21

WYETH-AYERST RESEARCH

JUSTIN R. VICTORIA
Vice President
Worldwide Regulatory Affairs

November 9, 1998

Ms. Jane Axelrad
Associate Director
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-005
Woodmont Office Complex 2
1451 Rockville Pike, Room 6027
Rockville, MD 20852

Dear Ms. Axelrad,

Enclosed, as requested, are copies of the overheads presented by Wyeth-Ayerst at the November 5, 1998 meeting with yourself and other representatives of the Agency regarding standards for approval and development of synthetic estrogen mixture products. I want to thank you and your colleagues again for taking the time to meet with us to discuss this very important issue.

If you have any questions regarding our presentation or the attached copies of the overheads, please don't hesitate to contact me at (610) 902-3712.

Sincerely,

Justin R. Victoria

Enclosures

JRV/lmc/JRV1998.3752

P.O. BOX 8299 • PHILADELPHIA, PA 19101-8299 • (610) 902-3712 • TELEFAX (610) 964-3898

Wyeth-Ayerst/FDA Meeting
November 5, 1998
Wyeth-Ayerst Attendees

Robert A. Essner, Executive Vice President, American Home Products
Joseph M. Mahady, President, Wyeth-Ayerst North America
Marily H. Rhudy, Vice President, Public Affairs, American Home Products
Michael S. Dey, Ph.D., President, ESI Lederle
Heidi Hunter, Vice President, Women's Health Care, Wyeth-Ayerst
Michael P. Peskoe, Assistant General Counsel, Regulatory Affairs, American Home Products
Justin R. Victoria, Vice President, Worldwide Regulatory Affairs, Wyeth-Ayerst
Donald O. Beers, Arnold & Porter
Nancy L. Buc, Buc & Beardsley
Jane E. Baluss, Buc & Beardsley

W-A/FDA MEETING
November 5, 1998

- Introductions
- Approval Standards --- Legal and Policy Issues --- N. L. Buc
- Premarin Characterization --- M. Dey
- USP Monograph Issues --- M. Dey
- Consumer/Substitution Issues --- H. Hunter
- Conclusions --- N. L. Buc
- Discussion

DESI
RIP

The Committee feels that insufficient data were presented to determine **whether or not** any individual component of Premarin or any combination of components in Premarin other than estrone sulfate and equilin sulfate must be present in order for Premarin to achieve its established levels of efficacy and safety [emphasis in original].

"Clinical tests, on which the findings of the safety and efficacy of Premarin were based, were performed on the entire mixture, not on individual components."

"It is not known to what extent, if any, differences in the types of estrogens used may affect safety. . . Therefore, sufficient clinical data do not exist to fully characterize the contributions (either positive or negative) of various Premarin components to its clinical safety."

