregnancy

Post-Marketing Surveillance

- Key Elements of Proposal
  - Methods
    - Surveys, toll-free, website & 3rd party data (i.e., IMS)
    - Consumers & healthcare professionals
    - Projectable samples
  - Pre-Launch Study
    - Baseline measurement on awareness and attitudes
      - Untreated (at risk) and Rx users
  - Post-Launch Studies
    - OTC users, untreated (at risk) and Rx users
    - Pre-defined measurement frequency (e.g., six-month interims)
  - Actions
    - Identify unanticipated behaviors and remedy
    - Implement ongoing improvement of program

Respondent Consistency in Self-Reported Behaviors

Behavior	Study: National Lipid Assoc.	National Consumer League	Cholesterol Segmentation	BASES Statins	Omnibus 2004	CUSTOM & Post-CUSTOM
Tried diet & exercise	58% diet & exercise	44% exercise 42% diet	45% low fat 44% healthy weight	59% weight 67% exercise		80% tried diet and/or exercise
Doctor visits past yr/ regular		88%	80%	91%		88%
Discussed choles. with Dr.			79%	81%		85%
Would ask Dr. about OTC statin	79%	76%		83%		57%
Had cholesterol test	82% reg. or occ.			70% 1 yr 90% 2 yrs	72% 1 yr 91% ever	98% ever
Use low dose ASA for heart health	47%		57%	49%	47%	49%
Use vitamins & supplements	57%		72%	64%		49%

1978

Patients With Previous Hx of Muscle Pain

CUSTOM Study