

→ Animal studies. <sup>→ appropriate animal model</sup>  
+ toxicology studies



## Phases of drug Trials in human beings.

Ph I : Drug is given to a small no. of healthy human volunteers with the principal objectives of looking for ① evidence of toxicity & determining the ② basic properties of the drug in humans.

Ph II : The drug's effects on a small pop<sup>n</sup> of patients with the appropriate disease (or in the case of contracep<sup>n</sup> healthy people) are examined to determine ① efficacy & to detect any ② adverse effects on ③ possible toxicity.

Dose Determination  
10-50 ♀

3,000 ♀, 100 cycles  
or  
200 ♀, 100 cycles

Ph III : Consists of larger scale testing i.e. 20,000 cycles to cover ① less common side effects & to approximate more closely the ② type of drug utilization that wd. occur in medical practice if the drug were marketed.

> 1000 ♀  
multi-centred

Ph IV : Prog. Intro study to assess the ① acceptability of the drug under existing F.P. & prog. condits with a focus to identify the ② operational requirements & ③ logistics.

Carcinogenic - Norplant 2, also - ring of vaginal ring. U

Clinical trials - issues

questionable "production" of convenient data.  
ethics - fact of trial.  
adverse effects.  
informed consent.  
what posit. - no to human trials?

Healthy ♀ for 20-25 yrs. of life.  
most productive yrs. of life.  
morbidity ques.

♀ } efficacy } acceptability  
no side effects. } Ph II  
reversible } Ph III  
availability. } Ph IV

- What effects are looked for? eg: after removal of Norplant - return of fert. but - contracep. does not affect only reprod. organs but - long term effect on other organs also

- Stats. - 9 months etc? ???? ?

- Ethics of manufacturer design & funding of clinical trials - New - en. 19 out of 21 studies Depo - Johnson funded \$6 million on one study in New Zealand alone - an amt equivalent to the annual budget of the Medical Research Council, N.Z. <sup>Subsiding</sup>

Court case - demand for order to direct respondents to frame rules relating to the conducting of trials - Specify the safe guards & conditions to which such trials are to be conducted providing

Public Hearing of  
the  
National Women's Health Network

Depo-Provera Public Board of Inquiry

Docket No. 783-0124

The National Women's Health Network ("Network") submits this post-hearing brief in support of its position that Depo-Provera should not be approved for use as a contraceptive in the United States. As the testimony presented at the hearing before the Public Board of Inquiry, written submissions, and entire record clearly reveal, the Upjohn Company ("Upjohn") has failed to meet the statutory burden of proving the safety of Depo-Provera.<sup>1/</sup>

A finding of safety must be based on reliable scientific evidence. Upjohn has not offered a single credible study to support its allegations that Depo-Provera is a safe drug. Rather, Upjohn's own research, which has focused on monkey and beagle dog testing, strongly suggests that Depo-Provera causes cancer.

Upjohn attempts to avoid the results of the monkey study by arguing that the data suggesting cancer are not statistically significant. However, as Dr. Shearer testified at the hearing, this analysis is fundamentally flawed. The

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<sup>1/</sup> See Section 305(b) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355. The Act also requires proof of effectiveness, but only the safety of Depo-Provera is at issue here.

reason that a conclusion of statistical significance cannot be drawn from the data is that Upjohn failed to conduct a study with a sufficient sample size. ~~Moreover, for a finding of~~

~~statistical nonsignificance, Upjohn should have used at least fifty animals.~~<sup>2/</sup>

Indeed, the fact that two carcinomas were found in a small group of sixteen monkeys strongly suggests that, if a proper-sized test group was used, the results would have been statistically significant.

The results of the beagle dog study likewise indicate carcinogenicity. Upjohn has asserted five purported reasons for discounting the positive results of the study. However, Dr. Shearer demonstrated at the hearing and in her written testimony the invalidity or irrelevancy of each of these reasons.

~~First, Upjohn claims that the positive carcinogenesis assays in beagle dogs are not valid because there are differences between dogs and humans in reproductive endocrinology.~~

As Dr. Shearer testified, however, this general statement is true of any two different species and ~~is irrelevant.~~ The only difference that would be significant in assessing human risk of mammary cancer would be the demonstration that progestogens do not enter human breast cells and so cannot contact the genetic material in the nucleus. ~~Even this is not relevant to the risk of cancers induced in other organs.~~<sup>3/</sup>

<sup>2/</sup> See Testimony of Ruth W. Shearer, Ph.D. at 1, citing Maugh, "Chemical Carcinogens: The Scientific Basis for Regulation," Science 201:1200-1205 (1978).

<sup>3/</sup> See Testimony of Ruth W. Shearer, M.D. at 3; Transcript of January 13, 1983 at 47.

Upjohn asserted that the growth response of a dog mammary gland to progestogens is unique. The growth response referred to is hyperplasia, an early response. Hyperplasia can be distinguished from neoplasia by appropriate genetic tests to determine multiple or single cell origin of the nodule. Upjohn's claim that most dog mammary nodules represent hyperplasia rather than neoplasia should be supported by such data. Hyperplasia is not a necessary prerequisite for neoplasia; therefore, this difference does not preclude neoplasia in treated women.<sup>4/</sup>

Next, Upjohn claims that the dog responds bizarrely to progestogens. However, uterine effects, diabetes-like syndrome, and acromegaly are not relevant to the interpretation of mammary neoplasia. The inclusion of malignant mammary tumors in the list of bizarre effects is circular reasoning, implying that this effect is not significant because it has not yet been confirmed in humans. It is widely accepted that a chemical which is carcinogenic in one species will be carcinogenic in others,<sup>5/</sup> but not necessarily in all others and often not in the same organ in different species.<sup>6/</sup> Therefore,

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<sup>4/</sup> See Testimony of Ruth W. Shearer, M.D. at 4, citing Berenblum, Carcinogenesis as a Biological Problem, American Elsevier Publishing Co., New York, pp. 276-277; Transcript of January 13, 1983 at 97-98.