Memorandum

Pages 26-27

PREMARIN CHARACTERIZATION UPDATE

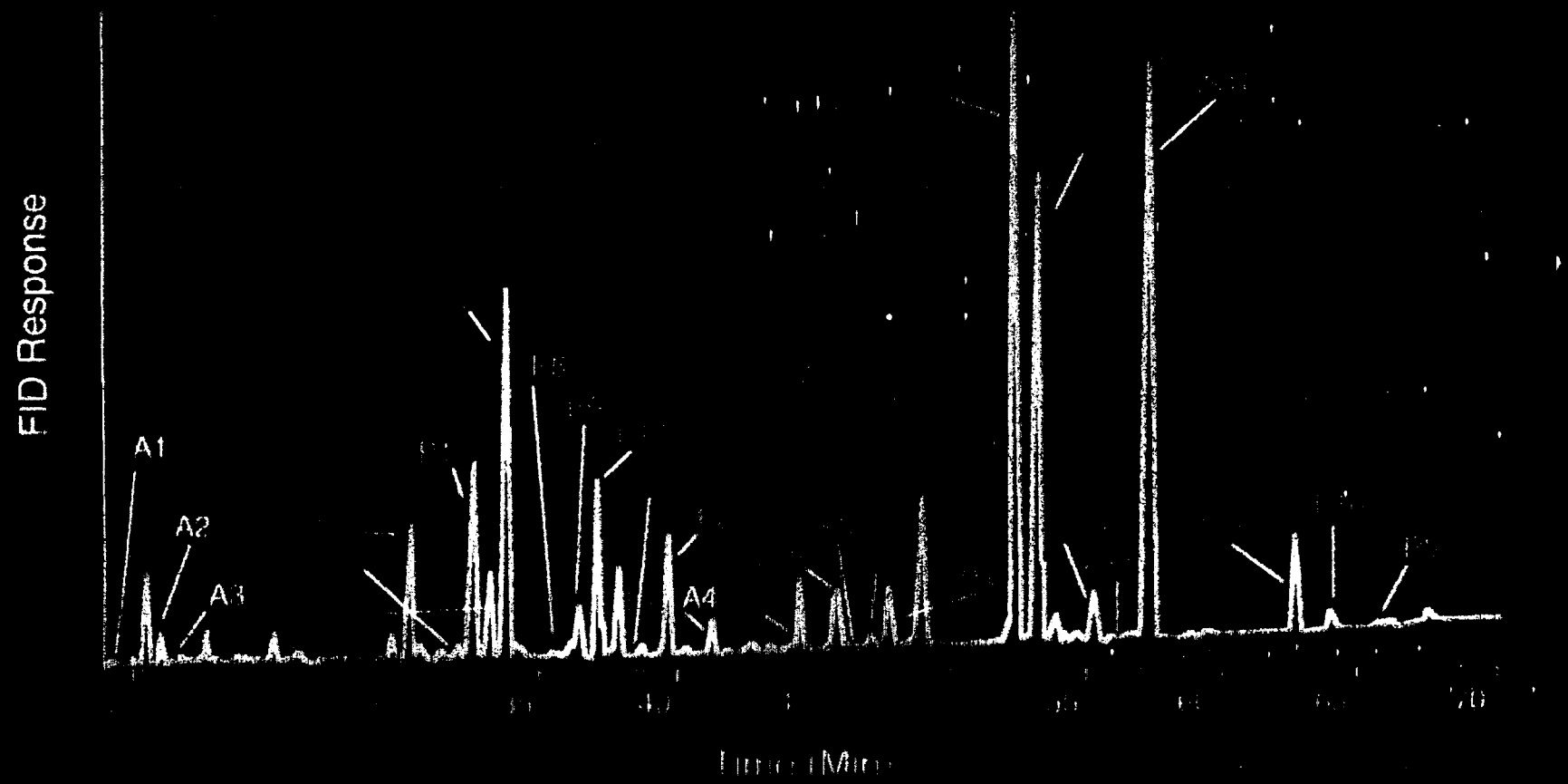
- April 15, 1997: Wyeth-Ayerst commits to continue characterizing active ingredient in Premarin.

- Wyeth-Ayerst/FDA Meetings
  - July 23, 1997
  - August 28, 1997
  - October 23, 1997

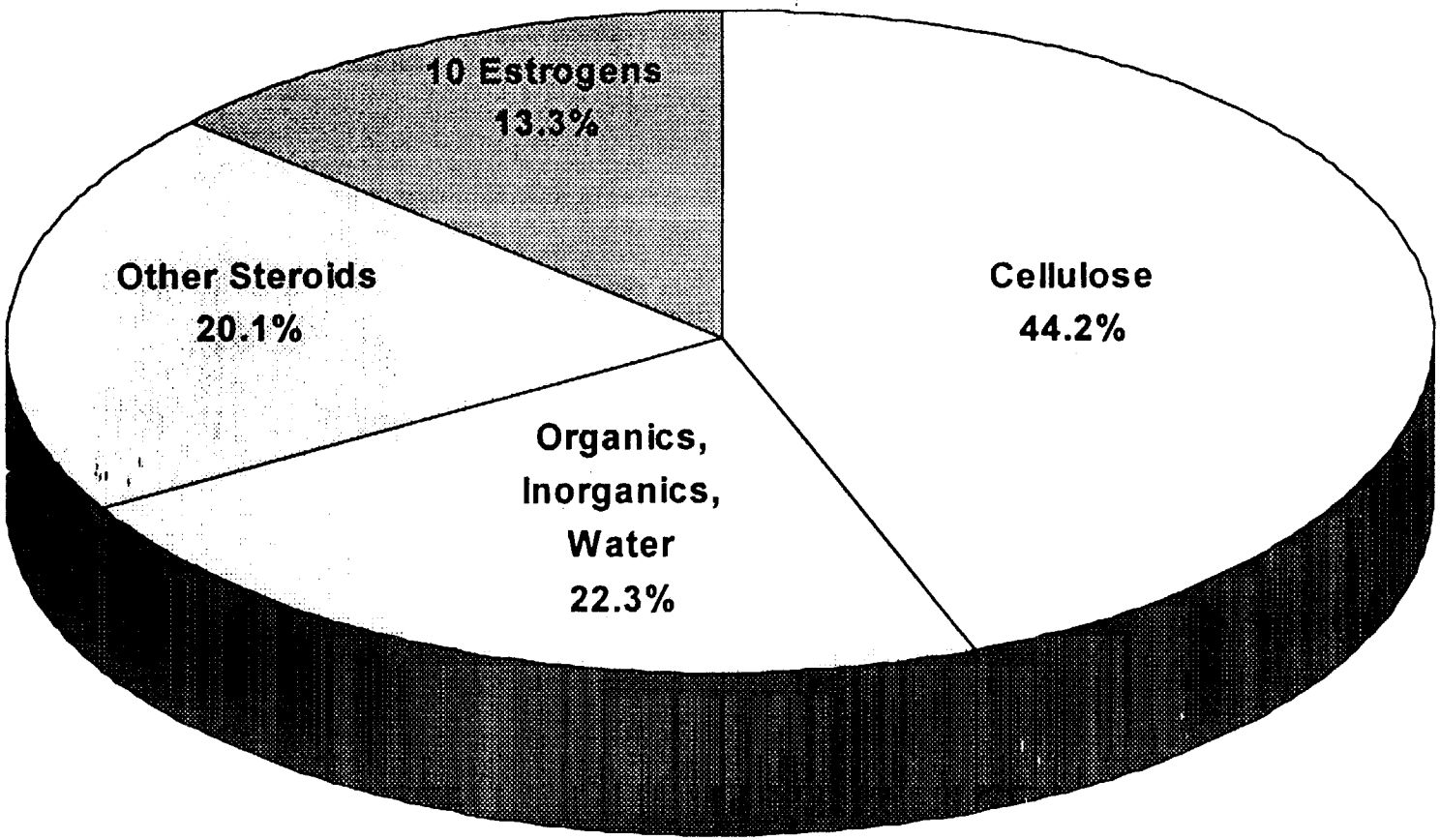
- Development of LC/MS method for component identification and quantitation.

- Components characterized to date
  - 39 Estrogens
  - 19 Pregnanes
  - 16 Androstanes