<sup>5/</sup> See Maugh, supra, cited in Testimony of Ruth W. Shearer, M.D. at 4.

<sup>6/</sup> See Schmahl and Habs, "Carcinogenicity of N-Nitroso Compounds," Oncology 37:237-242 (1980).

evidence of carcinogenesis in one mammalian species is strong  
evidence for potential human carcinogenicity.

Upjohn also claimed that the increase in growth hormone in DMPA-treated dogs is involved in mammary tumorigenesis. There is absolutely no evidence in support of this claim. The data indicate that these are two of the effects of DMPA in dogs but show no relationship other than the common cause. This claim is testable by administration of growth hormone to dogs using carcinogenesis bioassay methodology, and this excuse for DMPA carcinogenesis should not be accepted without such data.<sup>7/</sup>

Finally, Upjohn asserted that potencies of progestogens differ between dogs and humans. Although this statement is true, it has no relevance to the extrapolation of carcinogenic potential. It is relevant only to the selection of the maximum tolerated dose for carcinogenicity testing and for comparing that dose to the human dose in quantitating the cancer risk.

It is significant that Upjohn, in its rebuttal testimony, has not disputed any of Dr. Shearer's refutations of its arguments regarding the beagle or monkey studies. Because Upjohn's arguments do not withstand scrutiny, these animal studies warrant serious consideration by the Board.

After attempting to discount the animal test results, Upjohn relies on human data that is either inadequate or merely

<sup>7/</sup> See Transcript of January 13, 1982 at 98.

anecdotal in nature. Upjohn primarily seeks to rely on data gathered by clinics in foreign countries and the Grady Clinic in the United States. But as Dr. Richwald and other witnesses testified, each of these studies suffers from serious flaws, including lack of appropriate control group, small sample size, inadequate length of exposure, and loss of users for follow-up.<sup>8/</sup>

Most importantly, as Dr. Shearer testified, a good epidemiological study requires that women given Depo-Provera be followed twenty years to determine if cancer develops.<sup>9/</sup> The number of total women-years or total women-months obviously cannot replace the twenty years per woman follow-up required to assess the safety of the drug.

Although Depo-Provera has been used for almost two decades, no study exists that follows an adequate number of users for even close to the required twenty-year period. None, therefore, is sufficient to prove the safety of the drug. Perhaps Upjohn realized this when it recently designed a protocol for a more adequate human study (which should have been done many years ago). Upjohn has acknowledged that it questioned the validity of the beagle dog study as far back as the 1960's; at that time, the Company indicated its belief that human epidemiological studies were necessary. More than a

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8/ See Testimony of Gary A. Richwald, M.D., M.P.H. at 2-1; Transcript of January 13, 1983 at 78-92.

9/ See Transcript of January 13, 1983 at 99.

side has passed since then and Upjohn has failed to undertake a human study involving the collection of sufficient data throughout that time.

This Board should not permit Upjohn to rely on the absence of adverse human test results as a basis for approving the drug, when Upjohn has failed to conduct the human studies it admitted were necessary. It would be unfortunate if the Board were to accept that line of reasoning -- and thereby allow Upjohn to benefit from its own negligence.

Nor should the Board permit Upjohn to rely on anecdotal data, such as the fact that physicians and other health care personnel have not notified Upjohn of cancer or other risks. Anecdotal testimony is not probative evidence in a Public Board of Inquiry proceeding and certainly cannot prove safety.

Moreover, Upjohn is certainly aware of one potential medical risk arising from the drug's teratogenic effects. Depo-Provera, like Provera and other progestins, has been shown to have deleterious effects on a fetus. Dr. Done's written testimony, which is supported by the testimony of Drs. Goldman and Rhodes, shows that the number of positive studies linking progestins with teratogenic effects is overwhelming.<sup>10/</sup>

In addition to these cancer and teratogenic effects, it should be noted that other significant detrimental side

<sup>10/</sup> See Testimony of Alan K. Done (January 3, 1983); Addendum and Rebuttal Testimony (March 2, 1983).

effects may also result from taking Depo-Provera. Indeed, the ~~side effects of a drug such as Depo-Provera, which cannot be~~ ~~terminated quickly if adverse effects result,~~ must be seriously considered. In addition, there is not yet enough data to give a woman adequate information regarding the likelihood of side effects so that she can give "informed consent."

In short, there is absolutely no reliable scientific evidence to prove the safety of Depo-Provera. The human studies conducted to date are wholly inadequate for the reasons described by the experts. Further, Upjohn's own animal studies -- quite to the contrary of proving safety -- strongly suggest that Depo-Provera causes cancer. Along with this evidence showing lack of safety, the Board should seriously consider the facts that the drug is not life-saving and will be given to healthy women who have access to other adequate, viable, safe contraceptives. Under these circumstances and until competent studies are completed that refute the clearly indicated risks, the Network believes that the risks of Depo-Provera strongly outweigh its benefits. Accordingly, the Network urges the

Board not to approve Depo-Provera for contraceptive use in the United States at this time.

Respectfully submitted,

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