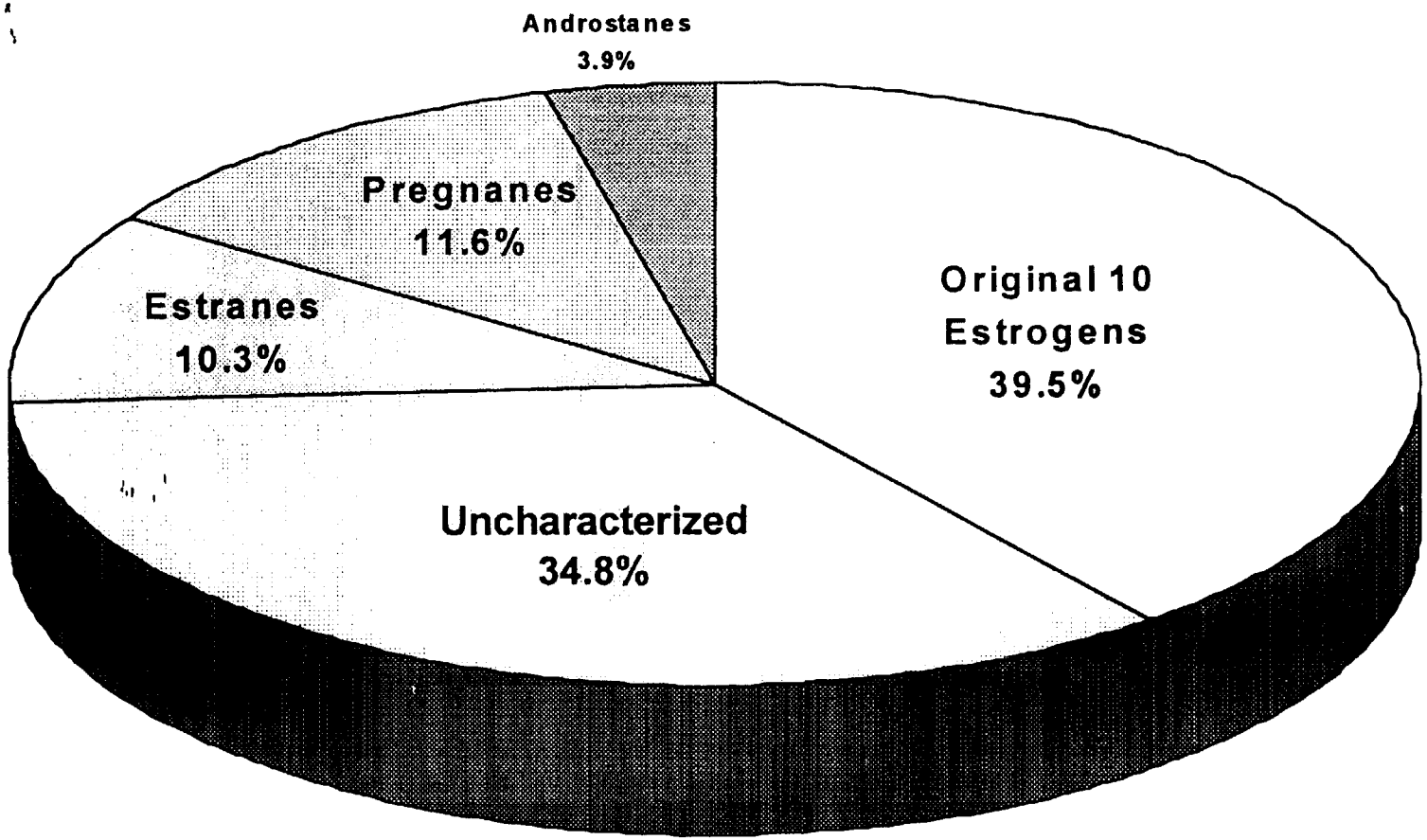
PREMARIN® CHROMATOGRAM 1997



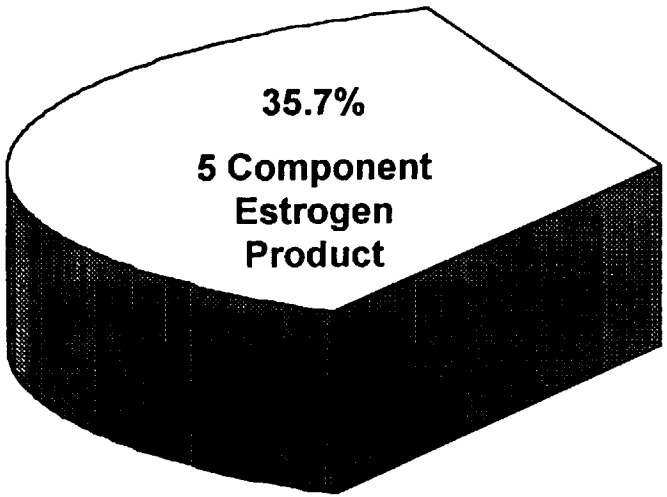
PREMARIN RAW MATERIAL COMPOSITION



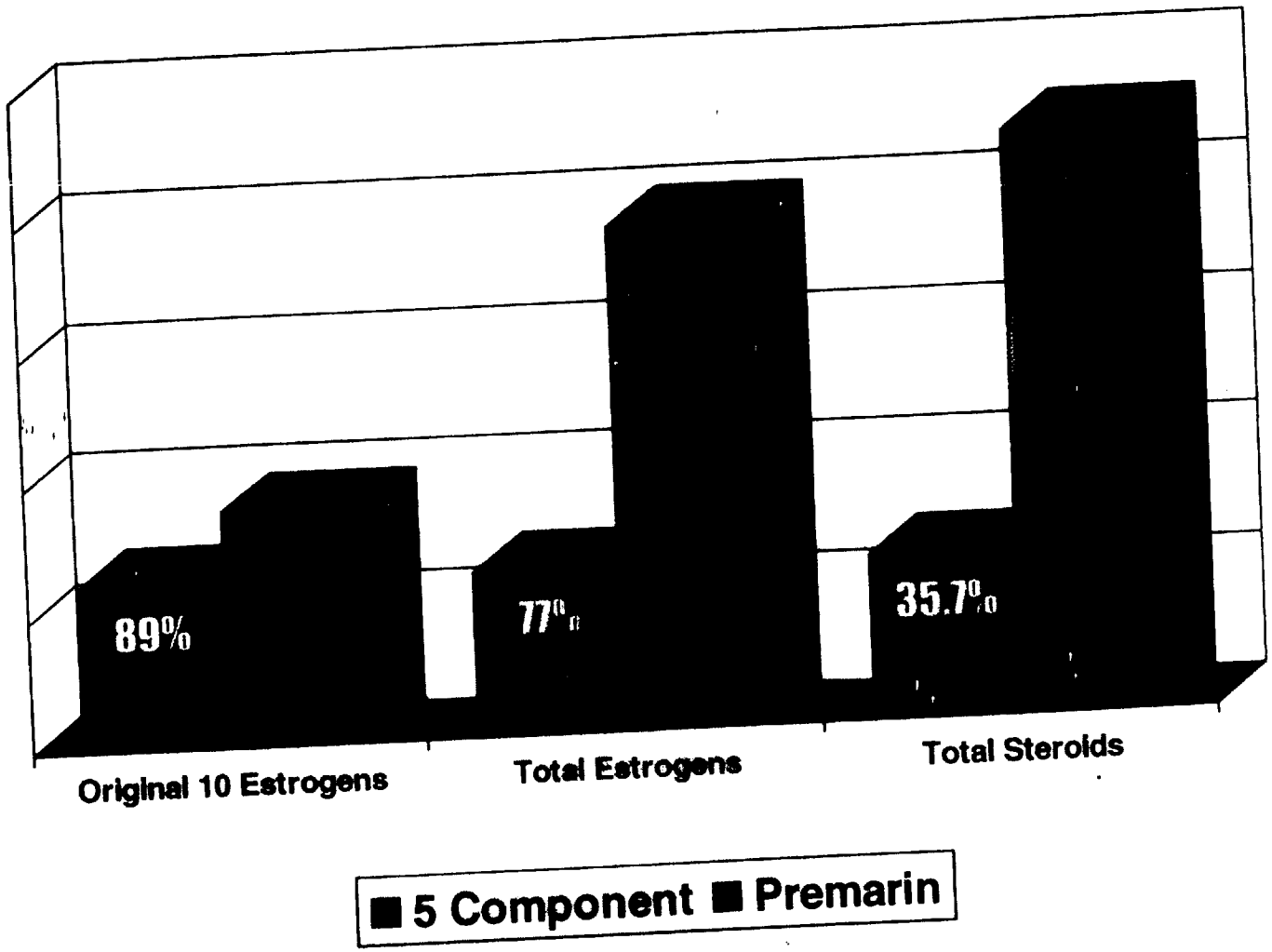
STEROIDAL COMPOSITION OF PREMARIN



RELATIVE STEROID CONTENT OF FIVE ESTROGEN COMPONENT PRODUCT VS. PREMARIN



RELATIVE STEROID CONTENT OF FIVE ESTROGEN COMPONENT PRODUCT VS. PREMARIN



BIOLOGICAL CHARACTERIZATION OF PREMARIN'S ACTIVE INGREDIENT

- Screen individual and component mixtures in cell assays
- Screen components from cell assays in rodents
  - Typical preclinical endpoints
    - lipids
    - uterine weight
    - bone density
    - etc.
  - Gene regulation and activation
- Screen components and component mixtures in clinical studies

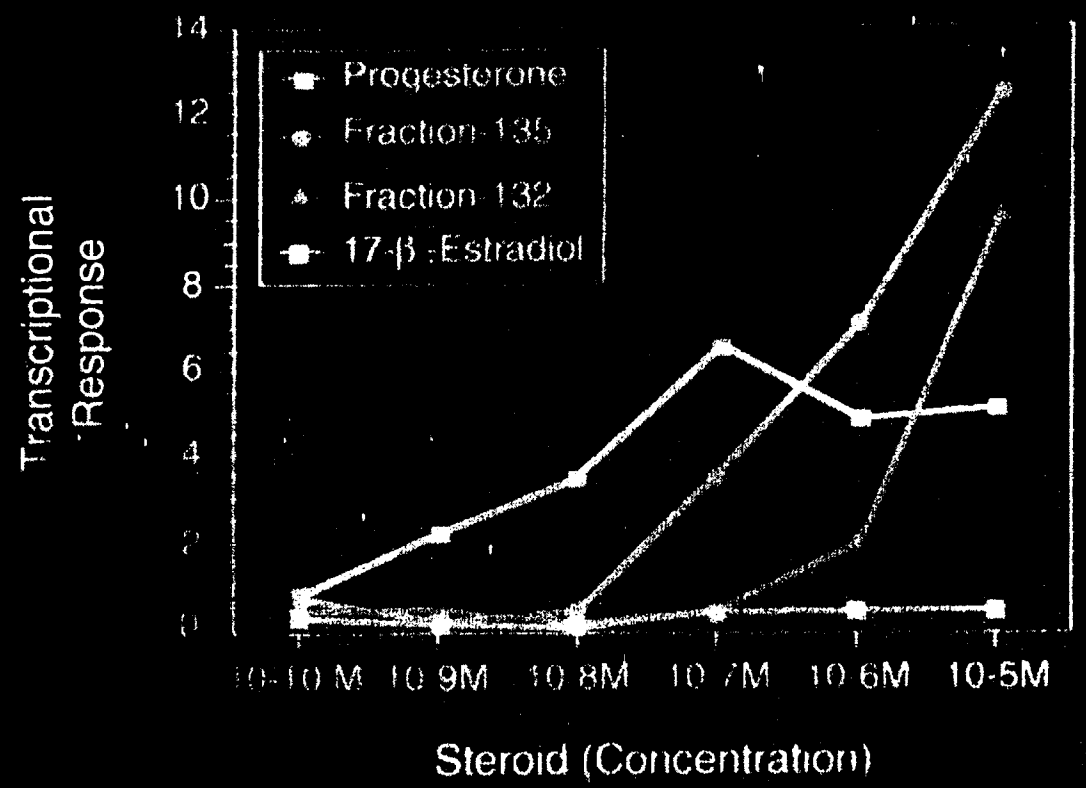
Premarin Estranes - Unconjugates

Chemical Name	ER-beta binding (LBD) (nM)	ER-alpha binding (LBD) (nM)
Estrone	91	55.5
Equilin	225	107
17a-Dihydroequilin	218	55
3b-Hydroxy-estra-5(10),7-dien-17-one	>5000	>5000
Delta8,9-dehydroestrone	181	93
17a-Estradiol	145	72
3b-Hydroxy-estr-5(10)-en-17-one	>5000	>5000
Estra-5(10),7-diene-3b,17a-diol	>5000	>5000
17b-Dihydroequilin	18.5	7
Estra-5(10),7-diene-3b,17b-diol	2700	2300
Estra-5(10),7-diene-3a,17b-diol	3900	2610
Equilenin	127	173
2-Methoxy-estrone	>5000	>5000
Estr-5(10)-en-3b,17a-diol	>5000	3510
17a-Dihydro-delta8,9-dehydroestrone	173	65
Estra-5,7,9-trien-3b-ol-17-one (Heard's ketone)	>5000	>5000
Estra-5,7,9-triene-3b,17b-diol (B-ring-estradiol)	>5000	>5000
Estra-5,7,9-triene-3b,17a-diol	>5000	>5000
Estra-5,7,9-triene-3a,17b-diol	>5000	>5000
Estra-3b,17b-diol (17b-Estradiol)	4.21 +/- 0.86	3.25 +/- 0.74
17a-Dihydroequilenin	81	141 +/-31
17b-Dihydro-delta8,9-dehydroestrone	25	17
3Hydroxy-2methoxy-estra1,3,5(10),7-tetraen-17one(2Methoxyequilin)	>5000	>5000
17b-Dihydroequilenin	16.3 +/-12	23 +/- 0.23
2,3-Dihydroxy-estra-1,3,5(10)-trien-17-one (2-Hydroxy-estrone)	740	110
3,6-Dihydroxy-estra-1,3,5,7,9-pentaen-17-one (6-Hydroxy equilenin)	127.5	1380
Estra-1,3,5(10)-triene-3,16a,17b-triol	32	46.7
Estra-1,3,5(10)-triene-3,16b,17a-triol	490	2690
Estra-1,3,5(10)-triene-3,16a,17a-triol	2.3	6.6
Estra-1,3,5(10)-triene-3,16b,17b-triol	19	12.7

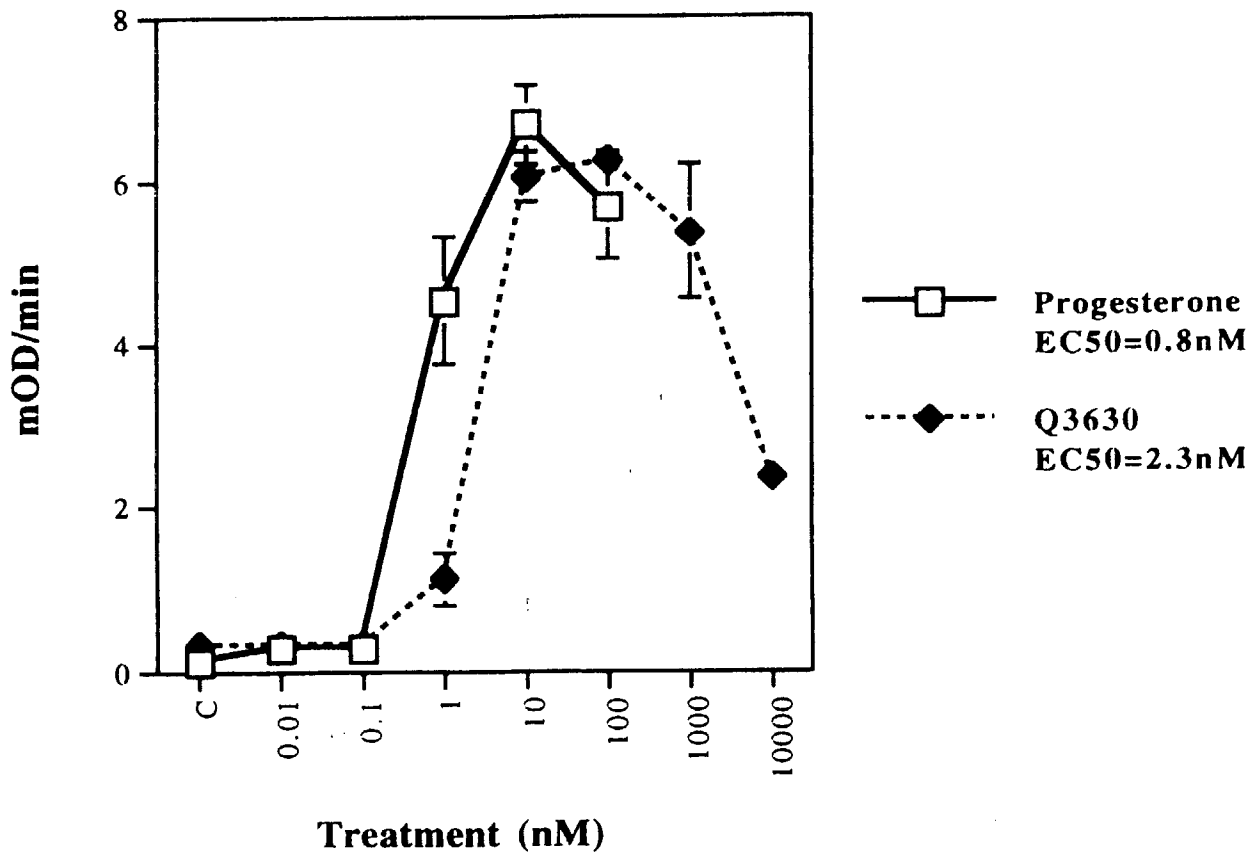
RELATIVE BINDING AFFINITY OF PREMARIN ESTRANES(nM)

Estrane	ERα	ERβ
Equilin	107	225
17α - dihydroequilin	55	218
Δ8,9 dehydroestrone	93	181
17α - estradiol	72	145
17β - dihydroequilin	7	18.5
17β - dihydroequilenin	23	16.3
17α - dihydroequilenin	141	81
Estra - 1,3,5(10)triene - 3,16a,17a - triol	6.6	2.3
Estra - 1,3,5(10)triene - 3,16a,17b - triol	46.7	32
Estra - 1,3,5(10)triene - 3,16b,17a - triol	2690	490
6 - hydroxy equilenin	1380	127.5

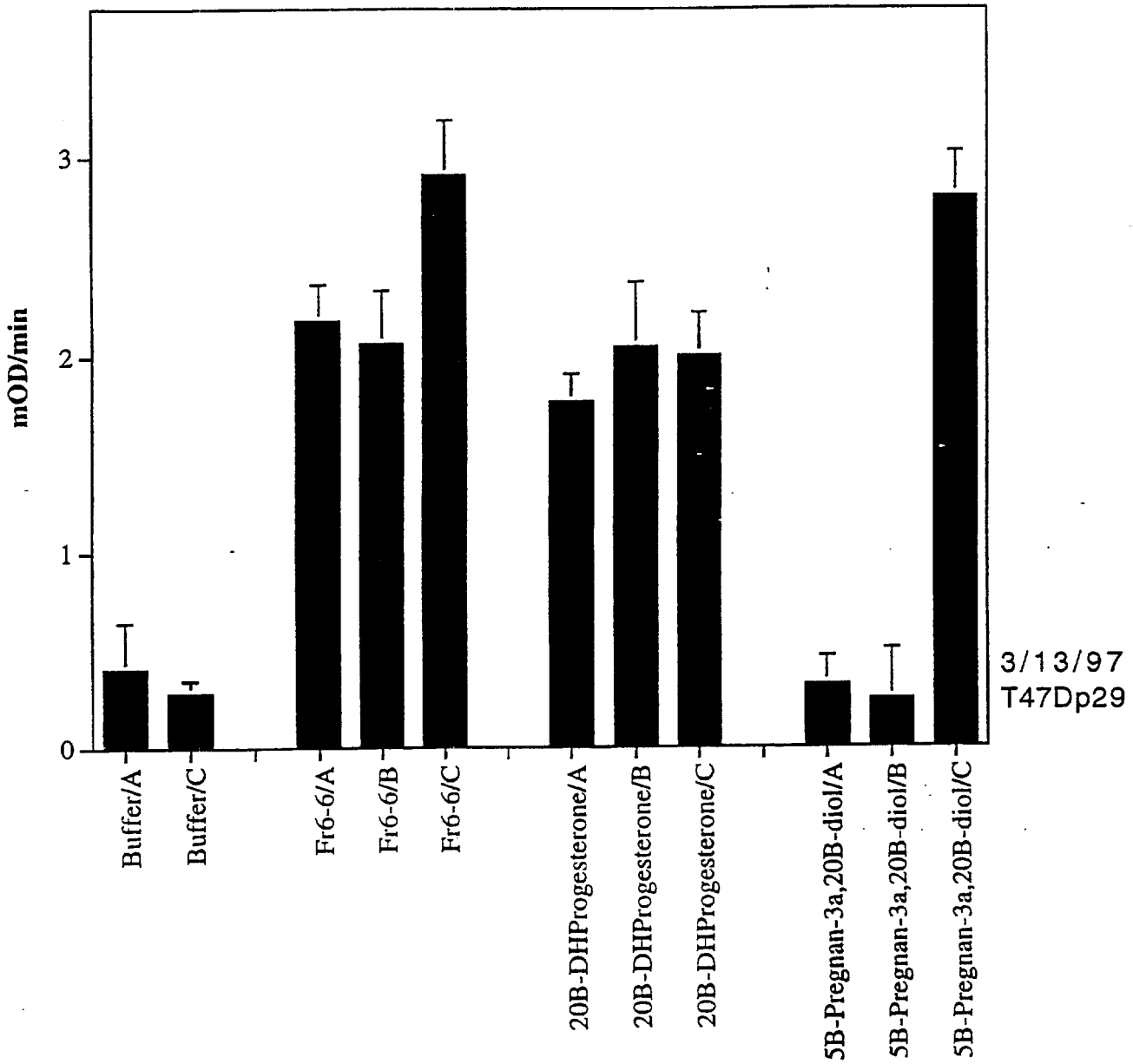
PROGESTERONE RECEPTOR-MEDIATED TRANSCRIPTIONAL ACTIVATION BY PREMARIN® FRACTIONS



The Effect of 4-pregnene-20β-ol-3-one (Q3630) on T47D Alk. Phos. Activity



The Effects of Microsome and NADPH on PCUD Components in T47D Alkaline Phosphatase Assay



A: Without Microsome & NADPH
B: Without NADPH
C: With Microsome & NADPH

INADEQUACY OF USP MONOGRAPH

- Does not describe Premarin
- Does not/will not describe 5 component product
  - Name:
    - Conjugated estrogens is not specific
      - 5 component product
      - Premarin (conjugated estrogens)
      - Next 5,6,7 . . . . component product
    - Natural vs. synthetic doesn't help